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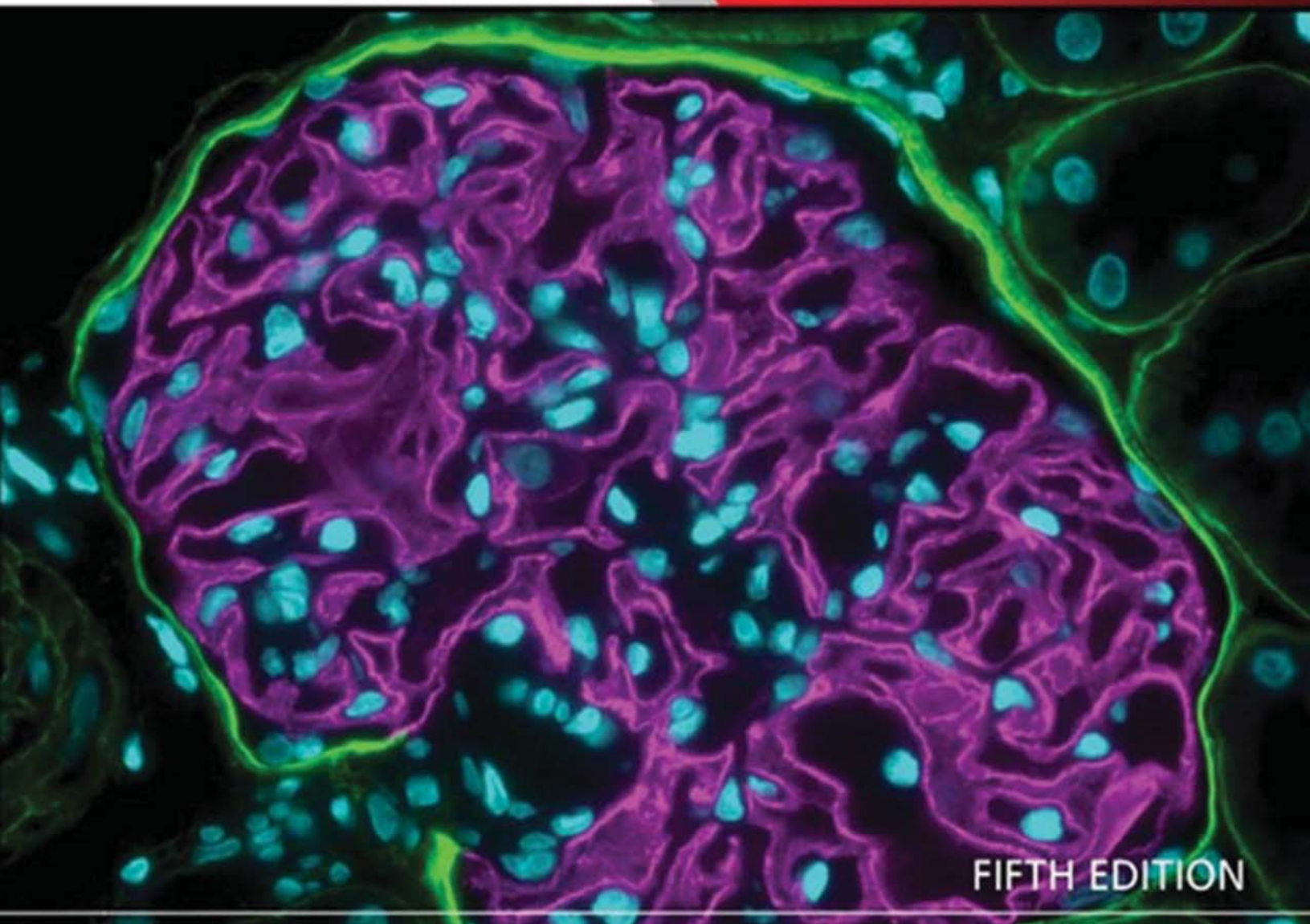

FIFTH EDITION

COMPREHENSIVE CLINICAL NEPHROLOGY

Richard J. Johnson
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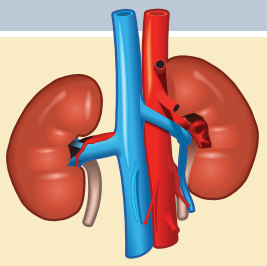

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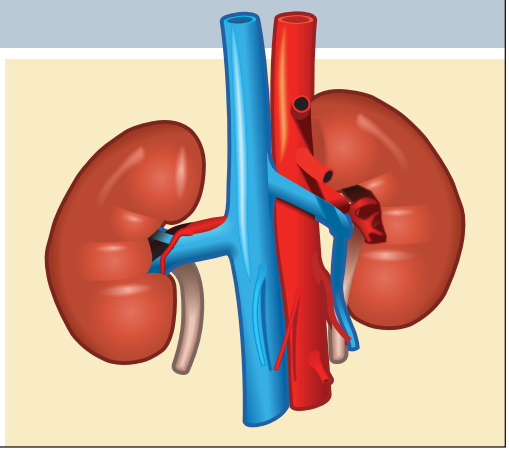

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To our mentors in nephrology—especially Bill Couser, Stewart Cameron, and Karl M. Koch

To our colleagues and collaborators, as well as others, whose research continues to light the way

To our wives and families, who have once again endured the preparation of this fifth edition with unfailing patience and support

To our patients with renal disease, for whom it is a privilege to care

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PREFACE

In the fifth edition of *Comprehensive Clinical Nephrology,* we continue to offer a text for fellows, practicing nephrologists, and internists that covers all aspects of the clinical work of the nephrologist, including fluids and electrolytes, hypertension, diabetes, dialysis, and transplantation. We continue to recognize that this single volume does not compete with multivolume, highly referenced texts, and it remains our goal to provide "comprehensive" coverage of clinical nephrology yet also ensure that inquiring nephrologists can find the scientific issues and pathophysiology that underlie their clinical work.

For this edition all chapters have been extensively revised and updated in response to the advice and comments that we have received from many readers and colleagues. These revisions include latest developments, such as the discovery of the major autoantigen in membranous nephropathy, and the latest data on important issues in therapeutics such as blood pressure targets and use of RAS blockade. New diseases (for example, C3 glomerulopathy) and new interventions (including renal denervation) have entered the scene since the fourth edition came out, and these are now covered. Another new feature of the fifth edition is coverage of the rapidly expanding field of renal disease in cancer patients.

For this edition, we have also refined the algorithms, which are a popular feature of the book, by using color more consistently to emphasize different aspects of the information being provided. Thus yellow boxes are used for general information, green boxes indicate therapeutic intervention, and blue boxes indicate necessary investigations.

By popular demand we continue to offer readers access to the images from the book that we are pleased to see used in lectures and seminars in many parts of the world.

This is the second edition that features access to a companion Expert Consult website, with fully searchable text, a downloadable image library, and links to PubMed. New to this edition is an online question bank with more than 400 multiple-choice questions.

Jürgen Floege
Richard J. Johnson
John Feehally

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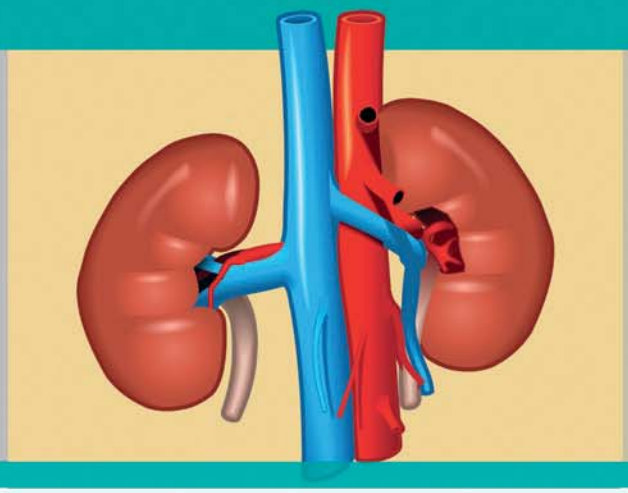

SECTION I

Essential Renal Anatomy and Physiology

CHAPTER 1

Renal Anatomy

Wilhelm Kriz and Marlies Elger

The complex structure of the mammalian kidney is best understood in the unipapillary form that is common to all small species. Figure 1-1 is a schematic coronal section through a unipapillary kidney, with a cortex enclosing a pyramid-shaped medulla, the tip of which protrudes into the renal pelvis. The medulla is divided into an outer and an inner medulla; the outer medulla is further subdivided into an outer and an inner stripe.

STRUCTURE OF THE KIDNEY

The specific components of the kidney are the nephrons, the collecting ducts, and a unique microvasculature.[1] The multipapillary kidney of humans contains about 1 million nephrons, although this number varies considerably. The number of nephrons is already established during prenatal development; after birth, new nephrons cannot be developed, and a lost nephron cannot be replaced.

Nephrons

A nephron consists of a renal corpuscle *(glomerulus)* connected to a complicated and twisted tubule that finally drains into a collecting duct (Fig. 1-2 and Table 1-1). Three types of nephron can be distinguished by the location of renal corpuscles within the cortex: superficial, midcortical, and juxtamedullary nephrons. The tubular part of the nephron consists of a proximal tubule and a distal tubule connected by a loop of Henle[2] (see later discussion). There are two types of nephron, those with long loops of Henle and those with short loops. Short loops turn back in the outer medulla or even in the cortex (cortical loops). Long loops turn back at successive levels of the inner medulla.

Collecting Ducts

A collecting duct is formed in the renal cortex when several nephrons join. A connecting tubule is interposed between a nephron and a cortical collecting duct. Cortical collecting ducts descend within the medullary rays of the cortex. These ducts traverse the outer medulla as unbranched tubes. On entering the inner medulla, the cortical collecting ducts fuse successively and open finally as papillary ducts into the renal pelvis (see Fig. 1-2 and Table 1-1).

Microvasculature

The microvascular pattern of the kidney is similarly organized in mammalian species[1,3] (Fig. 1-3; see also Fig. 1-1). The renal artery, after entering the renal sinus, finally divides into the interlobar arteries, which extend toward the cortex in the space between the wall of the pelvis (or calyx) and the adjacent cortical tissue. At the junction between cortex and medulla, the interlobar arteries divide and pass over into the arcuate arteries, which also branch. The arcuate arteries give rise to the cortical radial arteries (interlobular arteries), which ascend radially through the cortex. No arteries penetrate the medulla.

Afferent arterioles supply the glomerular tufts and generally arise from cortical radial arteries. *Aglomerular* tributaries to the capillary plexus are rarely found. As a result, the blood supply of the peritubular capillaries of the cortex and the medulla is exclusively *postglomerular.*

Glomeruli are drained by efferent arterioles. Two basic types of efferent arterioles can be distinguished, cortical and juxtamedullary. *Cortical* efferent arterioles, which derive from superficial and midcortical glomeruli, supply the capillary plexus of the cortex. The efferent arterioles of *juxtamedullary* glomeruli represent the supplying vessels of the renal medulla. Within the outer stripe of the medulla, these vessels divide into the *descending* vasa recta and then penetrate the inner stripe in cone-shaped vascular bundles. At intervals, individual vessels leave the bundles to supply the capillary plexus at the adjacent medullary level.

Ascending vasa recta drain the renal medulla. In the inner medulla, the vasa recta arise at every level, ascending as unbranched vessels, and traverse the inner stripe within the vascular bundles. The ascending vasa recta that drain the inner stripe may join the vascular bundles or may ascend directly to the outer stripe between the bundles. All the ascending vasa recta traverse the outer stripe as individual wavy vessels with wide lumina interspersed among the tubules. Because true capillaries derived from direct branches of efferent arterioles are relatively scarce, the ascending vasa recta form the capillary plexus of the outer stripe. The ascending vasa recta empty into arcuate veins.

The vascular bundles represent a countercurrent exchanger between the blood entering and that leaving the medulla. In addition, the organization of the vascular bundles results in a separation of the blood flow to the inner stripe from that to the inner medulla. Descending vasa recta supplying the inner medulla traverse the inner stripe within the vascular bundles. Therefore blood flowing to the inner medulla has not been exposed previously to tubules of the inner or outer stripe. All ascending vasa recta originating from the inner medulla traverse the inner stripe within the vascular bundles. Thus blood that has perfused tubules of the inner medulla does not subsequently perfuse tubules of the inner stripe. However, the blood returning from either the inner medulla or the inner stripe afterward does perfuse the tubules of the outer stripe. This arrangement in the outer stripe may function as the ultimate trap to prevent solute loss from the medulla.

The intrarenal veins accompany the arteries. Central to the renal drainage of the kidney are the arcuate veins, which, in contrast to arcuate arteries, do form real anastomosing arches at the corticomedullary border. The arcuate veins accept the veins from the cortex and the renal medulla. The arcuate veins join to form interlobar veins, which run alongside the corresponding arteries.

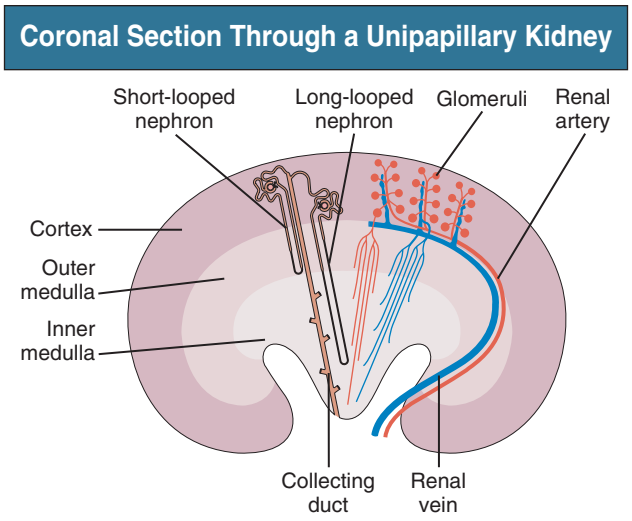

Figure 1-1 **Coronal section through a unipapillary kidney.**

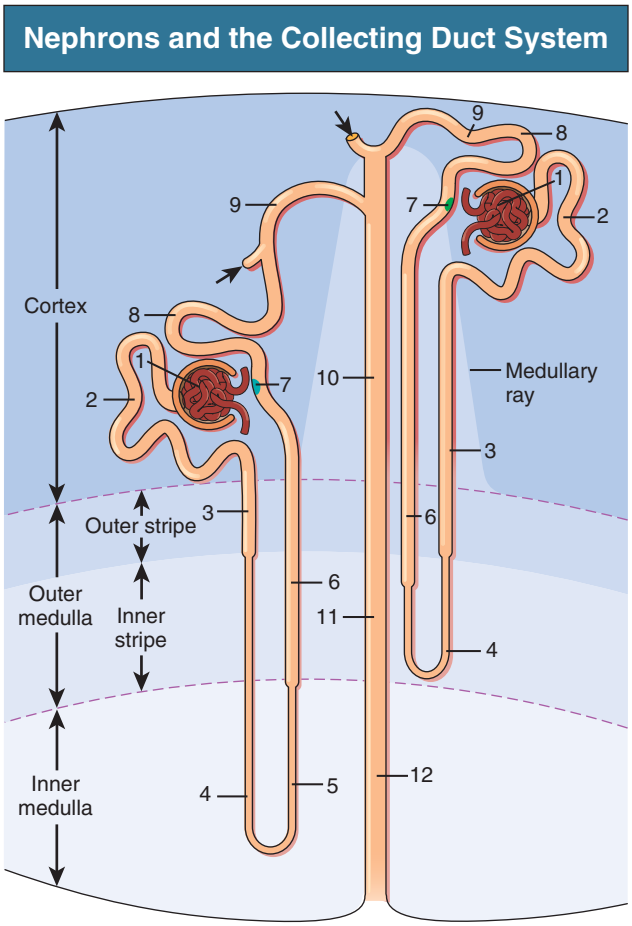

Figure 1-2 **Nephrons and the collecting duct system.** Shown are short-looped and long-looped nephrons, together with a collecting duct (not drawn to scale). *Arrows* denote confluence of further nephrons.

Subdivisions of the Nephron and Collecting Duct System

Section	Subsections
Nephron	
Renal corpuscle	*Glomerulus:* term used most frequently to refer to entire renal corpuscle Bowman capsule
Proximal tubule	Convoluted part Straight part (pars recta), or thick descending limb of Henle loop
Intermediate tubule	Descending part, or thin descending limb of Henle loop Ascending part, or thin ascending limb of Henle loop
Distal tubule	Straight part, or thick ascending limb of Henle loop: subdivided into medullary and cortical parts; the cortical part contains the macula densa in its terminal portion Convoluted part
Collecting Duct System	
Connecting tubule	Includes the arcades in most species
Collecting duct	Cortical collecting duct Outer medullary collecting duct: subdivided into an outer stripe and an inner stripe portion Inner medullary collecting duct: subdivided into basal, middle, and papillary portions

Table 1-1 **Subdivisions of the nephron and collecting duct system.**

The intrarenal arteries and the afferent and efferent glomerular arterioles are accompanied by sympathetic nerve fibers and terminal axons representing the efferent nerves of the kidney.[1] Tubules have direct contact to terminal axons only when the tubules are located around the arteries or the arterioles. Tubular innervation consists of "occasional fibers adjacent to perivascular tubules."[4] The density of nerve contacts to convoluted proximal tubules is low; contacts to straight proximal tubules, thick ascending limbs of Henle loops, and collecting ducts (located in medullary rays and outer medulla) have never been encountered. The vast majority of tubular portions have no direct relationships to nerve terminals. Afferent nerves of the kidney are believed to be sparse.[5]

NEPHRON

Renal Glomerulus (Renal Corpuscle)

The glomerulus comprises a tuft of specialized capillaries attached to the mesangium, both of which are enclosed in a pouch-like extension of the tubule, the glomerular capsule, or Bowman capsule (Figs. 1-4 and 1-5). The capillaries and mesangium are covered by epithelial cells (podocytes), forming the visceral epithelium of Bowman capsule. At the vascular pole, this structure is reflected to become the parietal epithelium of Bowman capsule. At the interface between the glomerular capillaries and the mesangium on one side and the podocyte layer on the other side, the glomerular basement membrane (GBM) develops. The space between both layers of Bowman capsule represents the urinary space, which at the urinary pole continues as the tubule lumen.

On entering the tuft, the afferent glomerular arteriole immediately divides into up to five primary capillary branches, each of which gives rise to an anastomosing capillary network representing a

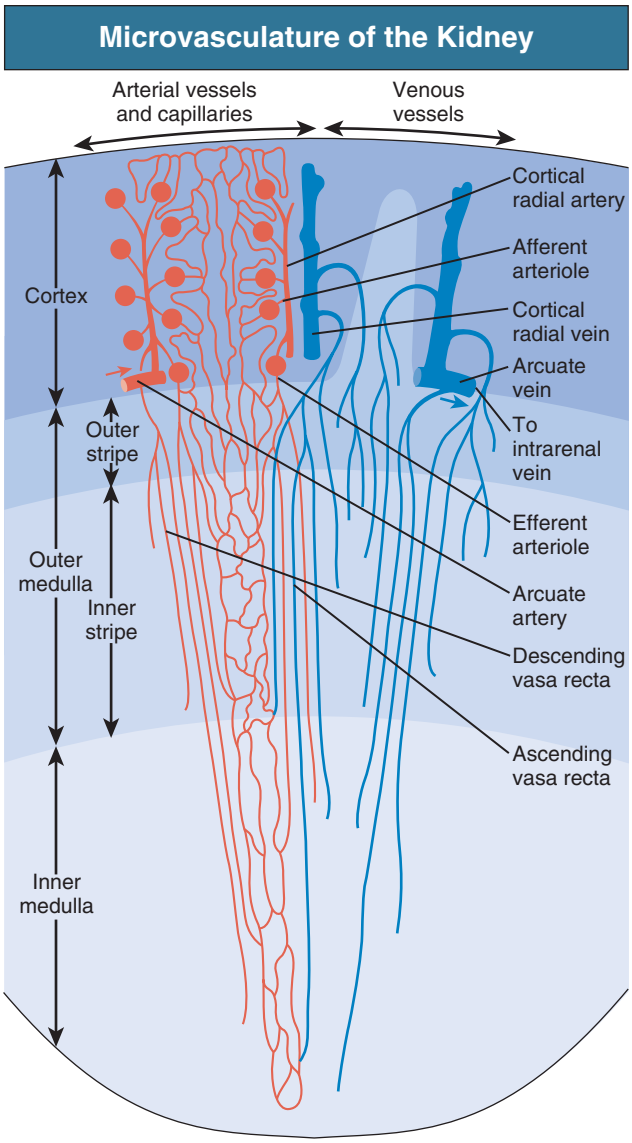

Figure 1-3 Microvasculature of the kidney. Afferent arterioles supply the glomeruli and efferent arterioles leave the glomeruli and divide into the descending vasa recta, which together with the ascending vasa recta form the vascular bundles of the renal medulla. The vasa recta ascending from the inner medulla all traverse the inner stripe within the vascular bundles, whereas most of the vasa recta from the inner stripe of the outer medulla ascend outside the bundles. Both types traverse the outer stripe as wide, tortuous channels.

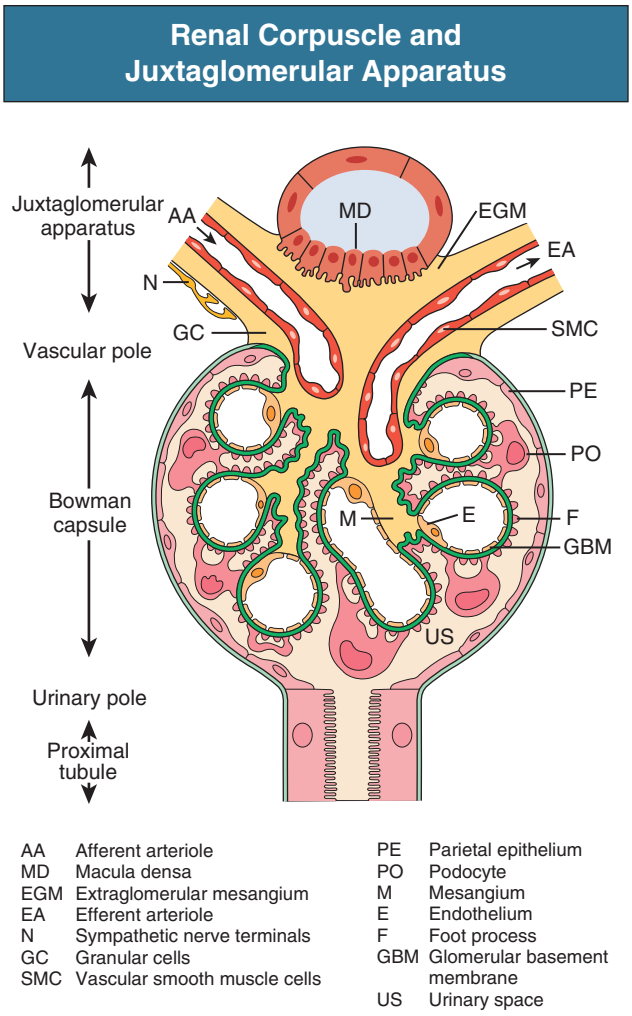

Figure 1-4 Renal corpuscle and juxtaglomerular apparatus. *(Modified with permission from reference 1.)*

glomerular lobule. In contrast to the afferent arteriole, the efferent glomerular arteriole is already established inside the tuft by confluence of capillaries from each lobule.[6] Thus the efferent arteriole has a significant intraglomerular segment located within the glomerular stalk.

Glomerular capillaries are a unique type of blood vessel consisting of only an endothelial tube (Figs. 1-6 and 1-7). A small stripe of the outer aspect of this tube directly abuts the mesangium; a major part bulges toward the urinary space and is covered by the GBM and the podocyte layer. This peripheral portion of the capillary wall is the filtration area. The glomerular mesangium represents the axis of a glomerular lobule to which the glomerular capillaries are attached.

Glomerular Basement Membrane

The GBM serves as the skeleton of the glomerular tuft. This membrane is a complexly folded sack with an opening at the glomerular hilum (see Fig. 1-4). The outer aspect of this GBM sack is completely covered with podocytes. The interior of the sack is filled with the capillaries and the mesangium. As a result, on its inner aspect, the GBM is in contact with either capillaries or the mesangium. At any transition between these two locations, the GBM changes from a convex pericapillary to a concave perimesangial course; the turning points are called *mesangial angles.*

In electron micrographs of traditionally fixed tissue, the GBM appears as a trilaminar structure, with a lamina densa bounded by two less dense layers, the lamina rara interna and lamina rara externa (see Fig. 1-7). Studies with freeze techniques reveal only one thick dense layer directly attached to the bases of the epithelium and endothelium.[7]

The major components of the GBM include type IV collagen, laminin, and heparan sulfate proteoglycans, as in basement membranes at other sites. Types V and VI collagen and nidogen (entactin) have also been demonstrated. However, the GBM has several unique properties, notably a distinct spectrum of type IV collagen and laminin isoforms. The mature GBM consists of type IV collagen made of α3, α4, and α5 chains (instead of α1 and α2 chains of most other basement membranes) and laminin 11, made of α5, β2, and γ1 chains.[8] Type IV collagen is the antigenic target in Goodpasture disease (see Chapter 24), and mutations in the genes of the α3, α4, and α5 chains of type IV collagen are responsible for Alport syndrome (see Chapter 48).

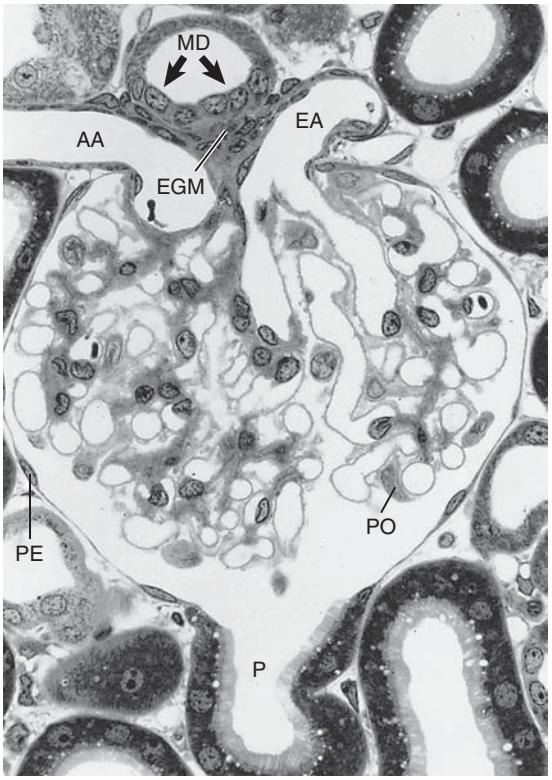

Figure 1-5 Longitudinal section through a glomerulus (rat). At the vascular pole, the afferent arteriole *(AA),* the efferent arteriole *(EA),* the extraglomerular mesangium *(EGM),* and the macula densa *(MD)* are seen; *PO,* podocyte. At the urinary pole, the parietal epithelium *(PE)* transforms into the proximal tubule *(P)*. (Light microscopy; magnification ×390.)

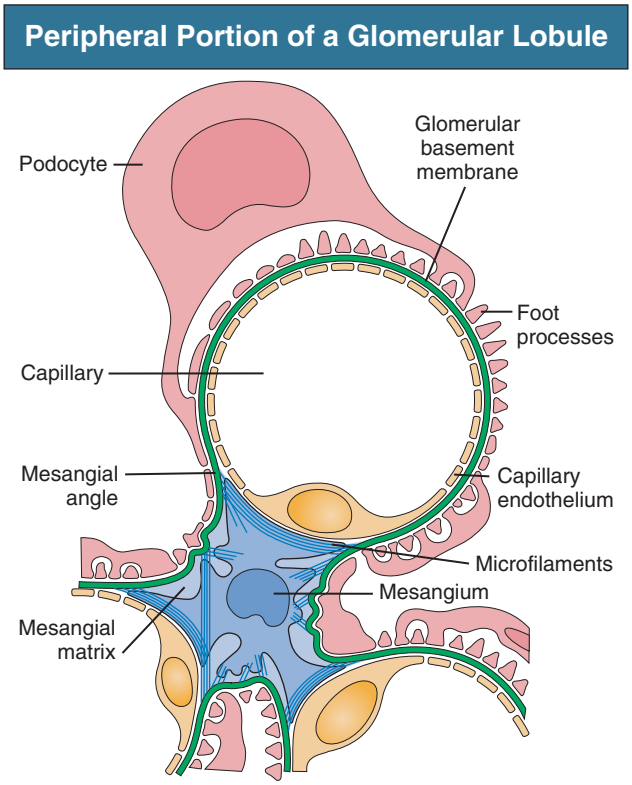

Figure 1-6 Peripheral portion of a glomerular lobule. This part shows a capillary, the axial position of the mesangium, and the visceral epithelium (podocytes). At the capillary-mesangial interface, the capillary endothelium directly abuts the mesangium.

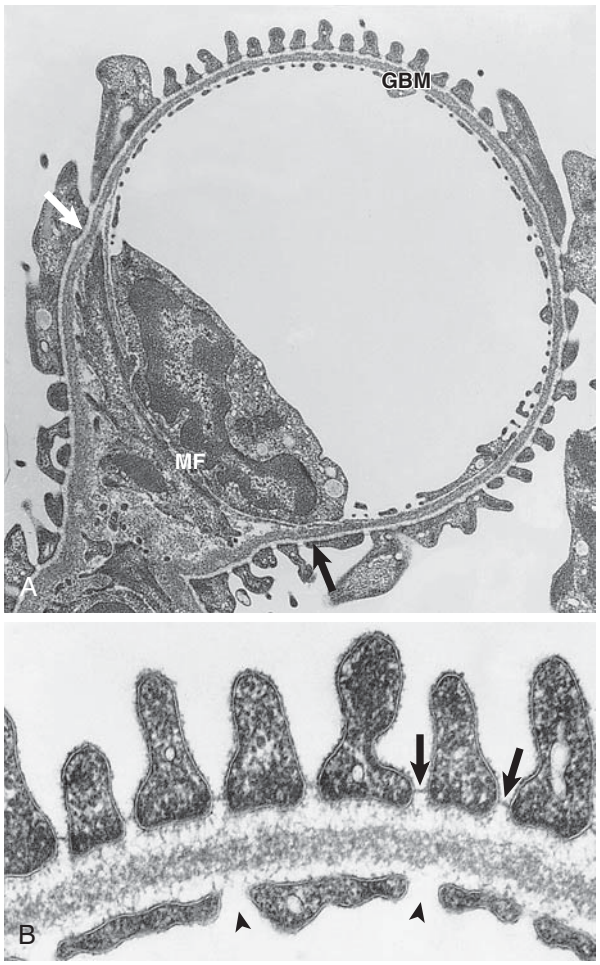

Figure 1-7 Glomerular capillary. A, The layer of interdigitating podocyte processes and the glomerular basement membrane *(GBM)* do not completely encircle the capillary. At the mesangial angles *(arrows),* both deviate from a pericapillary course and cover the mesangium. Mesangial cell processes containing dense bundles of microfilaments *(MF)* interconnect the GBM and bridge the distance between the two mesangial angles. **B,** Filtration barrier. The peripheral part of the glomerular capillary wall comprises the endothelium with open pores *(arrowheads),* the GBM, and the interdigitating foot processes. The GBM shows a lamina densa bounded by the lamina rara interna and externa. The foot processes are separated by filtration slits bridged by thin diaphragms *(arrows)*. (Transmission electron microscopy [TEM]; magnification: **A,** ×8770; **B,** ×50,440.)

Current models depict the basic structure of the GBM as a three-dimensional network of type IV collagen.[7] The type IV collagen monomer consists of a triple helix that is 400 nm in length, with a large, noncollagenous globular domain at its C-terminal end called NC1. At the N terminus, the helix possesses a triple helical rod 60 nm long: the 7S domain. Interactions between the 7S domains of two triple helices or the NC1 domains of four triple helices allow type IV collagen monomers to form dimers and tetramers. In addition, triple helical strands interconnect by lateral associations through binding of NC1 domains to sites along the collagenous region. This network is complemented by an interconnected network of laminin 11, resulting in a flexible, nonfibrillar polygonal assembly that provides mechanical strength to the basement membrane and serves as a scaffold for alignment of other matrix components.

The electronegative charge of the GBM mainly results from the presence of polyanionic proteoglycans. The major proteoglycans of the GBM are heparan sulfate proteoglycans, including perlecan and

agrin. Proteoglycan molecules aggregate to form a meshwork that is kept well hydrated by water molecules trapped in the interstices of the matrix. Abrahamson[9] provides an up-to-date summary of the molecular organization of the GBM.

Mesangium

Three major cell types occur within the glomerular tuft, all of which are in close contact with the GBM: mesangial cells, endothelial cells, and podocytes. The mesangial/endothelial/podocyte cell ratio is 2:3:1 in the rat. The mesangial cells and mesangial matrix establish the glomerular mesangium. In addition, some studies suggest that macrophages bearing HLA-DR/Ia-like antigens may also rarely be found in the normal mesangium.

Mesangial Cells Mesangial cells are irregular in shape, with many processes extending from the cell body toward the GBM (see Figs. 1-6 and 1-7). In these processes, dense assemblies of microfilaments are found, containing actin, myosin, and α-actinin.[10] The processes are attached to the GBM directly or through the interposition of microfibrils (see later discussion). The GBM represents the effector structure of mesangial contractility. Mesangial cell–GBM connections are especially prominent alongside the capillaries, interconnecting the two opposing mesangial angles of the GBM.

Mesangial cells possess a great variety of receptors, including those for angiotensin II (Ang II), vasopressin, atrial natriuretic factor, prostaglandins, transforming growth factor β (TGF-β), and other growth factors (PDGFs, EGF, CTGF)[11].

Mesangial Matrix The mesangial matrix fills the highly irregular spaces between the mesangial cells and the perimesangial GBM, anchoring the mesangial cells to the GBM.[6] The ultrastructural organization of this matrix is incompletely understood. In specimens prepared by a technique that avoids osmium tetroxide and uses tannic acid for staining, a dense network of elastic microfibrils is seen. Many common extracellular matrix proteins have been demonstrated within the mesangial matrix, including collagen types IV, V, and VI and microfibrillar protein components such as fibrillin and the 31-kilodalton microfibril-associated glycoprotein. The matrix also contains several glycoproteins, most abundantly fibronectin, as well as several types of proteoglycans.

Endothelium

Glomerular endothelial cells consist of cell bodies and peripherally located, attenuated, and highly fenestrated cytoplasmic sheets (see Figs. 1-6 and 1-7). Glomerular endothelial pores lack diaphragms, which are encountered only in the endothelium of the final tributaries to the efferent arteriole.[6] The round to oval pores have a diameter of 50 to 100 nm. The luminal membrane of endothelial cells is negatively charged because of the cell coat of several polyanionic glycoproteins, including podocalyxin. In addition, the endothelial pores are filled with sieve plugs mainly made of sialoglycoproteins.[12]

Visceral Epithelium (Podocytes)

The visceral epithelium of Bowman capsule comprises highly differentiated cells, the podocytes (Fig. 1-8; see also Fig. 1-6). In the developing glomerulus, podocytes have a simple polygonal shape. In rats, mitotic activity of these cells is completed soon after birth together with the cessation of forming new nephron anlagen (primordia). In humans, this point is already reached during prenatal life. Differentiated podocytes are unable to replicate; therefore degenerated podocytes cannot be replaced in the adult. All efforts of the last decade to find progenitor cells that might migrate into the tuft and replace lost podocytes have failed. In response to an extreme growth stimulus, as by basic fibroblast growth factor 2 (FGF-2), podocytes may undergo mitotic nuclear division. However, the cells are unable to complete cell division by cytokinesis, resulting in binucleated or multinucleated cells.[13]

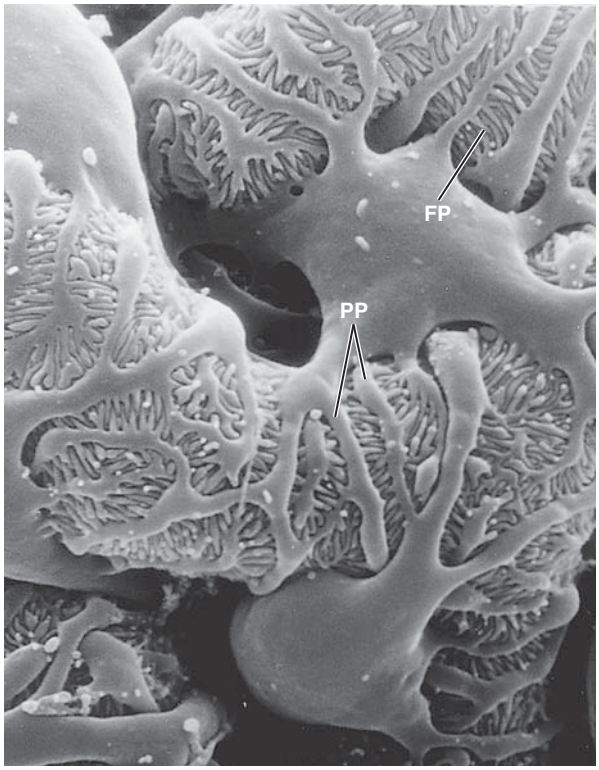

Figure 1-8 Glomerular capillaries in the rat. Urinary side of the capillary is covered by the highly branched podocytes. The interdigitating system of primary processes *(PP)* and foot processes *(FP)* lines the entire surface of the tuft, also extending beneath the cell bodies. The foot processes of neighboring cells interdigitate but spare the filtration slits in between. (Scanning electron microscopy; magnification ×2200.)

Podocytes have a voluminous cell body that floats within the urinary space, separated from the GBM by a subpodocyte space.[14] The cell bodies give rise to long primary processes that extend toward and affix to the capillaries by the most distal portions and by an extensive array of foot processes. This precarious situation of being fixed to the GBM only by the processes results in a unique vulnerability of podocytes: being lost as viable cells into the urine.[15] This is apparently the major mechanism for how podocytes are lost during life, with apoptosis (cell death) playing no relevant role.[16]

The most specific structural feature of podocytes is the pattern of foot processes covering the outer aspect of glomerular capillaries. The foot processes of neighboring podocytes regularly interdigitate with each other, leaving meandering slits (filtration slits) between the cells that are bridged by an extracellular structure, the *slit diaphragm* (Fig. 1-9; see also Figs. 1-6 to 1-8). Podocytes are polarized epithelial cells with a luminal and a basal cell membrane domain; the basal cell membrane domain corresponds to the sole plates of the foot processes that are embedded into the GBM. The border between basal and luminal membrane is the slit diaphragm.[17]

The luminal membrane and the slit diaphragm are covered by a thick surface coat that is rich in sialoglycoproteins, including podocalyxin and podoendin, and is responsible for the high negative surface charge of the podocytes. By comparison, the abluminal membrane (i.e., soles of podocyte processes) contains specific transmembrane proteins that connect the cytoskeleton to the GBM. Two systems are known: (1) $\alpha_3\beta_1$ integrin dimers interconnect the cytoplasmic focal adhesion proteins vinculin, paxillin, and talin with the α3, α4, and α5 chains of type IV collagen and laminin 521; and (2)

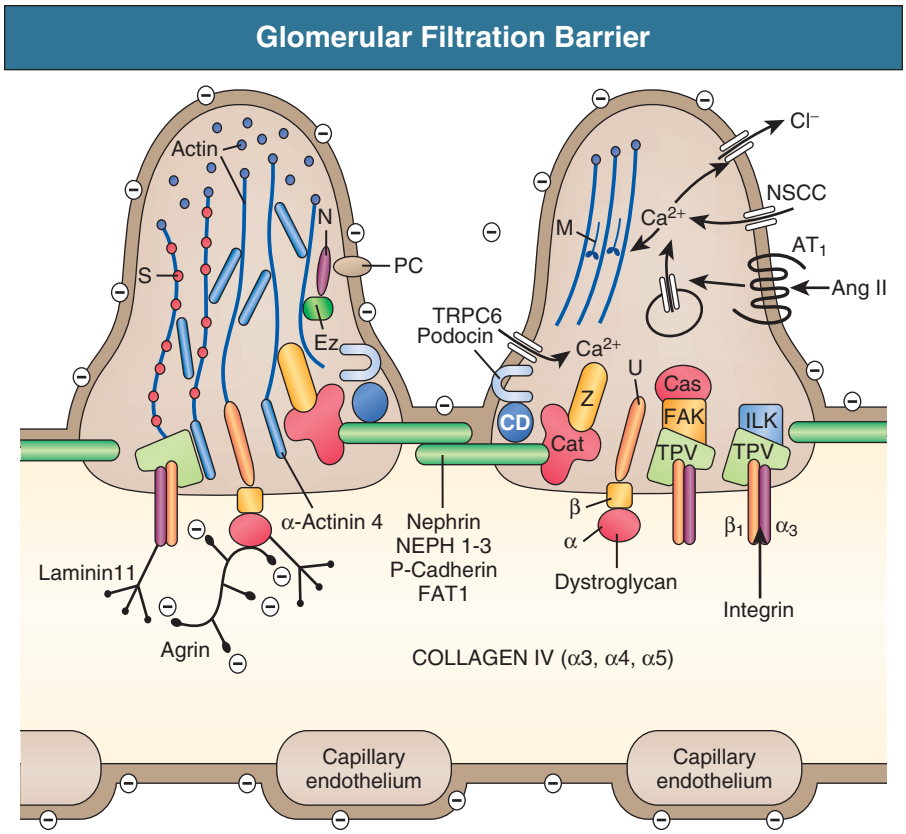

Figure 1-9 Glomerular filtration barrier. Two podocyte foot processes bridged by the slit membrane, the GBM, and the porous capillary endothelium are shown. The surfaces of podocytes and of the endothelium are covered by a negatively charged glycocalyx containing the sialoprotein podocalyxin *(PC).* The GBM is mainly composed of type IV collagen (α3, α4, and α5), laminin 11 (α5, β2, and γ1 chains), and the heparan sulfate proteoglycan agrin. The slit membrane represents a porous proteinaceous membrane composed of (as far as known) nephrin, NEPH 1-3, P-cadherin, and FAT1. The actin-based cytoskeleton of the foot processes connects to both the GBM and the slit membrane. Regarding the connections to the GBM, $\beta_1\alpha_3$ integrin dimers specifically interconnect the TPV complex (talin, paxillin, vinculin) to laminin 11; the β- and α-dystroglycans interconnect utrophin to agrin. The slit membrane proteins are joined to the cytoskeleton by various adapter proteins, including podocin, zonula occludens protein 1 (ZO-1; *Z*), CD2-associated protein *(CD),* and catenins *(Cat).* Among the nonselective cation channels *(NSCC),* TRPC6 associates with podocin (and nephrin, not shown) at the slit membrane. Only the angiotensin II *(Ang II)* type 1 receptor (AT_1) is shown as an example of the many surface receptors. *Cas,* p130Cas; *Ez,* ezrin; *FAK,* focal adhesion kinase; *ILK,* integrin-linked kinase; *M,* myosin; *N,* Na^+-H^+ exchanger regulatory factor (NHERF2); *S,* synaptopodin. *(Modified from reference 41.)*

β-α-dystroglycans interconnect the cytoplasmic adapter protein utrophin with agrin and laminin α5 chains in the GBM.[9]

In contrast to the cell body, which harbors a prominent endoplasmic reticulum and Golgi system and has well-developed autophagic machinery, the cell processes contain only a few organelles. A sophisticated cytoskeleton accounts for the complex shape of the cells. In the cell body and the primary processes, microtubules and intermediate filaments (vimentin, desmin) dominate. Within the foot processes, microfilaments form prominent U-shaped bundles arranged in the longitudinal axis of two successive foot processes in an overlapping pattern. Centrally, the bends of these bundles are linked to the microtubules of the primary processes; peripherally, the bends are linked to the GBM by integrins and dystroglycans. α-Actinin-4 and synaptopodin establish the podocyte-specific bundling of the microfilament.

Podocytes contain a great variety of surface receptors, including those for cyclic guanosine monophosphate (cGMP) signaling, stimulated by natriuretic peptides (ANP, BNP, and CNP) as well as by nitric oxide (NO); cyclic adenosine monophosphate (cAMP) signaling stimulated by prostaglandin E_2 (PGE_2), dopamine, isoproterenol, parathyroid hormone (PTH) and PTH-related peptide; and calcium ion (Ca^{2+}) signaling stimulated by numerous ligands, including Ang II, acetylcholine, PGF_2, arginine vasopressin (AVP), adenosine triphosphate (ATP), endothelin, and histamine).[17] Among the transient receptor potential (TRP) cation channels, TRPC5 and TRPC6 have recently received much attention.[18-20] The major target of this signaling orchestra is the cytoskeleton, although the concrete effects are poorly understood. Other receptors, such as for C3b, TGF-β, FGF-2, and other cytokines/chemokines, have been shown to be involved in the development of podocyte diseases.[17] Megalin is a multiligand endocytotic receptor and the major antigen of Heymann nephritis in the rat,[21] but is not present in humans.

The filtration slits are the sites of convective fluid flow through the visceral epithelium (see Figs. 1-7 and 1-9). Filtration slits have a constant width of about 30 to 40 nm and are bridged by the slit diaphragm, a proteinaceous membrane with an incompletely defined molecular composition. Chemically fixed and tannic acid–treated tissue reveals a zipper-like structure with a row of pores approximately 14 nm^2 on either side of a central bar. Currently, the proteins known to establish the slit membrane or mediate its connection to the actin cytoskeleton of the foot processes include nephrin, P-cadherin, FAT1, NEPH 1-3, and podocin.[17] However, how these molecules interact with each other to establish a size-selective porous membrane is not yet known. In addition to its barrier function, the slit membrane is a platform for signaling to the cytoskeleton.[22]

Parietal Epithelium

The parietal epithelium of Bowman capsule consists of squamous epithelial cells resting on a basement membrane (see Figs. 1-4 and 1-5). The flat cells are filled with bundles of actin filaments running in all directions. In contrast to the GBM, the parietal basement membrane comprises several proteoglycan-dense layers that, in addition to type IV, contain type XIV collagen. The predominant proteoglycan of the parietal basement membrane is a chondroitin sulfate proteoglycan.[23] Recent observations suggest that a niche of glomerular epithelial stem cells resides within the parietal epithelium at the transition to the proximal tubule,[24] but unequivocal evidence is lacking.

Filtration Barrier

Filtration through the glomerular capillary wall occurs along an extracellular pathway, including the endothelial pores, GBM, and slit diaphragm (see Figs. 1-7 and 1-9). All these components are quite permeable for water; the high permeability for water, small solutes,

and ions results because no cell membranes are interposed. The hydraulic conductance of the individual layers of the filtration barrier is difficult to study. In a mathematical model of glomerular filtration, the hydraulic resistance of the endothelium was predicted to be small, whereas the GBM and the filtration slits each contribute about one half to the total hydraulic resistance of the capillary wall.[25]

The barrier function of the glomerular capillary wall for macromolecules is selective for size, shape, and charge.[17] The charge selectivity of the barrier results from the dense accumulation of negatively charged molecules throughout the entire depth of the filtration barrier, including the surface coat of endothelial cells, and from the high content of negatively charged heparan sulfate proteoglycans in the GBM. Polyanionic macromolecules, such as plasma proteins, are repelled by the electronegative shield originating from these dense assemblies of negative charges.

The crucial structure accounting for the size selectivity of the filtration barrier appears to be the slit diaphragm.[25] Uncharged macromolecules up to an effective radius of 1.8 nm pass freely through the filter. Larger components are increasingly restricted (indicated by their fractional clearances, which progressively decrease) and are totally restricted at effective radii of more than 4 nm. Plasma albumin has an effective radius of 3.6 nm; without the repulsion from the negative charge, plasma albumin would pass through the filter in considerable amounts. As recently proposed, an electric field (streaming potential) may be generated by filtration across the glomerular capillary wall, which in turn may prevent the passage of the negatively charged plasma proteins across the barrier by electrophoresis.[26]

Stability of Glomerular Tuft

The main challenge for the glomerular capillaries is to combine selective leakiness with stability. The capillary walls are constantly exposed to high transmural pressure gradients from the high perfusion pressure of glomerular capillaries.

The major system for the maintenance of the complex structure of the tuft consists of the GBM and the mesangium. In fact, cylinders of the GBM largely define the shape of glomerular capillaries. These cylinders do not completely encircle the capillary tube, however, and are open toward the mesangium. Mechanically, the cylinders are completed by contractile mesangial cell processes that bridge the gaps of the GBM between two opposing mesangial angles, permitting these two structures together to develop wall tension.[27]

Traditionally, podocytes have been interpreted as a type of pericyte contributing to the development of wall tension by varying the tonus of its contractile system. In a recent challenge to this view,[16] however, the only remaining system capable of creating wall tension consists of the open cylinders of the GBM bridged by mesangial cells.

In addition to the need to develop wall tension to prevent dilation of glomerular capillaries, the folding pattern of the GBM (i.e., arrangement of glomerular capillaries) must be stabilized against the centrifugal pressure gradients as well. This occurs by interconnecting the turning points of the GBM by mesangial cells from inside and by podoytes from outside.[10]

Renal Tubule

The renal tubule is subdivided into several distinct segments: a proximal tubule, an intermediate tubule, a distal tubule, a connecting tubule (CNT), and the collecting duct (see Fig. 1-1 and Table 1-1).[1,2] The loop of Henle comprises the straight part of the proximal tubule (representing thick descending limb), the thin descending and thin ascending limbs (representing intermediate tubule), and the thick ascending limb (representing straight portion of distal tubule),

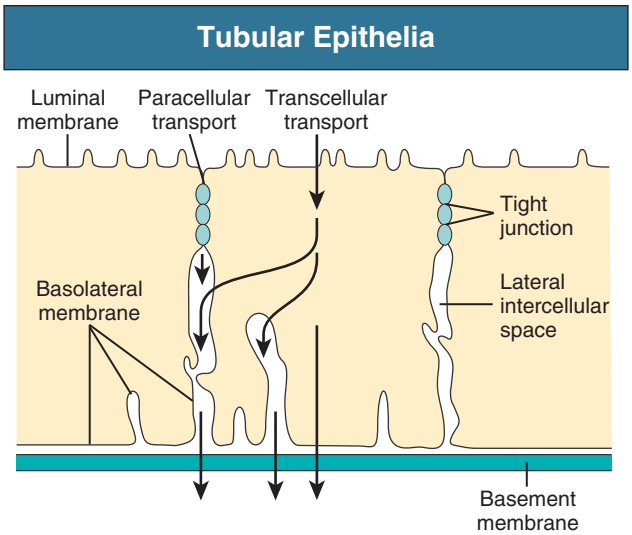

Figure 1-10 Tubular epithelia. Transport across the epithelium may follow two routes: transcellular, across luminal and basolateral membranes, and paracellular, through the tight junction and intercellular spaces.

which includes the macula densa. The CNT and various collecting duct segments form the collecting duct system.

The renal tubules are outlined by a single-layer epithelium anchored to a basement membrane. The epithelium is a transporting epithelium consisting of flat or cuboidal epithelial cells connected apically by a junctional complex consisting of a tight junction (zonula occludens), an adherens junction, and rarely a desmosome. As a result of this organization, two different pathways through the epithelium exist (Fig. 1-10): a *transcellular* pathway, including transport across the luminal and basolateral cell membranes and through the cytoplasm, and a *paracellular* pathway through the junctional complex and lateral intercellular spaces. The functional characteristics of paracellular transport are determined by the tight junction, which differs greatly in its elaboration in the various tubular segments. Transcellular transport is determined by the specific channels, carriers, and transporters included in the apical and basolateral cell membranes. The various nephron segments differ in function, distribution of transport proteins, and responsiveness to hormones and drugs such as diuretics.

Proximal Tubule

The proximal tubule reabsorbs the bulk of filtered water and solutes (Fig. 1-11, *A*). The epithelium shows numerous structural adaptations to this role. The proximal tubule has a prominent brush border (increasing the luminal cell surface area) and extensive interdigitation by basolateral cell processes (increasing the basolateral cell surface area). This lateral cell interdigitation extends up to the leaky tight junction, thus increasing the tight junctional belt in length and providing a greatly increased passage for the passive transport of ions. Proximal tubules have large, prominent mitochondria intimately associated with the basolateral cell membranes, where the sodium-potassium (Na^+,K^+)–adenosine triphosphatase (ATPase) is located; this machinery dominates the transcellular transport. The luminal transporter for Na^+ entry specific for the proximal tubule is the sodium-hydrogen ion (Na^+-H^+) exchanger. The high hydraulic permeability for water is rooted in abundant occurrence of the water channel protein aquaporin 1 (AQP1). A prominent lysosomal system is known as the "apical vacuolar endocytotic apparatus" and is responsible for the reabsorption of macromolecules (polypeptides

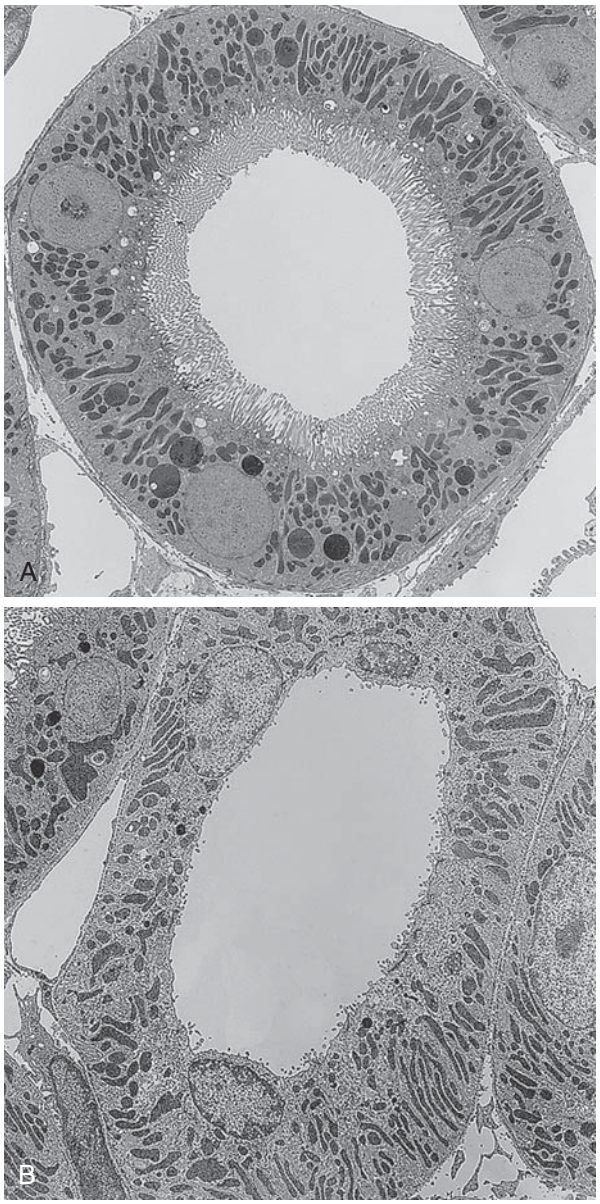

Figure 1-11 Tubules of the renal cortex. A, Proximal convoluted tubule is equipped with a brush border and a prominent vacuolar apparatus in the apical cytoplasm. The rest of the cytoplasm is occupied by a basal labyrinth consisting of large mitochondria associated with basolateral cell membranes. **B,** Distal convoluted tubule also has interdigitated basolateral cell membranes intimately associated with large mitochondria. In contrast to the proximal tubule, however, the apical surface is amplified only by some stubby microvilli. (TEM; **A,** ×1530; **B,** ×1830.)

and proteins such as albumin) that have passed through the glomerular filter. The proximal tubule is generally subdivided into three segments (known as S_1, S_2, S_3, or P_1, P_2, P_3) that differ considerably in cellular organization and therefore also in function.[28]

Loop of Henle

The loop of Henle consists of the straight portion of the proximal tubule, thin descending limb and (in long loops) thin ascending limb, and thick ascending limb (Fig. 1-12; see also Fig. 1-2). The thin descending limb, as with the proximal tubule, is highly permeable for water (channels are of AQP1), whereas beginning exactly at the turning point, the thin ascending limb is impermeable for water. The specific transport functions of the thin limbs of Henle contributing

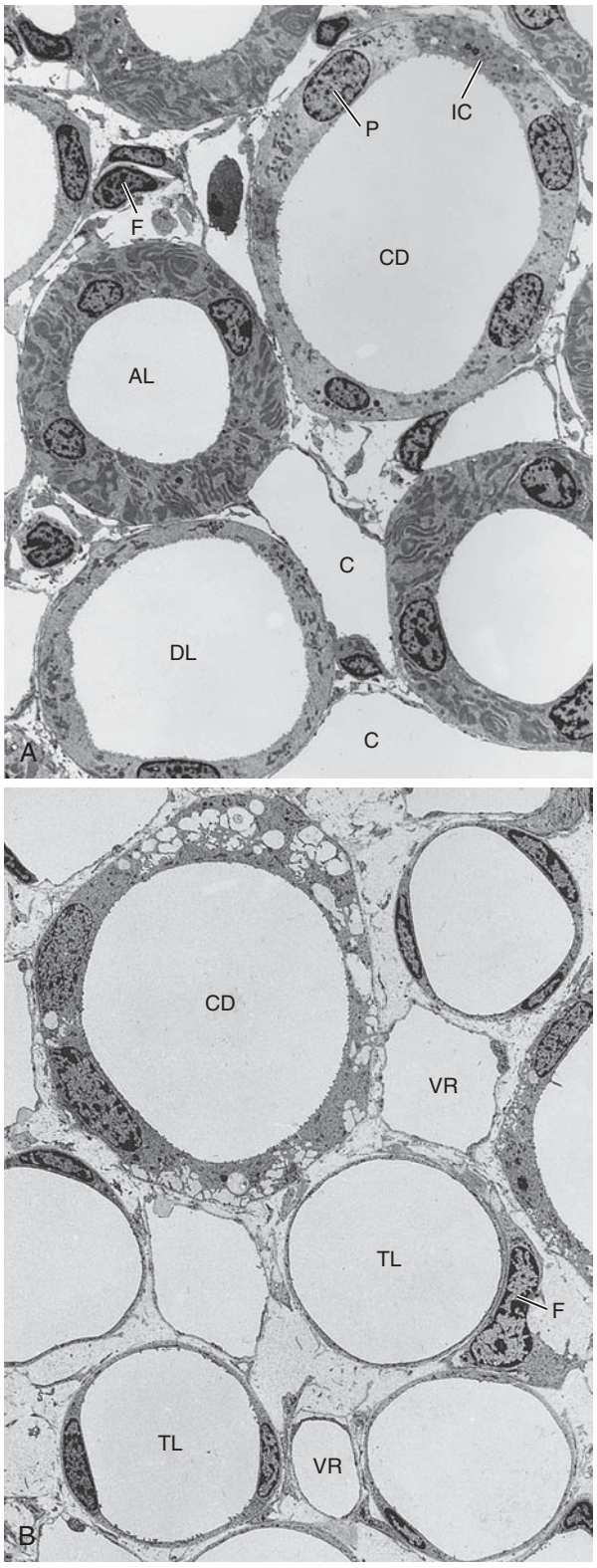

Figure 1-12 Tubules in the medulla. A, Cross section through the inner stripe of the outer medulla shows a descending thin limb of a long Henle loop *(DL),* the medullary thick ascending limbs of Henle *(AL),* and a collecting duct *(CD)* with principal cells *(P)* and intercalated cells *(IC); C,* peritubular capillaries; *F,* fibroblast. **B,** In the inner medulla cross section, thin descending and ascending limbs *(TL),* a collecting duct *(CD),* and vasa recta *(VR)* are seen. (TEM; **A,** ×990; **B,** ×1120.)

to the generation of the osmotic medullary gradient are under debate.

The thick ascending limb of Henle is often called the "diluting segment." It is water impermeable but reabsorbs considerable sodium chloride (NaCl, salt), resulting in the separation of salt from water. The salt is trapped in the medulla, whereas the water is carried to the cortex, where it may return into the systemic circulation. The specific transporter for Na^+ entry in this segment is the luminal Na^+-K^+-$2Cl^-$ cotransporter, which is the target of diuretics such as furosemide. The tight junctions of the thick ascending limb have a comparatively low permeability. The cells heavily interdigitate by basolateral cell processes, associated with large mitochondria supplying the energy for the transepithelial transport. The cells synthesize a specific protein, the Tamm-Horsfall protein, and release it into the tubular lumen. Tamm-Horsfall protein is thought to be important later for preventing the formation of kidney stones. In contrast to the proximal tubule, the luminal membrane is only sparsely amplified by microvilli. Just before the transition to the distal convoluted tubule, the thick ascending limb of Henle contains the macula densa, which adheres to the parent glomerulus (see Juxtaglomerular Apparatus).

Distal Convoluted Tubule

The epithelium is quite highly differentiated, exhibiting the most extensive basolateral interdigitation of the cells and the greatest density of mitochondria in all nephron portions (see Fig. 1-11, *B*). Apically, the cells are equipped with numerous microvilli. The specific Na^+ transporter of the distal convoluted tubule is the luminal Na^+-Cl^- cotransporter, which is the target of thiazide diuretics.

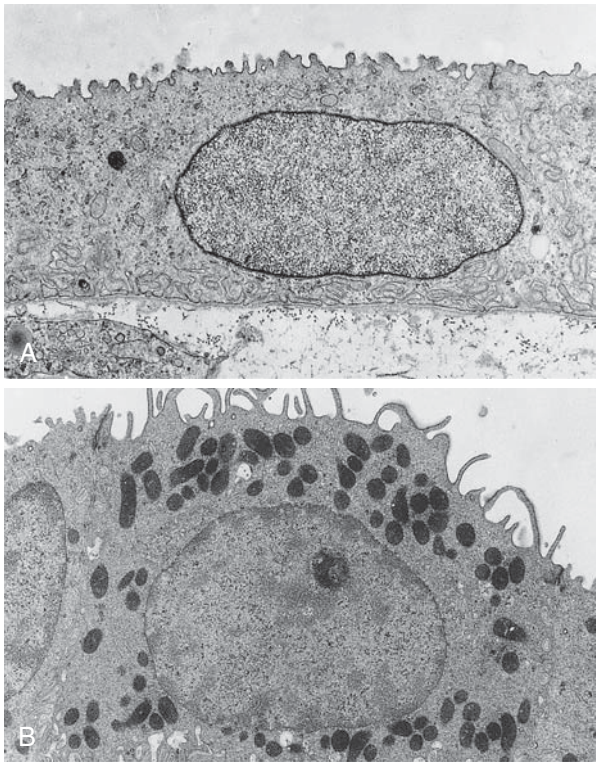

Figure 1-13 Collecting duct cells. A, Principal cell (CD cell) of a medullary collecting duct. The apical cell membrane bears some stubby microvilli covered by a prominent glycocalyx; the basal cell membrane forms invaginations. Note the deep tight junction. **B,** Intercalated cells, type A. Note the dark cytoplasm (dark cells) with many mitochondria and apical microfolds; the basal membrane forms invaginations. (TEM; **A,** ×8720; **B,** ×6970.)

COLLECTING DUCT SYSTEM

The collecting duct system includes the CNT and the cortical and medullary collecting ducts (see Fig. 1-2). Two nephrons may join at the level of the CNT, forming an arcade that cytologically is a CNT. Two types of cell line the connecting tubule: the CNT cell, which is specific to CNTs, and the intercalated (IC) cell, which also occurs later in the collecting duct. The CNT cells are similar to the collecting duct (CD) cells in cellular organization. Both cell types share sensitivity to vasopressin (see next section); the CNT cell, however, lacks sensitivity to mineralocorticoids.

Collecting Ducts

The collecting ducts may be subdivided into cortical and medullary ducts, and the medullary ducts into outer and inner; the transitions are gradual (see Fig. 1-12). As with the CNT, the collecting ducts are lined by two types of cell: CD cells (principal cells) and IC cells. The IC cells decrease in number as the collecting duct descends into the medulla and are absent from the papillary collecting ducts.

The CD cells are simple, polygonal cells increasing in size toward the tip of the papilla (Fig. 1-13, *A*). The basal surface of these cells is characterized by invaginations of the basal cell membrane (basal infoldings). The tight junctions have great apicobasal depth, and the apical cell surface has a prominent glycocalyx. Along the entire collecting duct, these cells contain a luminal shuttle system for aquaporin 2 under the control of antidiuretic hormone (ADH, vasopressin), providing the potential to switch the water permeability of the collecting ducts from zero (or at least from low) to permeable.[29] A luminal amiloride-sensitive Na^+ channel is involved in the responsiveness of cortical collecting ducts to aldosterone. The terminal portions of the collecting duct in the inner medulla express the urea transporter UTB1, which in ADH-dependent manner accounts for the recycling of urea, a process that is crucial in the urine-concentrating mechanism.[30]

The second cell type, the IC cell, is present in both the CNT and the collecting duct (Fig. 1-13, *B*). There are at least two types, designated A and B intercalated cells, distinguished by structural, immunocytochemical, and functional characteristics. Type A cells have been defined as expressing H^+-ATPase at their luminal membrane; these IC cells secrete protons. Type B cells express the H^+-ATPase at their basolateral membrane; these IC cells secrete bicarbonate (HCO_3^-) ions and reabsorb protons.[31]

With these different cell types, the collecting ducts are the final regulators of fluid and electrolyte balance, playing important roles in the handling of Na^+, Cl^-, and K^+, as well as acid and base. The responsiveness of the collecting ducts to vasopressin enables an organism to live in arid conditions, allowing it to produce a concentrated urine and, if necessary, a dilute urine.

JUXTAGLOMERULAR APPARATUS

The juxtaglomerular apparatus comprises the macula densa, the extraglomerular mesangium, the terminal portion of the afferent arteriole with its renin-producing granular cells (also often termed *juxtaglomerular cells*), and the beginning portions of the efferent arteriole (see Fig. 1-4).

The macula densa is a plaque of specialized cells in the wall of the thick ascending limb of Henle at the site where the limb attaches to the extraglomerular mesangium of the parent glomerulus (Fig. 1-14, *A*; see also Fig. 1-5). The most obvious structural feature is the

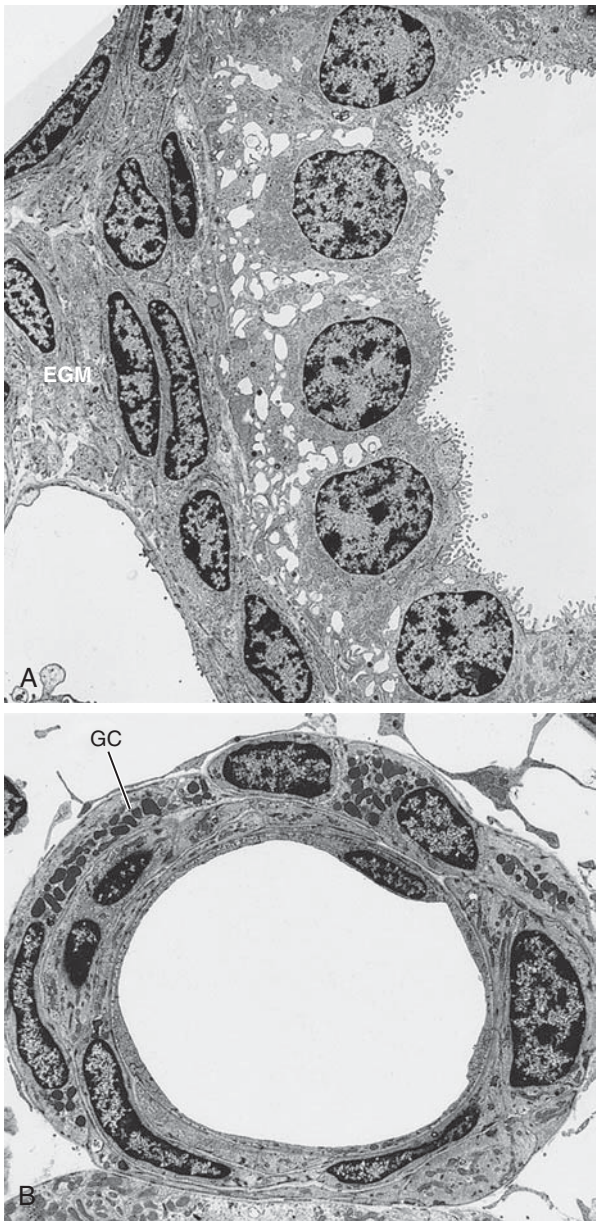

Figure 1-14 Juxtaglomerular apparatus. A, Macula densa of a thick ascending limb of Henle. The cells have prominent nuclei and lateral intercellular spaces. Basally, they attach to the extraglomerular mesangium *(EGM).* **B,** Afferent arteriole near the vascular pole. Several smooth muscle cells are replaced by granular cells *(GC)* containing accumulations of renin granules. (TEM; **A,** ×1730; **B,** ×1310.)

narrowly packed cells with large nuclei, which account for the name macula *densa.* The cells are anchored to a basement membrane, which blends with the matrix of the extraglomerular mesangium. The cells are joined by tight junctions with very low permeability and have prominent lateral intercellular spaces. The width of these spaces varies under different functional conditions.[1] The most conspicuous immunocytochemical difference between macula densa cells and other epithelial cells of the nephron is the high content of neuronal nitric oxide synthase and cyclooxygenase-2 in macula densa cells.[32,33]

The basal aspect of the macula densa is firmly attached to the extraglomerular mesangium, a solid complex of cells and matrix penetrated by neither blood vessels nor lymphatic capillaries. As with the mesangial cells proper, extraglomerular mesangial cells are heavily branched. Their processes are interconnected by gap junctions, contain prominent bundles of microfilaments, and are connected to the basement membrane of Bowman capsule as well as to the walls of both glomerular arterioles. As a whole, the extraglomerular mesangium interconnects all structures of the glomerular entrance.[6]

The granular cells are assembled in clusters within the terminal portion of the afferent glomerular arteriole (Fig. 1-14, *B*), replacing ordinary smooth muscle cells. "Granular" refers to the specific cytoplasmic granules in which renin, the major secretion product of these cells, is stored. Granular cells are the main site of the body where renin is secreted. Renin release occurs by exocytosis into the surrounding interstitium. Granular cells are connected to extraglomerular mesangial cells, adjacent smooth muscle cells, and endothelial cells by gap junctions and are densely innervated by sympathetic nerve terminals. Granular cells are modified smooth muscle cells; under conditions requiring enhanced renin synthesis (e.g., volume depletion, renal artery stenosis), additional smooth muscle cells located upstream in the wall of the afferent arteriole may transform into granular cells.

The structural organization of the juxtaglomerular apparatus suggests a regulatory function. Some component of the distal urine, probably chloride, is sensed by the macula densa. This information is used first to adjust the tone of the glomerular arterioles, producing a change in glomerular blood flow and filtration rate. Even if many details of this mechanism are still subject to debate, studies have verified the essence of this system, known as the "tubular glomerular feedback mechanism."[34] Second, the juxtaglomerular system determines the amount of renin that is released, through the interstitium, into the circulation, thereby acquiring great systemic relevance.[35,36]

RENAL INTERSTITIUM

The interstitium of the kidney is comparatively sparse. Its fractional volume in the cortex ranges from 5% to 7%, with a tendency to increase with age. Renal interstitium increases across the medulla from cortex to papilla. In the outer stripe, it is 3% to 4%, the lowest value of all kidney zones; this is interpreted as forming a barrier to prevent loss of solutes from a hyperosmolar medulla into the cortex. Renal interstitium is 10% in the inner stripe and up to about 30% in the inner medulla. The cellular constituents of the interstitium include resident fibroblasts, which establish the scaffold frame for renal corpuscles, tubules, and blood vessels, as well as varying numbers of migrating cells of the immune system, especially dendritic cells. The space between the cells is filled with extracellular matrix, namely, ground substance (proteoglycans, glycoproteins), fibrils, and interstitial fluid.[37]

Morphologically, fibroblasts are the central cells in the renal interstitium. Fibroblasts are interconnected by specialized contacts and adhere by specific attachments to the basement membranes surrounding the tubules, renal corpuscles, capillaries, and lymphatics.

Renal fibroblasts are difficult to distinguish from interstitial dendritic cells on a morphologic basis because both may show a stellate cellular shape and both display substantial amounts of mitochondria and endoplasmic reticulum. However, renal fibroblasts may easily be distinguished by immunocytochemical techniques. Dendritic cells constitutively express the major histocompatibility complex class II antigen and may express antigens such as CD11c. Dendritic cells may have an important role in maintaining peripheral tolerance in the kidney (Fig. 1-15).[38] In contrast, fibroblasts in the renal cortex (not in the medulla) contain the enzyme ecto-5′-nucleotidase (5′-NT). A subset of 5′-NT–positive fibroblasts of the renal cortex

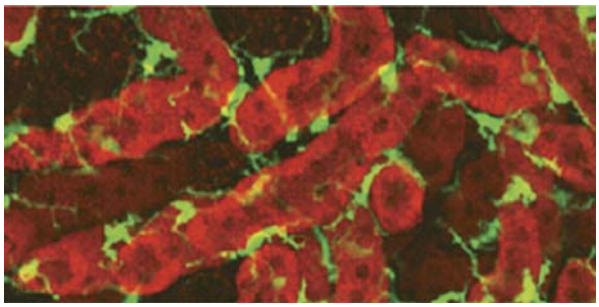

Figure 1-15 Renal dendritic cells. Dendritic cells (CX_3CR1^+ cells, *green*) surrounding tubular segments in the medulla of mice (three-dimensional reconstruction). *(Reprinted with permission from reference 42.)*

Figure 1-16 Intrarenal arteries in a periarterial connective tissue sheath. Cross section through a cortical radial artery *(A)* surrounded by the sheath containing the renal nerves *(N)* and lymphatics *(Ly)*. A vein *(V)* lies outside the sheath. (TEM; ×830.)

synthesizes epoetin.[39] Under normal conditions, these fibroblasts are exclusively found within the juxtamedullary portions of the cortical labyrinth. When there is an increasing demand for epoetin, the synthesizing cells extend to more superficial portions of the cortical labyrinth and, to a lesser degree, to the medullary rays.[40]

Fibroblasts within the medulla, especially within the inner medulla, have a particular phenotype known as *lipid-laden interstitial cells*. The cells are oriented strictly perpendicularly toward the longitudinal axis of the tubules and vessels (running all in parallel) and contain conspicuous lipid droplets. These fibroblasts of the inner medulla produce large amounts of glycosaminoglycans and, possibly related to the lipid droplets, vasoactive lipids, in particular PGE_2.[38]

The intrarenal arteries are accompanied by a prominent sheath of loose interstitial tissue (Fig. 1-16); the renal veins are in apposition to this sheath but not included in it. Intrarenal nerve fibers and lymphatics run within this periarterial tissue. Lymphatics start in the vicinity of the afferent arteriole and leave the kidney running within the periarterial tissue sheath toward the hilum. Together with the lymphatics, the periarterial tissue constitutes a pathway for interstitial fluid drainage of the renal cortex; the renal medulla has no lymphatic drainage.

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CHAPTER 2

Renal Physiology

Matthew A. Bailey, David G. Shirley, and Robert J. Unwin

The prime function of the kidney is to maintain a stable *milieu intérieur* by the selective retention or elimination of water, electrolytes, and other solutes. This is achieved by three processes: (1) filtration of circulating blood from the glomerulus to form an ultrafiltrate of plasma in the urinary space (Bowman space), (2) selective reabsorption (from tubular fluid to blood) across the cells lining the renal tubule, and (3) selective secretion (from peritubular capillary blood to tubular fluid).

GLOMERULAR STRUCTURE AND ULTRASTRUCTURE

The process of urine formation begins by the production of an ultrafiltrate of plasma. Chapter 1 describes glomerular anatomy and ultrastructure, so this discussion provides only the essentials for understanding how the ultrafiltrate is formed. The pathway for ultrafiltration of plasma from the glomerulus to Bowman space consists of the fenestrated capillary endothelium, the capillary basement membrane, and the visceral epithelial cell layer (podocytes) of Bowman capsule; the podocytes have large cell bodies and make contact with the basement membrane only by cytoplasmic foot processes. Mesangial cells, which fill the spaces between capillaries, have contractile properties and are capable of altering the capillary surface area available for filtration.

Filtration is determined principally by the molecular size and shape of the solute and, to a much lesser extent, by its charge. The size cutoff is not absolute; resistance to filtration begins at an effective molecular radius of slightly less than 2 nm, whereas substances with an effective radius exceeding about 4 nm are not filtered at all. The fenestrations between capillary endothelial cells have a diameter of 50 to 100 nm. The podocyte foot processes have gaps with a diameter of 30 to 40 nm, although these filtration slits are bridged by the slit diaphragms, which are themselves penetrated by small pores. The slit diaphragms likely constitute the main filtration barrier, although both the endothelium (by preventing the passage of blood cells) and the basement membrane contribute.[1] The "subpodocyte space" also provides an additional and variable resistance to glomerular filtration.[2] Furthermore, the podocytes and the endothelial cells are covered by a glycocalyx composed of negatively charged glycoproteins, glycosaminoglycans, and proteoglycans, and the basement membrane is rich in heparan sulfate proteoglycans. This accumulation of fixed negative charges further restricts the filtration of large, negatively charged ions, mainly proteins (Fig. 2-1). Thus, with an effective radius (3.6 nm) permitting significant filtration, albumin is normally almost completely excluded. If these fixed negative charges are lost, as in some forms of early or mild glomerular disease (e.g., minimal change disease), albumin filterability increases and proteinuria results. Although it has been proposed that albumin is normally filtered and then almost completely reabsorbed along the proximal tubule, the evidence is controversial. The glomerular barrier is usually considered as a passive unidirectional filter. However, recent studies indicate that filtration pressure generates a potential difference between the glomerular capillaries and Bowman space. Although small in magnitude, this potential difference may help to clear the filter continuously, driving negatively charged proteins such as albumin out of the slit diaphragm and back into the blood.[3]

GLOMERULAR FILTRATION RATE

At the level of the single glomerulus, the driving force for glomerular filtration (the *net ultrafiltration pressure*) is determined by the net hydrostatic and oncotic (colloid osmotic) pressure gradients between glomerular plasma and the filtrate in Bowman space. The single-nephron glomerular filtration rate (SNGFR) is determined by the product of the net ultrafiltration pressure and the *ultrafiltration coefficient;* the latter being a composite of the surface area available for filtration and the hydraulic conductivity of the glomerular membranes. Therefore, the single-nephron glomerular filtration rate is as follows:

$$K_f[(P_{gc} - P_{bs}) - (\pi_{gc} - \pi_{bs})]$$

where K_f is the ultrafiltration coefficient, P_{gc} is glomerular capillary hydrostatic pressure (~45 mm Hg), P_{bs} is Bowman space hydrostatic pressure (~10 mm Hg), π_{gc} is glomerular capillary oncotic pressure (~25 mm Hg), and π_{bs} is Bowman space oncotic pressure (0 mm Hg).

Net ultrafiltration pressure is about 10 mm Hg at the afferent end of the capillary tuft. As filtration of plasma from blood proceeds along the glomerular capillaries, proteins are concentrated and the glomerular capillary oncotic pressure (π_{gc}) increases. Theoretically, toward the efferent end of a glomerular capillary, π_{gc} may equal the net hydrostatic pressure gradient, at which point ultrafiltration pressure would fall to zero: *filtration equilibrium* in the human kidney is approached, but rarely (if ever) achieved (Fig. 2-2).

The total glomerular filtration rate (GFR) is the sum of the SNGFRs of the functioning nephrons in each kidney. The normal range for GFR is wide but typically cited at about 120 ml/min per 1.73 m^2 surface area. GFR can be measured with renal clearance techniques. The renal clearance of any substance not metabolized by the kidneys is the volume of plasma required to provide that amount of the substance excreted in the urine per unit time. This is a virtual volume that can be expressed mathematically as follows:

$$C_y = U_y / P_y \times V$$

where C_y is the renal clearance of *y;* U_y and P_y is the concentration of *y* in the urine and plasma, respectively; and *V* is the urine flow rate. If a substance is freely filtered by the glomerulus and is not reabsorbed or secreted by the tubule, its renal clearance equals GFR; that is, renal clearance measures the volume of plasma filtered through the glomeruli per unit time. The various methods for measuring GFR and their pitfalls are discussed in Chapter 3.

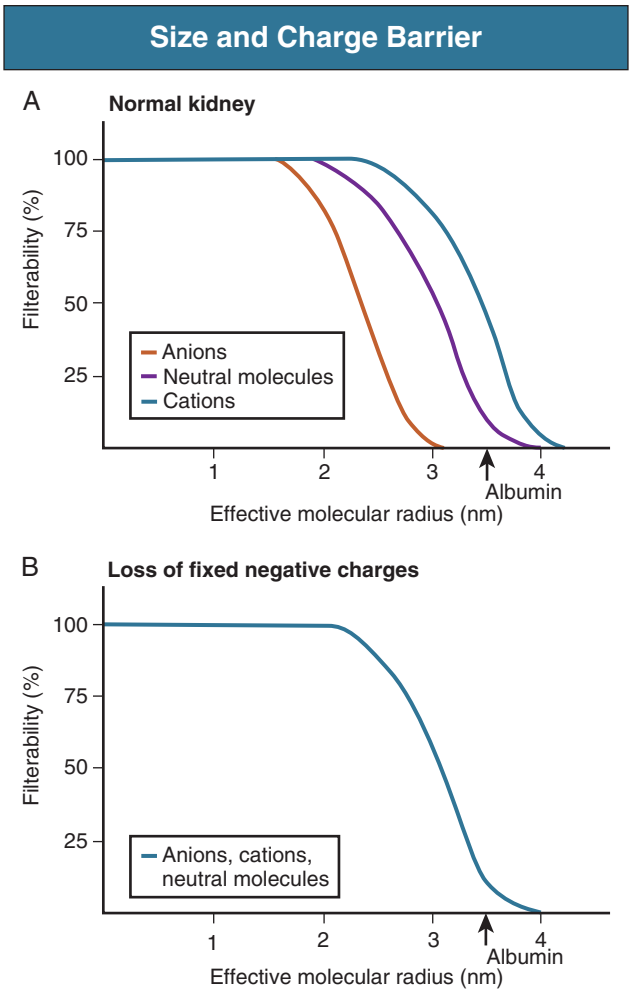

Figure 2-1 Effects of size and electrical charge on filterability. **A,** Normal kidney. **B,** Loss of fixed negative charges. Filterability of 100% indicates that the substance is freely filtered; that is, its concentration in Bowman space equals that in glomerular capillary plasma. For molecules and small ions (e.g., Na^+, Cl^-), charge has no effect on filterability; but for ions whose effective molecular radius exceeds 1.6 nm, anions are filtered less easily than neutral molecules or cations. Thus insignificant amounts of albumin (anion) are normally filtered. If the fixed negative charges of the glomerular basement membranes are lost, as in early minimal change nephropathy, charge no longer influences filterability; consequently, significant albumin filtration occurs.

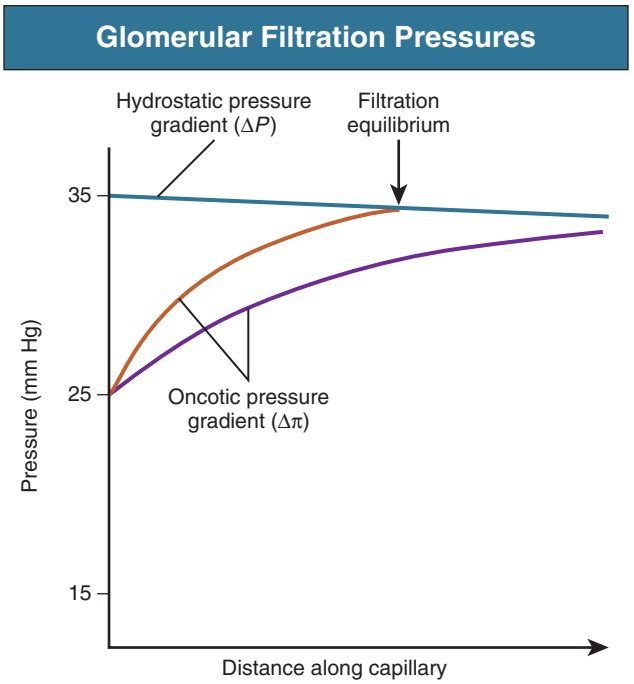

Figure 2-2 Glomerular filtration pressures along a glomerular capillary. The hydrostatic pressure gradient ($\Delta P = P_{gc} - P_{bs}$) is relatively constant along the length of a capillary, whereas the opposing oncotic pressure gradient ($\Delta\pi = \pi_{gc}$) increases as protein-free fluid is filtered, thereby reducing net ultrafiltration pressure. Two curves are shown, one where filtration equilibrium is reached and one where it is merely approached.

MEASUREMENT OF RENAL PLASMA FLOW

The use of the clearance technique and the availability of substances that undergo both glomerular filtration and virtually complete (or *effective*) tubular secretion have made it possible to measure renal plasma flow (RPF; typically ~650 ml/min). Para-aminohippuric acid (PAH, hippurate) is an organic acid that is filtered by the glomerulus and actively secreted by the proximal tubule through organic anion transporters in the cell membranes. The amount of PAH found in the urine is the sum of that filtered plus that secreted. PAH clearance is a robust marker of RPF when the plasma concentration is less than 10 mg/dl, because most of the PAH reaching the peritubular capillaries is cleared by tubular secretion. Under these circumstances, little PAH appears in renal venous plasma and the amount found in the final urine approximates that delivered to the kidneys in the plasma. Therefore:

$$RPF \times P_{PAH} = U_{PAH} \times V$$

$$or\ RPF = (U_{PAH} \times V)/P_{PAH} = PAH\ clearance$$

where U_{PAH} and P_{PAH} are the concentrations of PAH in the urine and plasma, respectively, and V is the urine flow rate. Renal blood flow (RBF) can be calculated as follows:

$$RBF = [RPF/(100 - Hematocrit)] \times 100$$

Typically, RBF is about 1200 ml/min.

The most important limitation of this method is the renal extraction of PAH, which is always less than 100%. At high plasma concentrations, greater than 10 to 15 mg/dl, the tubular transport proteins become saturated, the fractional tubular secretion of PAH declines, and considerable amounts of PAH appear in the renal veins. Under these circumstances, PAH clearance significantly underestimates RPF. In patients with liver or renal failure, the production of toxins and weak organic acids can interfere with PAH secretion or cause tubular damage, leading to inhibition of PAH transport. Certain drugs, such as probenecid, are organic acids and compete with PAH for tubular secretion, thereby reducing PAH clearance. Also, the expression of transport proteins that mediate PAH secretion is hormonally regulated, and the clearance of PAH can therefore change independent of true RPF.

AUTOREGULATION OF RENAL BLOOD FLOW AND GLOMERULAR FILTRATION RATE

Although acute physiologic variations in arterial blood pressure inevitably cause corresponding changes in RBF and GFR, these are short-lived because compensatory mechanisms return both RBF and GFR toward normal within a few seconds.[4] This is the phenomenon of *autoregulation* (Fig. 2-3). Autoregulation is achieved primarily at

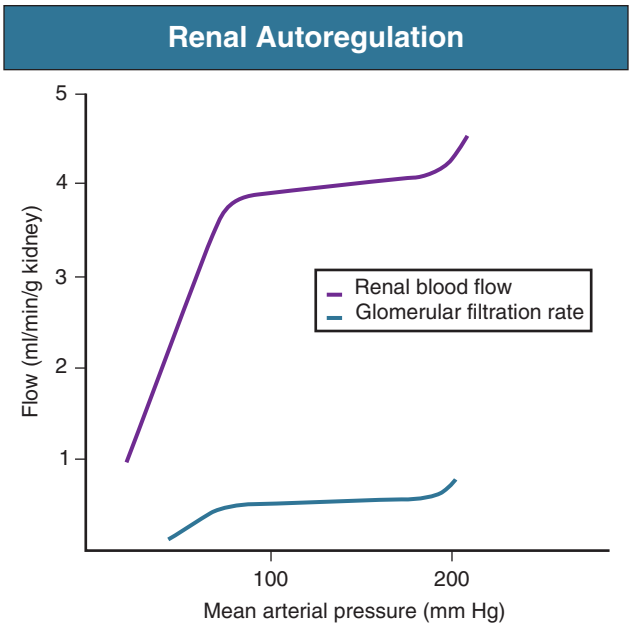

Figure 2-3 Renal autoregulation of renal blood flow and glomerular filtration rate. If mean arterial blood pressure is in the range of 80 to 180 mm Hg, fluctuations in blood pressure have only marginal effects on renal blood flow and glomerular filtration rate. This is an intrinsic mechanism and can be modulated or overridden by extrinsic factors.

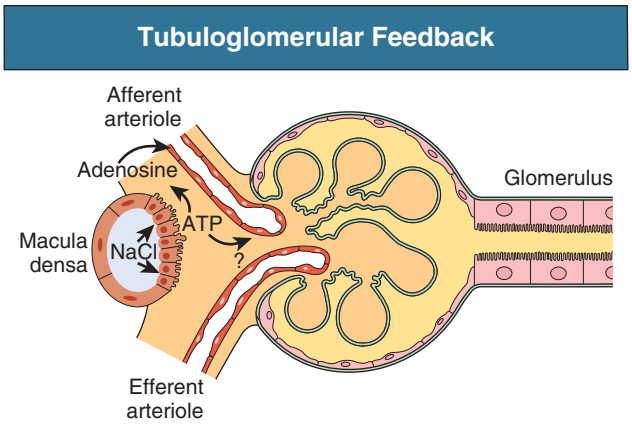

Figure 2-4 Tubuloglomerular feedback. Changes in the delivery of NaCl to the macula densa region of the thick ascending limb of Henle loop cause changes in the afferent arteriolar caliber. The response is mediated by adenosine triphosphate *(ATP),* either directly or after metabolism to adenosine, and modulated by other locally produced agents such as angiotensin II and nitric oxide. Increased macula densa NaCl delivery results in afferent arteriolar constriction, thereby reducing GFR.

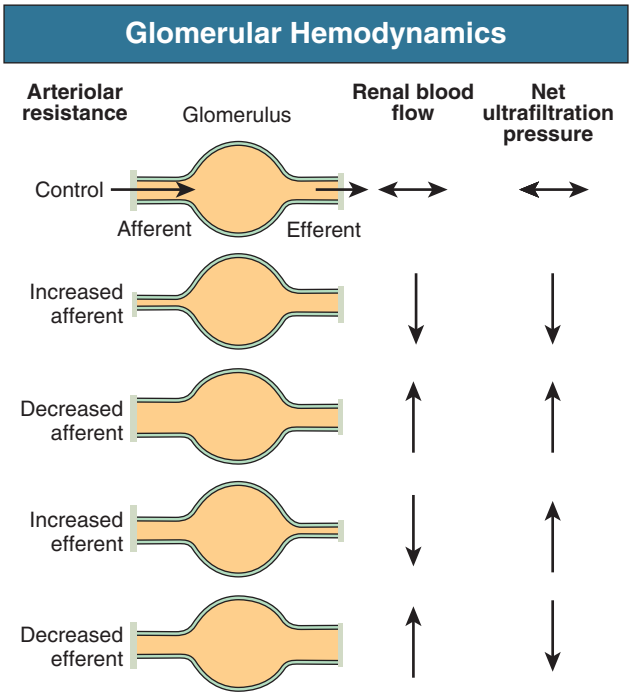

Figure 2-5 Glomerular hemodynamics. Changes in afferent or efferent arteriolar resistance will alter renal blood flow and (usually) net ultrafiltration pressure. However, the effect on ultrafiltration pressure depends on the relative changes in afferent and efferent arteriolar resistance. The overall effect on glomerular filtration rate will depend not only on renal blood flow and net ultrafiltration pressure, but also on the ultrafiltration coefficient (K_f; see Table 2-1).

the level of the afferent arterioles and believed to result from a combination of the following two mechanisms:

Myogenic reflex. Afferent arteriolar smooth muscle wall constricts automatically when renal perfusion pressure rises.

Tubuloglomerular feedback (TGF). Increased delivery of sodium chloride (NaCl) to the nephron's macula densa region (specialized plaque of cells at distal end of ascending limb of Henle) results from increases in renal perfusion pressure and causes vasoconstriction of the afferent arteriole supplying the same nephron's glomerulus.

Because these mechanisms restore both RBF and P_{gc} toward normal, the initial change in GFR is also reversed. The TGF system is possible because of the juxtaglomerular apparatus (see Chapter 1), which consists of the macula densa region of each nephron and the adjacent glomerulus and afferent and efferent arterioles (Fig. 2-4). The primary mediator of TGF is adenosine triphosphate (ATP). Increased NaCl delivery to the macula densa leads to increased NaCl uptake by these cells, which triggers ATP release into the surrounding extracellular space.[5] It is thought that ATP has a direct vasoconstrictor effect, acting on $P2X_1$ purinoceptors on afferent arteriolar cells; although evidence also indicates that nucleotidases present in this region degrade ATP to adenosine, which, acting on afferent arteriolar A_1 receptors, can also cause vasoconstriction.[6] The sensitivity of TGF is modulated by locally produced angiotensin II, nitric oxide, and certain eicosanoids (see later discussion).

The TGF regulation of filtration rate may be more complex than typically described, with evidence for regulatory crosstalk between the distal nephron and the vasculature at sites beyond the macula densa,[7] as well as for synchronization of blood flow across networks of nephrons in response to changes in sodium delivery.[8]

Despite renal autoregulation, a number of extrinsic factors (nervous and humoral) can alter renal hemodynamics. Independent or unequal changes in the resistance of afferent and efferent glomerular arterioles, together with alterations in K_f (thought to result largely from mesangial cell contraction/relaxation), can result in disproportionate, or even contrasting, changes in RBF and GFR. In addition, changes in regional vascular resistance can alter the distribution of blood flow within the kidney. For example, medullary vasoconstriction may affect whole-kidney blood flow because blood can be diverted through the cortex: nevertheless, this renders the medulla hypoxic and vulnerable to ischemic injury.[9] Figure 2-5 indicates how,

Physiologic and Pharmacologic Influences on Glomerular Hemodynamics

	Arteriolar Resistance					
	Afferent	*Efferent*	*Renal Blood Flow*	*Net Ultrafiltration Pressure*	K_f	*GFR*
Renal sympathetic nerves	↑↑	↑	↓	↓	↓	↓
Epinephrine	↑	↑	↓	→	?	↓
Adenosine	↑	→	↓	↓	?	↓
Cyclosporine	↑	→	↓	↓	?	↓
NSAIDs	↑↑	↑	↓	↓	?	↓
Angiotensin II	↑	↑↑	↓	↑	↓	↓→
Endothelin-1	↑	↑↑	↓	↑	↓	↓
High-protein diet	↓	→	↑	↑	→	↑
Nitric oxide	↓	↓	↑	?	↑	↑(?)
ANP (high dose)	↓	→	↑	↑	↑	↑
PGE_2/PGI_2	↓	↓(?)	↑	↑	?	↑
Calcium channel blockers	↓	→	↑	↑	?	↑
ACE inhibitors, ARBs	↓	↓↓	↑	↓	↑	?*

Table 2-1 Physiologic and pharmacologic influences on glomerular hemodynamics. The overall effect on glomerular filtration rate (GFR) will depend on renal blood flow, net ultrafiltration pressure, and the ultrafiltration coefficient (K_f), which is controlled by mesangial cell contraction and relaxation. The effects shown are those seen when the agents are applied (or inhibited) in isolation; the actual changes that occur are dose dependent and are modulated by other agents. *ACE,* Angiotensin-converting enzyme; *ARBs,* angiotensin receptor blockers; *ANP,* atrial natriuretic peptide; *NSAIDs,* nonsteroidal anti-inflammatory drugs: *PGE_2/PGI_2*, prostaglandins E_2 and I_2.
*In clinical practice, GFR is usually either decreased or unaffected.

in principle, changes in afferent and efferent arteriolar resistance can affect net ultrafiltration. Table 2-1 outlines vasoactive factors that alter renal hemodynamics (see Integrated Control of Renal Function). In addition, damage to the renal afferent arteriole, as in patients with hypertension and progressive kidney disease, may also interfere with renal autoregulatory mechanisms.

TUBULAR TRANSPORT

Vectorial transport is net movement of substances from tubular fluid to blood (reabsorption), or vice versa (secretion). The cell membrane facing the tubular fluid (*luminal* or *apical*) must have different properties than the membrane facing the blood (*peritubular* or *basolateral*). Such epithelia are said to be "polarized," thus allowing the net movement of substances across the cell (transcellular route). The *tight junction*, which is a contact point close to the apical side of adjacent cells, limits water and solute movement between cells (paracellular route).

Solute transport across cell membranes uses either passive or active mechanisms.

Passive Transport

Simple diffusion always occurs down an electrochemical gradient, which is a composite of the concentration gradient and the electrical gradient. With an undissociated molecule, only the concentration gradient is relevant, whereas for a charged ion, the electrical gradient must also be considered. Simple diffusion does not require a direct energy source, although an active transport process is usually necessary to establish the initial concentration and electrical gradients.

Facilitated diffusion (or carrier-mediated diffusion) depends on an interaction of the molecule or ion with a specific membrane carrier protein that facilitates its passage across the cell membrane's lipid bilayer. In almost all cases of carrier-mediated transport in the kidney, two or more ions or molecules share the carrier; one moiety moves down its electrochemical gradient, while the other(s) move against the gradient.

Diffusion through a membrane channel (or pore) formed by specific integral membrane proteins is also a form of facilitated diffusion, because it allows charged and lipophobic molecules to pass through the membrane at a high rate.

Active Transport

Ion movement directly against an electrochemical gradient ("uphill") requires a source of energy and is known as active transport. In cells, this energy is derived from ATP production and its hydrolysis. The most important active cell transport mechanism is the sodium pump, which extrudes sodium ions (Na^+) from inside the cell in exchange for potassium ions (K^+) from outside the cell.[10] In the kidney, this process is confined to the basolateral membrane. The Na pump derives energy from the enzymatic hydrolysis of ATP and thus is more precisely termed Na^+,K^+-ATPase. It exchanges $3Na^+$ for $2K^+$ and is electrogenic because it extrudes a net positive charge from the cell; Na^+,K^+-ATPase is an example of a *primary* active transport mechanism. Other well-defined primary active transport processes in the kidney are the proton-secreting H^+-ATPase, important in hydrogen ion secretion in the distal nephron, and the Ca^{2+}-ATPase, partly responsible for calcium reabsorption.

Activity of the basolateral Na^+,K^+-ATPase underpins the operation of all the passive transport processes outlined earlier. It ensures that the intracellular Na^+ concentration is kept low (10 to

20 mmol/l) and the K^+ concentration high (~150 mmol/l), compared with their extracellular concentrations (~140 and 4 mmol/l, respectively). The *pump-leak* model of sodium transport uses the electrochemical gradient established and maintained by the Na pump to allow "leak" of Na^+ into the cell through a variety of membrane transport proteins. These can be Na^+ channels (in the distal nephron) or specific membrane carrier proteins that couple Na^+ entry to the influx (*symport* or *cotransport*) or efflux (*antiport* or *countertransport*) of other molecules or ions. In various parts of the nephron, glucose, phosphate, amino acids, K^+, and chloride ions (Cl^-) can all be cotransported with Na^+; moreover, H^+ and Ca^{2+} can be countertransported against Na^+ entry. In each case, the non-Na molecule or ion is transported against its electrochemical gradient, using energy derived from the "downhill" movement of Na^+. Their ultimate dependence on the Na^+,K^+-ATPase makes them *secondary* active transport mechanisms.

TRANSPORT IN SPECIFIC NEPHRON SEGMENTS

Given a typical GFR, approximately 180 liters of plasma (largely protein-free) is filtered each day, necessitating massive reabsorption by the whole nephron. Figure 2-6 shows the major transport mechanisms operating along the nephron (except the loop of Henle, dealt with separately).

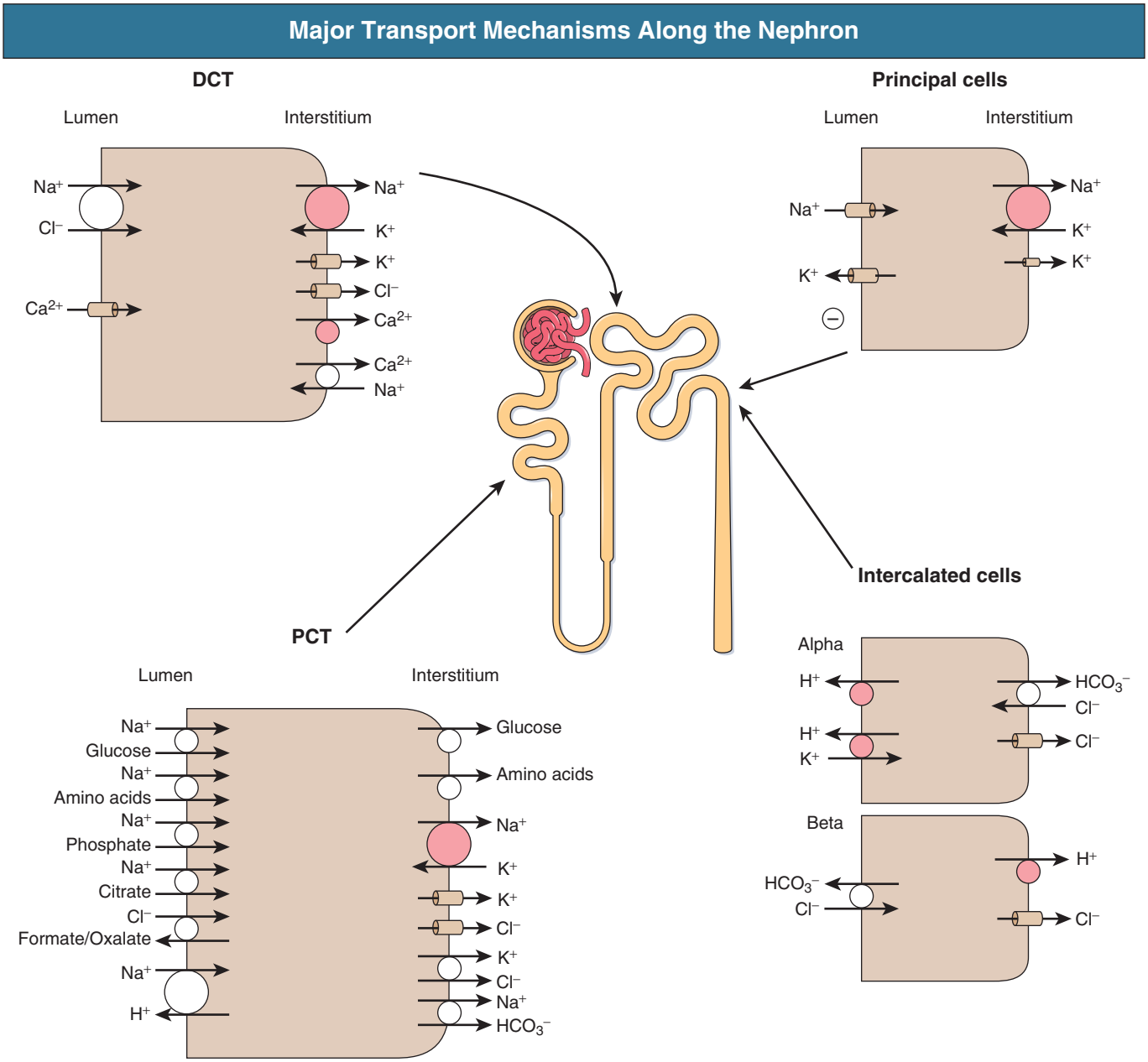

Figure 2-6 Major transport mechanisms along the nephron. Major transport proteins for solutes in the apical and basolateral membranes of tubular cells in specific regions of the nephron. Stoichiometry is not indicated; it is not 1 : 1 in all cases. *Red circles* represent primary active transport; *white circles* represent carrier-mediated transport (secondary active); *cylinders* represent ion channels. In the proximal convoluted tubule *(PCT),* Na^+ enters the cell through an Na^+-H^+ exchanger and a series of cotransporters. In the distal convoluted tubule *(DCT),* Na^+ enters the cell through the thiazide-sensitive Na^+-Cl^- cotransporter. In the principal cells of the cortical collecting duct, Na^+ enters through the epithelial sodium channel (ENaC). In all cases, Na^+ is extruded from the cells through the basolateral Na^+,K^+-ATPase. Transporters in the thick ascending limb of Henle are dealt with separately (see Fig. 2-10).

Proximal Tubule

The proximal tubule is adapted for bulk reabsorption of the glomerular filtrate. The epithelial cells have microvilli (brush border) on their apical surface that provide a large absorptive area, and the basolateral membrane has folds, also increasing the surface area. The cells are rich in mitochondria (concentrated near the basolateral membrane) and rely predominantly on aerobic metabolism, thus rendering the proximal tubule susceptible to hypoxic insult. The proximal convoluted tubule (PCT, pars convoluta) makes up the first two thirds of the proximal tubule; the final third is the proximal straight tubule (pars recta). On the basis of subtle structural and functional differences, the proximal tubule epithelium is subdivided into three segments: S_1 makes up the initial short segment of the PCT; S_2, the remainder of the PCT and the cortical segment of the pars recta; and S_3, the medullary segment of the pars recta.

The NHE3 isoform of the Na^+-H^+ exchanger (antiport) is the main route of Na^+ entry into proximal tubule cells. A battery of specialized transporters is also expressed in the apical membrane, coupling Na^+ entry to that of other species. Thus, the proximal tubule accounts for the bulk of Na^+, K^+, Cl^-, and bicarbonate (HCO_3^-) reabsorption, and almost complete reabsorption of glucose, amino acids, and low-molecular-weight proteins (e.g., retinol binding protein, α- and β-microglobulin) that have passed the filtration barrier. Most other filtered solutes are also reabsorbed to some extent in the proximal tubule (e.g., ~60% of calcium, 80% of phosphate, 50% of urea). Constitutive expression of aquaporin 1 (AQP1) water channels in both membranes confers a large hydraulic permeability.[11] About 65% of the filtered water is reabsorbed in the proximal tubule and is isosmotic because the junctions between cells are leaky and unable to sustain a large transepithelial osmotic gradient. In the final section of the proximal tubule (late S_2 and S_3), there is secretion of weak organic acids and bases, including most diuretics and PAH.

Loop of Henle

The loop of Henle is defined anatomically as comprising the pars recta of the proximal tubule (thick descending limb), the thin descending and ascending limbs (thin ascending limbs are present only in long-looped nephrons), the thick ascending limb, and the macula densa. In addition to its role in the continuing reabsorption of solutes (Na^+, Cl^-, K^+, Ca^{2+}, Mg^{2+}), the loop of Henle is responsible for the kidney's ability to generate a concentrated or dilute urine, which is described in detail later. The thick limb of Henle also produces the Tamm-Horsfall protein, also called *uromodulin,* normally the most abundant protein in the urine. Physiologic roles of uromodulin are not exactly defined. Uromodulin may contribute to sodium homeostasis, act as a constitutive inhibitor of calcium crystallization in tubular fluid and also help protect the kidney from inflammation and infection. Human genetic studies have associated uromodulin expression with altered risk of chronic kidney disease; mutations in the encoding gene cause rare autosomal dominant disorders of renal injury and cyst formation, hyperuricemia, and progressive decline in renal function.[12]

Distal Nephron

The distal tubule comprises three segments: the distal convoluted tubule (DCT), where thiazide-sensitive NaCl reabsorption through an apical NaCl cotransporter (NCC)[13] occurs; the connecting tubule (CNT), whose function is essentially intermediate between that of the DCT and that of the next segment; and the initial collecting duct, made of the same epithelial cell type as the cortical collecting duct (see Fig. 2-6). Two cell types make up the cortical collecting duct. The predominant cell, the *principal* cell (or CD cell), is responsible for Na^+ reabsorption and K^+ secretion (as well as water reabsorption; see later discussion). Na^+ enters the principal cell from the lumen through apical epithelial sodium channels (ENaC) and exits by the basolateral Na^+,K^+-ATPase. This process is electrogenic and sets up a lumen-negative transepithelial potential difference. K^+ enters the principal cell by the same basolateral Na^+,K^+-ATPase and leaves by K^+ transport pathways in both membranes; however, the relative depolarization of the apical membrane (caused by Na^+ entry) favors K^+ secretion into the lumen, the major route for which is through renal outer medullary potassium (ROMK) channels. The other cell type in the late distal tubule and cortical collecting duct, the *intercalated* (IC) cell, is responsible for H^+ secretion (by type A, or α, IC cells) or HCO_3^- secretion (by type B, or β, IC cells) into the final urine (see Fig. 2-6). In the medullary collecting duct there is a gradual transition in the epithelium. There are fewer and fewer IC cells, whereas the principal-like cells are modified such that they reabsorb Na^+ but, lacking apical K^+ channels, do not secrete K^+.

Figures 2-7 and 2-8 show the sites of Na^+ and K^+ reabsorption/secretion along the nephron. Table 2-2 outlines the pathophysiologic consequences of known genetic defects in some of the major transporters in the nephron (see Chapter 49 for details).

Genetic Defects in Transport Proteins Resulting in Renal Disease

Transporter	Consequence of Mutation
Proximal Tubule	
Apical Na^+-cystine cotransporter	Cystinuria
Apical Na^+-glucose cotransporter (SGLT2)	Renal glycosuria
Basolateral Na^+-HCO_3^- cotransporter	Proximal renal tubular acidosis
Intracellular H^+-Cl^- exchanger (ClC5)	Dent disease
Thick Ascending Limb	
Apical Na^+-K^+-$2Cl^-$ cotransporter	Bartter syndrome type 1
Apical K^+ channel	Bartter syndrome type 2
Basolateral Cl^- channel	Bartter syndrome type 3
Basolateral Cl^- channel accessory protein	Bartter syndrome type 4
Distal Convoluted Tubule	
Apical Na^+-Cl^- cotransporter	Gitelman syndrome
Collecting Duct	
Apical Na^+ channel (principal cells)	Overexpression: Liddle syndrome Underexpression: pseudohypoaldosteronism type 1b
Aquaporin 2 channel (principal cells)	Nephrogenic diabetes insipidus
Basolateral Cl^-/HCO_3^- exchanger (intercalated cells)	Distal renal tubular acidosis
Apical H^+-ATPase (intercalated cells)	Distal renal tubular acidosis (with or without deafness)

Table 2-2 Genetic defects in transport proteins resulting in renal disease. For more detailed coverage of these clinical conditions, see Chapter 49.

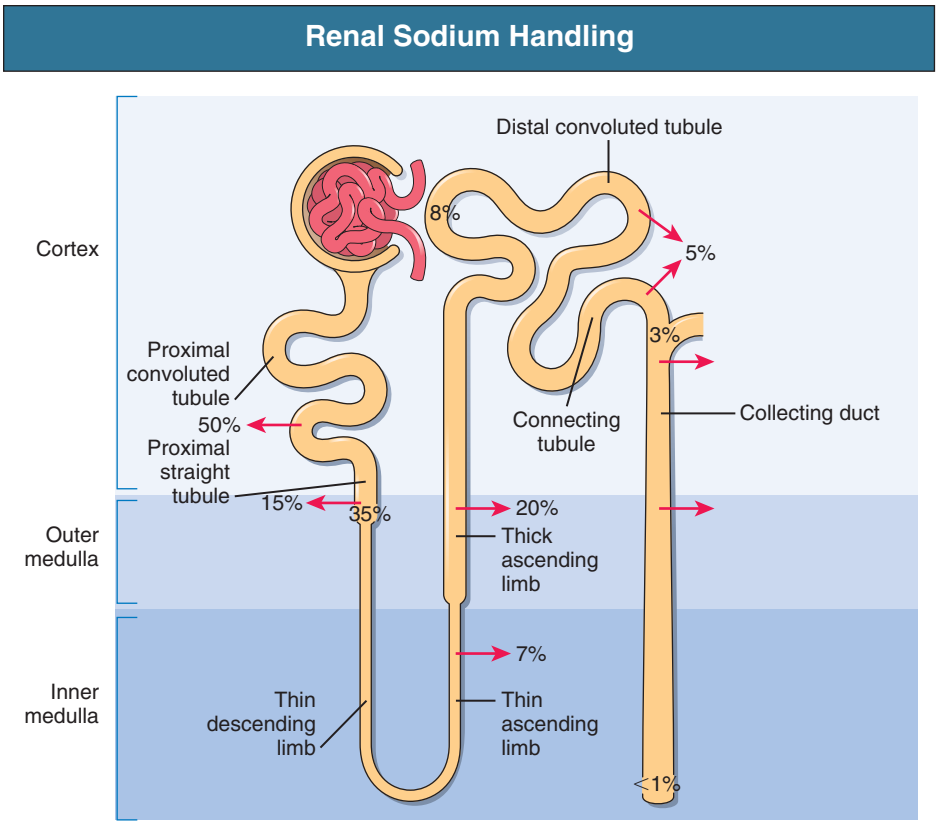

Figure 2-7 Renal sodium handling along the nephron. Figures outside the nephron represent the approximate percentage of the filtered load reabsorbed in each region. Figures within the nephron represent the percentages remaining. Most filtered sodium is reabsorbed in the proximal tubule and loop of Henle; normal day-to-day control of sodium excretion is exerted in the distal nephron.

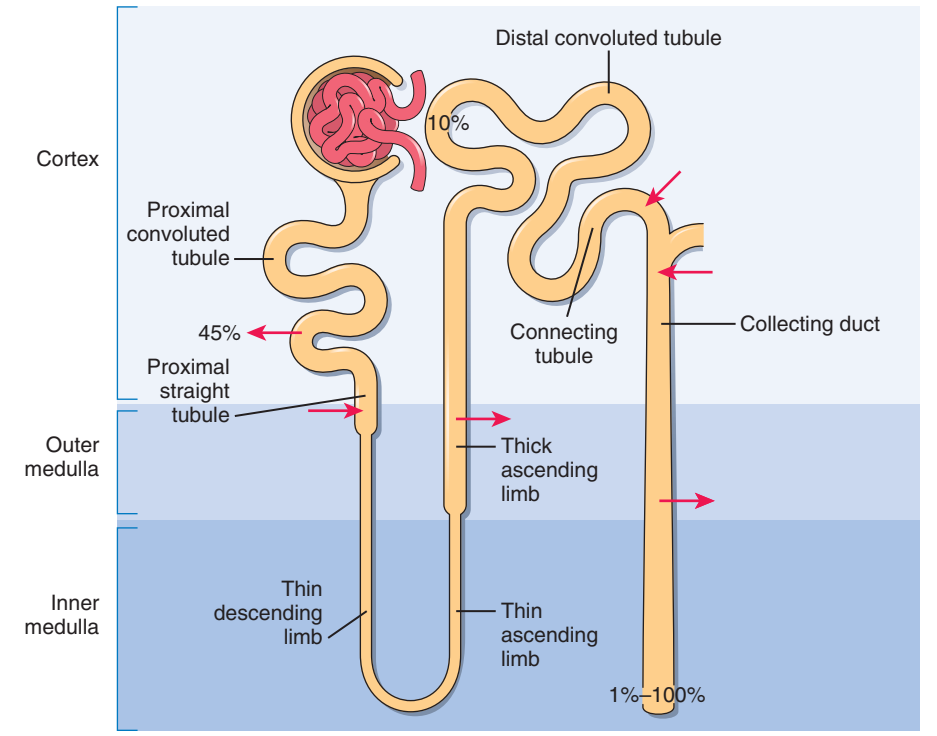

Figure 2-8 Renal potassium handling along the nephron. Figures are not given for percentages reabsorbed or remaining in every region because quantitative information is incomplete, but most filtered potassium is reabsorbed in the proximal convoluted tubule and thick ascending limb of Henle; approximately 10% of the filtered load reaches the early distal tubule. Secretion by connecting tubule cells and principal cells in the late distal tubule–cortical collecting duct is variable and is the major determinant of potassium excretion.

GLOMERULOTUBULAR BALANCE

Because the proportion of filtered Na^+ excreted in the urine is so small (normally <1%), it follows that without a compensatory change in reabsorption, even small changes in the filtered load would cause major changes in the amount excreted. For example, if GFR were to increase by 10%, and the rate of reabsorption remained unchanged, Na^+ excretion would increase more than 10-fold. However, an intrinsic feature of tubular function is that the extent of Na^+ reabsorption in a given nephron segment is about proportional to the Na^+ delivery to that segment. This process is called *glomerulotubular balance*. In perfect balance, both the reabsorption and the excretion of Na^+ would change in exactly the same proportion as the change in GFR, but glomerulotubular balance is usually less than perfect. Most studies have focused on the proximal tubule because glomerulotubular balance by this segment serves to stabilize delivery of Na^+ and fluid to the distal nephron, permitting efficient secretion of K^+ and H^+. However, Na^+ reabsorption in the thick limb of Henle and distal tubule is also delivery dependent. This partly explains why diuretics acting on the proximal tubule are relatively ineffective compared with those acting more distally. With distal-acting diuretics, there is less scope further downstream for compensatory Na^+ reabsorption. This also explains why combining two diuretics (acting at different nephron sites) causes a more striking diuresis and natriuresis.

The mechanism of glomerulotubular balance is not fully understood. In the proximal tubule, physical factors (Starling forces) operating across peritubular capillary walls may be involved. Glomerular filtration of an essentially protein-free fluid means that the plasma leaving the glomeruli in efferent arterioles and supplying the peritubular capillaries has a relatively high oncotic pressure, favoring reabsorption of fluid from the proximal tubules. If GFR were reduced in the absence of a change in renal plasma flow, the *filtration fraction* (GFR-RPF ratio) would fall. Peritubular capillary oncotic pressure would also be reduced, and the tendency of the peritubular vasculature to take up fluid reabsorbed from the proximal tubule would be diminished. Backflux of this fluid is thought to occur through the (leaky) tight junctions, reducing net reabsorption (Fig. 2-9). However, this mechanism could work only if GFR changed in the absence of a corresponding change in RPF; if the two changed in parallel, filtration fraction would stay constant, with no change in oncotic pressure.

A second contributory factor to glomerulotubular balance in the proximal tubule could be the filtered loads of glucose and amino acids; if their loads increase because of increased GFR, the rates of Na^+-coupled glucose and amino acid reabsorption in the proximal tubule will also increase. It has also been proposed that the proximal tubular brush border microvilli serve a "mechanosensing" function, transmitting changes in torque (caused by altered tubular flow rates) to the cells' actin cytoskeleton and thereby modulating transporter activity.[14] The mechanisms are unknown, but the release of paracrine mediators such as ATP,[15] dopamine,[16] or angiotensin II[17] into the lumen fluid may contribute.

Although the renal sympathetic nerves and certain hormones can influence reabsorption in the proximal tubule and loop of Henle, under normal circumstances the combined effects of autoregulation and glomerulotubular balance ensure that a relatively constant load of glomerular filtrate is delivered to the distal tubule. It is the final segments of the nephron that exert normal day-to-day control of Na^+ excretion. Evidence indicates important roles for the late DCT[13] and the CNT,[18] in addition to the collecting duct. Aldosterone, secreted from the adrenal cortex, stimulates mineralocorticoid receptors within principal cells and CNT cells, which leads to generation of

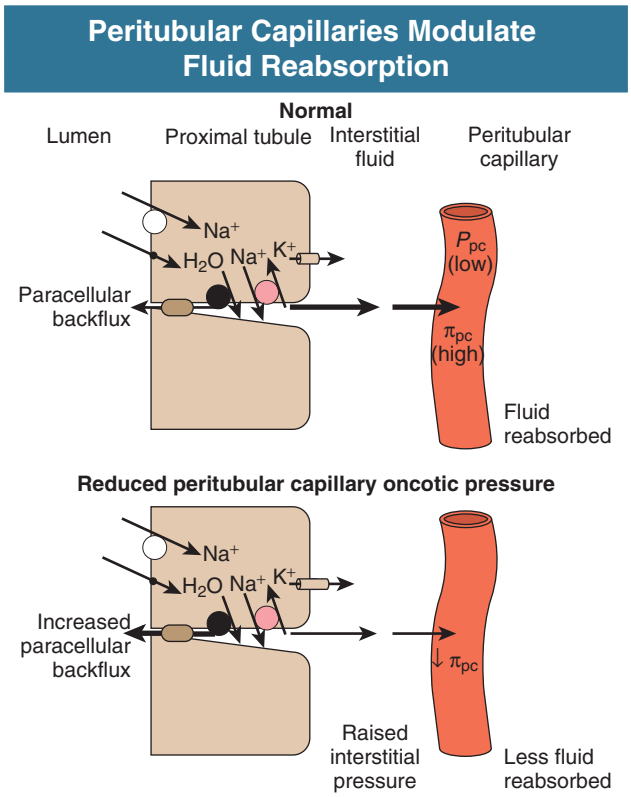

Figure 2-9 Physical factors and proximal tubular reabsorption. Influence of peritubular capillary oncotic pressure on net reabsorption in proximal tubules. Uptake of reabsorbate into peritubular capillaries is determined by the balance of hydrostatic and oncotic pressures across the capillary wall. Compared with those in systemic capillaries, the peritubular capillary hydrostatic (P_{pc}) and oncotic (π_{pc}) pressures are low and high, respectively, so that uptake of proximal tubular reabsorbate into the capillaries is favored. If peritubular capillary oncotic pressure decreases (or hydrostatic pressure increases), less fluid is taken up, interstitial pressure increases, and more fluid may leak back into the lumen paracellularly; net reabsorption in proximal tubules would therefore be reduced.

the regulatory protein serum- and glucocorticoid-inducible kinase 1 (SGK1), which in turn increases the density of Na^+ channels (ENaC) in the apical membrane (see Fig. 2-6). This stimulates Na^+ uptake and further depolarizes the apical membrane, thereby facilitating K^+ secretion in the late distal tubule/cortical collecting duct. Aldosterone also stimulates Na^+ reabsorption and K^+ secretion by upregulating the basolateral Na^+,K^+-ATPase.

The mineralocorticoid receptors have equal affinity *in vitro* for aldosterone and other adrenal corticosteroids, such as cortisol. The circulating concentrations of cortisol vastly exceed those of aldosterone, but *in vivo* the mineralocorticoid receptors show specificity for aldosterone because of the presence along the distal nephron of the enzyme 11β-hydroxysteroid dehydrogenase 2, which inactivates cortisol in the vicinity of the receptor.[19] Mutations in the gene that encodes 11β-hydroxysteroid dehydrogenase 2,[20] or inhibition of the enzyme by derivatives of glycyrrhetinic acid (found in licorice) can cause hypertension[21] from excessive and unregulated stimulation of Na^+ transport by cortisol (see also Chapter 40).

COUNTERCURRENT SYSTEM

A major function of the loop of Henle is the generation and maintenance of the interstitial osmotic gradient that increases from the

renal cortex (~290 mOsm/kg) to the tip of the medulla (~1200 mOsm/kg). As indicated in Chapter 1, the loops of Henle of superficial nephrons turn at the junction between outer and inner medulla, whereas those of deep nephrons (long-looped nephrons) penetrate the inner medulla to varying degrees. The anatomic loops of Henle reabsorb approximately 40% of filtered Na^+, mostly in the pars recta and the thick ascending limb (TAL), and approximately 25% of filtered water, in the pars recta and the thin descending limbs of deep nephrons. Evidence suggests that the thin descending limb of superficial nephrons is relatively impermeable to water.[22] Both the thin ascending limb (found only in deep nephrons) and the TAL are essentially impermeable to water, although Na^+ is reabsorbed—passively in the thin ascending limb, but actively in the TAL. The TAL also operates as a pump-leak system; the basolateral Na^+,K^+-ATPase maintains the electrochemical driving force for passive Na^+ entry from the lumen through the Na^+-$2Cl^-$-K^+ cotransporter (NKCC-2) and, to a much lesser extent, the Na^+-H^+ exchanger (Fig. 2-10). The apical NKCC-2 is the site of action of loop diuretics such as furosemide and bumetanide. Na^+ exits the cell through the Na^+ K^+-ATPase, and Cl^- and K^+ exit through basolateral ion channels and a K^+-Cl^- cotransporter. K^+ also reenters the lumen through apical membrane channels. This "recycling" of K^+ into the tubular lumen is necessary for normal operation of the Na^+-$2Cl^-$-K^+ cotransporter because the availability of K^+ is a limiting factor for the transporter (K^+ concentration in tubular fluid is much lower than Na^+ and Cl^-). Potassium recycling is also partly responsible for generating the lumen-positive transepithelial potential difference found in the TAL, which drives additional Na^+ reabsorption through the paracellular pathway; for each Na^+ reabsorbed by the transcellular route, another is reabsorbed paracellularly (see Fig. 2-10). Other cations (K^+, Ca^{2+}, Mg^{2+}) are also reabsorbed by this route. The reabsorption of NaCl along the TAL in the absence of significant water reabsorption means that the tubular fluid leaving this segment is hypotonic; thus the TAL is also called the *diluting segment*.

The reabsorption in the TAL of solute without water generates a "horizontal" osmotic gradient of about 200 mOsm/kg between the tubule fluid and interstitium. This separation is the *single osmotic effect*. The U-shaped arrangement of the loop of Henle, in which flow in the ascending limb is in the opposite direction to that in the descending limb, multiplies the single effect to generate a much larger vertical (corticomedullary) osmotic gradient by a process called *countercurrent multiplication* (Fig. 2-11). Fluid entering the descending limb from the proximal tubule is isotonic (~290 mOsm/

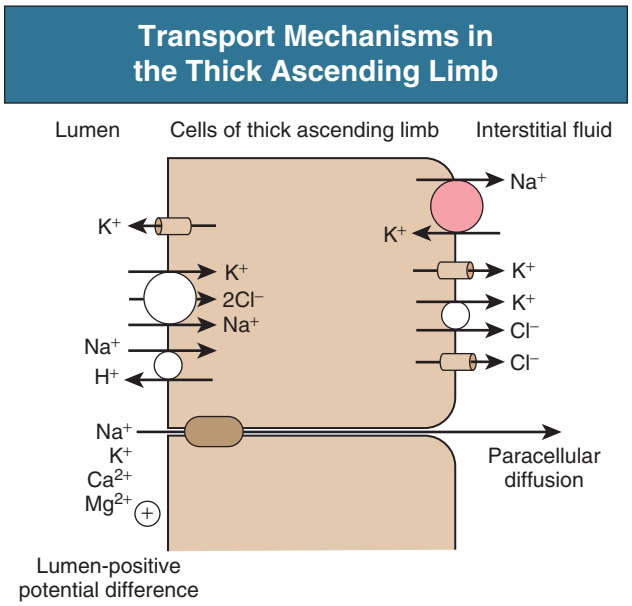

Figure 2-10 Transport mechanisms in the thick ascending limb of Henle. The major cellular entry mechanism is the Na^+-K^+-$2Cl^-$ cotransporter. The transepithelial potential difference drives paracellular transport of Na^+, K^+, Ca^{2+}, and Mg^{2+}.

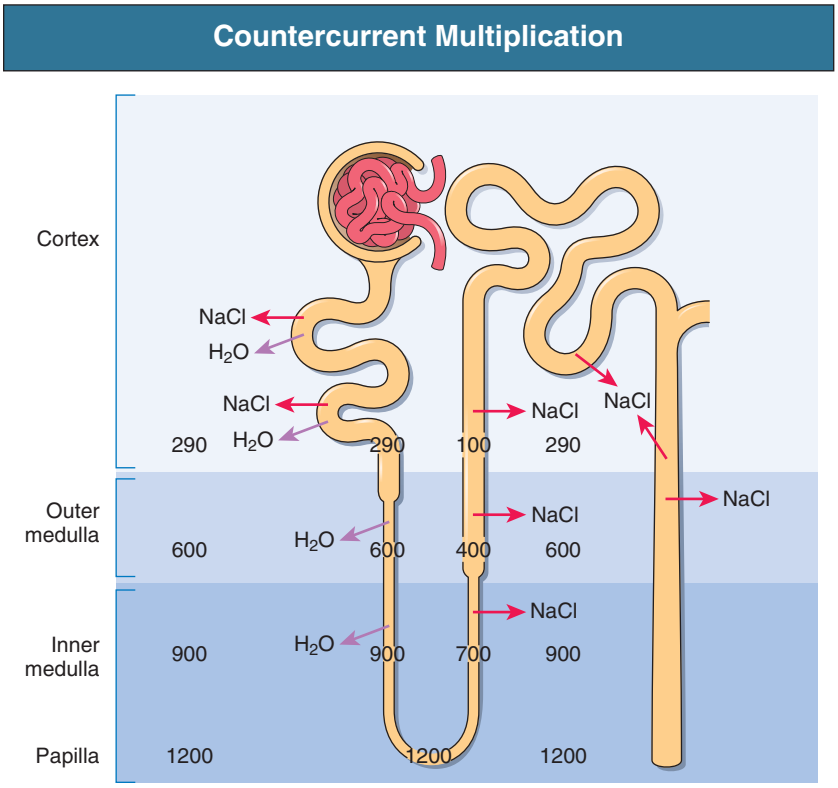

Figure 2-11 Countercurrent multiplication by loop of Henle. The nephron drawn represents a deep (long-looped) nephron. Figures represent approximate osmolalities (mOsm/kg). Osmotic equilibration occurs in the thin descending limb of Henle, whereas NaCl is reabsorbed in the water-impermeable ascending limb; hypotonic fluid is delivered to the distal tubule. In the absence of vasopressin, this fluid remains hypotonic during its passage through the distal tubule and collecting duct, despite the large osmotic gradient favoring water reabsorption. A large volume of dilute urine is therefore formed. During maximal vasopressin secretion, water is reabsorbed down the osmotic gradient, so that tubular fluid becomes isotonic in the cortical collecting duct and hypertonic in the medullary collecting duct. A small volume of concentrated urine is formed.

kg). On encountering the hypertonicity of the medullary interstitial fluid (caused by NaCl reabsorption in water-impermeable ascending limb), the fluid in the descending limb comes into osmotic equilibrium with its surroundings, either by solute entry into the descending limb (superficial nephrons) or by water exit by osmosis (deep nephrons). These events, combined with continuing NaCl reabsorption in the ascending limb, result in a progressive increase in medullary osmolality from corticomedullary junction to papillary tip. A similar osmotic gradient exists in the thin descending limb, while at any level in the ascending limb, the osmolality is less than in the surrounding tissue. Thus, hypotonic fluid (~100 mOsm/kg) is delivered to the distal tubule. Ultimately, the energy source for countercurrent multiplication is active Na^+ reabsorption in the TAL. As indicated earlier, Na^+ reabsorption in the thin ascending limb is passive, although the mechanism is not yet understood.

Role of Urea

The thin limbs of loop of Henle are relatively permeable to urea (ascending more permeable than descending), but the TAL and beyond are urea impermeable up to the final section of the inner medullary collecting duct. During antidiuresis, vasopressin-induced water reabsorption from the collecting ducts concentrates urea such that in the terminal inner medullary collecting duct, there is a large concentration gradient between the luminal fluid and interstitium. This section of the inner medullary collecting duct expresses urea transporters (UT-A1 and UT-A3), allowing passive reabsorption of urea into the inner medullary interstitium. This process is also under the control of vasopressin (ADH).[23] The interstitial urea exchanges with vasa recta capillaries (see next section) and some urea enters the S_3 segment of the pars recta and the descending and ascending thin limbs; it is then returned to the inner medullary collecting ducts to be reabsorbed. The net result of this urea recycling process is to add urea to the inner medullary interstitium, thereby increasing interstitial osmolality. The fact that the high urea concentration within the medullary collecting duct is balanced by a similarly high urea concentration in the medullary interstitium allows large quantities of urea to be excreted without incurring the penalty of an osmotic diuresis, since the urea in the collecting duct is rendered osmotically ineffective. Moreover, the high urea concentration in the medullary interstitium should also increase osmotic water abstraction from the thin descending limbs of deep nephrons, thus raising the intraluminal Na^+ concentration within the thin descending limbs.

Although until recently this process was thought to prepare for passive Na^+ reabsorption from the thin ascending limbs, mice with genetic deletion of UT-A1 and UT-A3 have a greatly reduced urea concentration in the inner medullary interstitium but a normal interstitial NaCl gradient.[23] Therefore the mechanisms responsible for the inner medullary electrolyte gradient are still unclear. It is worth emphasizing, however, that the ultimate driving force for countercurrent multiplication is active Na^+ reabsorption in the TAL. For this reason, loop diuretics disrupt the osmotic gradient, and genetic mutations in the pathways contributing to efficient Na^+ reabsorption in the TAL cause the salt-wasting Bartter syndrome (see Chapter 49).

Vasa Recta

If the capillaries that supply the renal medulla had a more conventional anatomic arrangement, these vessels would soon dissipate the medullary osmotic gradient because of equilibration of the hypertonic interstitium with the isotonic capillary blood. This does not happen to any appreciable extent, because the U-shaped arrangement ensures that solute entry and water loss in the descending vasa recta are offset by solute loss and water entry in the ascending vasa recta. This is the process of *countercurrent exchange* and is entirely passive (Fig. 2-12).

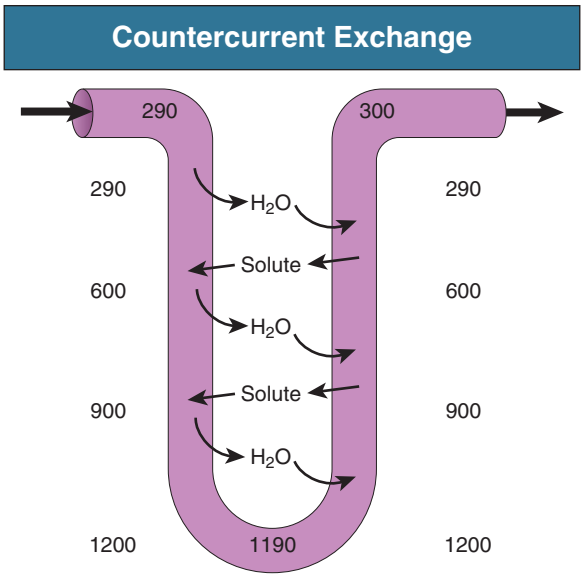

Figure 2-12 Countercurrent exchange by the vasa recta. Figures represent approximate osmolalities (mOsm/kg). The vasa recta capillary walls are highly permeable, but the U-shaped arrangement of the vessels minimizes the dissipation of the medullary osmotic gradient. Nevertheless, because equilibration across the capillary walls is not instantaneous, a certain amount of solute is removed from the interstitium.

Renal Medullary Hypoxia

Countercurrent exchange by the medullary capillaries applies also to oxygen, which diffuses from descending to ascending vasa recta, bypassing the deeper regions. This phenomenon, combined with ongoing energy-dependent Na^+ transport in the (outer medullary) TAL, renders medullary tissue relatively hypoxic. Thus the partial pressure of oxygen normally decreases from about 50 mm Hg in the cortex to 10 mm Hg in the inner medulla.[24] Indeed, administration of furosemide, which inhibits oxygen consumption in the TAL, increases medullary oxygenation. As part of the adaptation to this relatively hypoxic environment, medullary cells have a higher capacity for glycolysis than cortical cells. Moreover, a number of *heat shock proteins* are expressed in the medulla, which assist cell survival by restoring damaged proteins and by inhibiting apoptosis.[24]

The degree of medullary hypoxia depends on the balance between medullary blood flow (influenced by contractile cells called *pericytes*) and oxygen consumption in the TAL. In health, this balance is modulated by a variety of autocrine/paracrine agents (e.g., nitric oxide, eicosanoids, ATP, adenosine; see later discussion), several of which can increase medullary oxygenation by simultaneously reducing pericyte contraction and TAL transport. Some cases of radiocontrast-induced nephropathy result from a disturbance of the balance between oxygen supply and demand, with consequent hypoxic medullary injury in which the normal cellular adaptations are overwhelmed, with subsequent apoptotic and necrotic cell death.

VASOPRESSIN (ANTIDIURETIC HORMONE) AND WATER REABSORPTION

Vasopressin, or antidiuretic hormone (ADH), is a nonapeptide synthesized in specialized neurons of the supraoptic and paraventricular

nuclei. ADH is transported from these nuclei to the posterior pituitary and released in response to increases in plasma osmolality and decreases in blood pressure. Osmoreceptors are found in the hypothalamus, and there is also input to this region from arterial baroreceptors and atrial stretch receptors. The actions of vasopressin are mediated by three receptor subtypes: V_{1a}, V_{1b}, and V_2. The V_{1a} receptors are found in vascular smooth muscle and are coupled to the phosphoinositol pathway; they cause an increase in intracellular Ca^{2+} resulting in contraction. V_{1a} receptors have also been identified in the apical membrane of several nephron segments; activation by luminal vasopressin can influence Na^+ transport in these segments. V_{1b} receptors are found in the anterior pituitary, where vasopressin modulates adrenocorticotropic hormone release. V_2 receptors are found in the basolateral membrane of principal cells in the late distal tubule and the whole length of the collecting duct; they are coupled by a G_s protein to cyclic adenosine monophosphate generation, which ultimately leads to the insertion of aquaporin 2 (AQP2) water channels into the apical membrane of this otherwise water-impermeable segment (Fig. 2-13). In the X-linked form of nephrogenic diabetes insipidus, the most common inherited form, the V_2 receptor is defective.[25]

Several aquaporins have been identified in the kidney.[26] AQP1 is found in apical and basolateral membranes of all proximal tubules and of thin descending limbs of long-looped nephrons; it is largely responsible for the permanently high water permeability of these segments. AQP3 is constitutively expressed in the basolateral membrane of CNT cells and cortical and outer medullary principal cells. AQP4 is constitutively expressed in the basolateral membrane of outer medullary principal cells and inner medullary collecting duct cells; however, AQP2 is responsible for the variable water permeability of the late distal tubule and collecting duct. Acute vasopressin release causes shuttling of AQP2 from intracellular vesicles to the apical membrane, while chronically raised vasopressin levels increase transcription and translation of the gene encoding AQP2. The apical insertion of AQP2 allows reabsorption of water, driven by the high interstitial osmolality that is achieved and maintained by the countercurrent system. Vasopressin also contributes to the effectiveness of this system by stimulating Na^+ reabsorption in the TAL and urea reabsorption through the UT-A1 and UT-A3 transporters in the inner medullary collecting duct. In the (rare) autosomal recessive and (even rarer) autosomal dominant forms of nephrogenic diabetes insipidus, AQP2 is abnormal and/or fails to translocate to the apical membrane.[26]

More frequently, defects in AQP2 shuttling contribute to the urine-concentrating defects associated with both hypokalemia and hypercalcemia. With chronic hypokalemia, AQP2 expression in the collecting duct is reduced,[27] possibly reflecting the generalized suppression of proteins central to urine concentration[28] and reduction in the medullary osmotic gradient. With hypercalcemia, increased intraluminal Ca^{2+} concentrations activate the apical calcium-sensing receptor, thereby preventing insertion of AQP2 in the apical membrane.[29] In addition, stimulation of a calcium receptor in the basolateral membrane of the TAL inhibits solute transport in this nephron segment, through inhibition of the apical NKCC-2 and ROMK channels, thereby reducing the medullary osmotic gradient.[30]

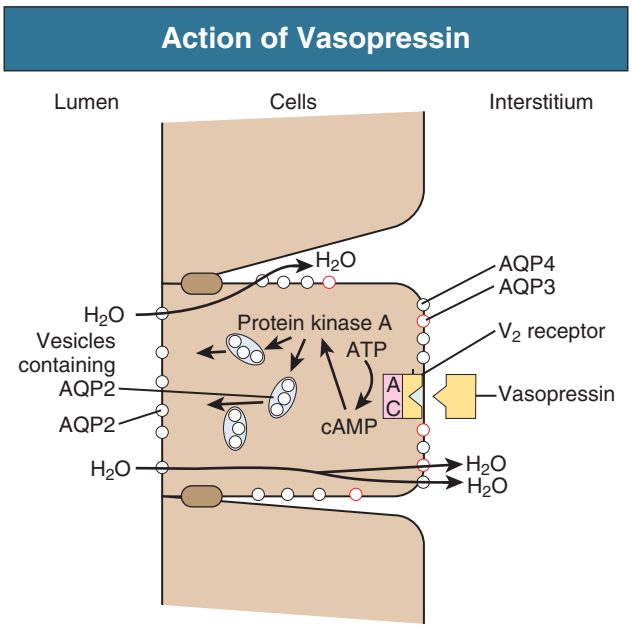

Figure 2-13 Mechanism of action of vasopressin (antidiuretic hormone). Vasopressin binds to V_2 receptors on the basolateral membrane of collecting duct principal cells and increases intracellular cyclic adenosine monophosphate *(cAMP)* production, causing insertion of preformed aquaporin 2 *(AQP2)* water channels into the apical membrane through intermediate reactions involving protein kinase A. The water permeability of the basolateral membrane, which contains aquaporins 3 and 4, is permanently high. Therefore, vasopressin secretion allows transcellular movement of water from lumen to interstitium. *AC,* Adenylate cyclase.

INTEGRATED CONTROL OF RENAL FUNCTION

One of the major functions of the kidneys is the regulation of blood volume, through the regulation of *effective circulating volume,* a conceptual volume reflecting the degree of fullness of the vasculature. This is achieved largely by controlling the sodium content of the body. Chapter 7 describes the mechanisms involved in the regulation of effective circulating volume. This discussion introduces some of the more important mediator systems.

Renal Interstitial Hydrostatic Pressure and Nitric Oxide

Acute increases in arterial blood pressure lead to *pressure natriuresis.* Because autoregulation is not perfect, part of this response is mediated by increases in RBF and GFR (see Fig. 2-3), but the main cause is reduced tubular reabsorption resulting from an increase in *renal interstitial hydrostatic pressure* (RIHP). An elevated RIHP reduces net reabsorption in the proximal tubule by increasing paracellular backflux through the tight junctions of the tubular wall (see Fig. 2-9). The increase in RIHP is thought to depend on intrarenally produced nitric oxide (NO) and modulated by reactive oxygen species.[31] Moreover, increased NO production in macula densa cells, which contain the neuronal (type I) isoform of nitric oxide synthase (nNOS), blunts the sensitivity of TGF, thereby allowing increased NaCl delivery to the distal nephron without incurring a TGF-mediated decrease in GFR.[32]

Another renal action of NO results from the presence of inducible (type II) nitric oxide synthase (iNOS) in glomerular mesangial cells. Local NO production counteracts the mesangial contractile response to agonists such as angiotensin II and endothelin (see later discussion). Furthermore, NO may contribute to the regulation of medullary blood flow. Locally synthesized NO offsets the vasoconstrictor effects of other agents on the pericytes of the descending vasa recta, and it reduces Na^+ reabsorption in the TAL; both actions help to protect the renal medulla from hypoxia. NO also may promote natriuresis and diuresis through direct actions on the renal tubule. Thus, in addition to its effect on the TAL, locally produced NO inhibits Na^+ and water reabsorption in the collecting duct.[33]

Renal Sympathetic Nerves

Reductions in arterial pressure and/or central venous pressure result in reduced afferent signaling from arterial baroreceptors and atrial volume receptors, which elicits a reflex increase in renal sympathetic nervous discharge. This reduces urinary Na^+ excretion in at least three ways: (1) constriction of afferent and efferent glomerular arterioles (predominantly afferent), thereby directly reducing RBF and GFR, and indirectly reducing RIHP; (2) direct stimulation of Na^+ reabsorption in the proximal tubule and the TAL of Henle loop; and (3) stimulation of renin secretion by afferent arteriolar cells (see later discussion). Renal sympathetic overactivity has long been associated with Na^+ retention and experimental hypertension. Recent clinical studies indicate that bilateral sympathetic efferent denervation effects long-lasting reductions in blood pressure in patients with resistant hypertension[34] (see also Chapter 38).

Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) is central to the control of extracellular fluid volume (ECFV) and blood pressure. Renin is synthesized and stored in specialized afferent arteriolar cells that form part of the juxtaglomerular apparatus[35] and is released into the circulation in response to (1) increased renal sympathetic nervous discharge, (2) reduced stretch of the afferent arteriole after a reduction in renal perfusion pressure, and (3) reduced delivery of NaCl to the macula densa region of the nephron (see Fig. 2-4).

Renin catalyzes the production of the decapeptide angiotensin I (Ang I) from circulating angiotensinogen (synthesized in the liver). Ang I is in turn converted by the ubiquitous angiotensin-converting enzyme (ACE) to the octapeptide angiotensin II. Ang II influences the control of ECFV and blood pressure as follows:

- Causes general arteriolar vasoconstriction, including renal afferent and (particularly) efferent arterioles, thereby increasing arterial pressure but reducing RBF. The tendency of P_{gc} to increase is offset by Ang II–induced mesangial cell contraction and reduced K_f; thus the overall effect on GFR is unpredictable.
- Directly stimulates sodium reabsorption in the proximal tubule.
- Directly stimulates thiazide-sensitive NaCl cotransport.[36]
- Stimulates aldosterone secretion from the zona glomerulosa of adrenal cortex. As described earlier, aldosterone stimulates sodium reabsorption in the distal tubule and collecting duct.

Eicosanoids

Eicosanoids are a family of metabolites of arachidonic acid (AA) produced enzymatically by three systems: *cyclooxygenase,* with two isoforms, COX-1 and COX-2, both expressed in the kidney; *cytochrome P-450* (CYP-450); and *lipoxygenase*. The major renal eicosanoids produced by the COX system are the prostaglandins E_2 (PGE_2) and I_2 (PGI_2), both of which are renal vasodilators and act to buffer the effects of renal vasoconstrictor agents (e.g., Ang II, norepinephrine) and the vasoconstrictor thromboxane A_2. Under normal circumstances, PGE_2 and PGI_2 have minimal effect on renal hemodynamics, but during stressful situations such as hypovolemia, help to protect the kidney from excessive functional changes. Consequently, nonsteroidal anti-inflammatory drugs (NSAIDs), which are COX inhibitors, can cause dramatic falls in GFR. PGE_2 also has tubular effects, inhibiting Na^+ reabsorption in the TAL of Henle loop, as well as both Na^+ and water reabsorption in the collecting duct.[37] The action of PGE_2 in the TAL, together with a dilator effect on vasa recta pericytes, is another paracrine regulatory mechanism that helps to protect the renal medulla from hypoxia. This may explain why inhibition of COX-2 can reduce medullary blood flow and cause apoptosis of medullary interstitial cells.

The metabolism of AA by renal CYP-450 enzymes yields epoxyeicosatrienoic acids (EETs), 20-hydroxyeicosatetraenoic acid (20-HETE), and dihydroxyeicosatrienoic acids (DHETs). These compounds appear to have multiple autocrine/paracrine/second messenger effects on the renal vasculature and tubules not yet fully unraveled.[38] As with prostaglandins, EETs are vasodilator agents, whereas 20-HETE is a potent renal arteriolar constrictor and may be involved in the vasoconstrictor effect of Ang II, as well as the TGF mechanism. 20-HETE also constricts vasa recta pericytes and may be involved in the control of medullary blood flow. Some evidence suggests that locally produced 20-HETE and EETs can inhibit sodium reabsorption in the proximal tubule and TAL.[39] Indeed, CYP-450 metabolites of AA may contribute to the reduced proximal tubular reabsorption seen in pressure natriuresis.

The third enzyme system that metabolizes AA, the lipoxygenase system, is activated (in leukocytes, mast cells, and macrophages) during inflammation and injury, and is not considered here.

Cyclooxygenase-2 is present in macula densa cells and has a critical role in the release of renin from juxtaglomerular cells (granular cells) in response to reduced NaCl delivery to the macula densa.[37] A low-sodium diet increases COX-2 expression in the macula densa and simultaneously increases renin secretion; the renin response is virtually abolished in COX-2 knockout mice or during pharmacologic inhibition of COX-2. It is therefore likely that the hyporeninemia observed during administration of NSAIDs is largely a consequence of COX-2 inhibition. In addition to COX-2, the enzyme prostaglandin E synthase is expressed in macula densa cells, and the principal COX-2 product responsible for enhancing renin secretion apparently is PGE_2, acting on specific receptors identified in juxtaglomerular cells; it is not clear whether PGI_2 is also synthesized in macula densa cells. As previously discussed, nNOS (type I isomer) is also present in macula densa cells and produces NO that blunts TGF.[40] NO also has a permissive role in renin secretion, although the mechanism is not understood. The increase in macula densa COX-2 expression induced by a low-sodium diet is attenuated during administration of selective nNOS inhibitors, which has led to speculation that NO is responsible for the increase in COX-2 activity and the resulting increase in juxtaglomerular renin secretion.[35] Figure 2-14 diagrams the established and proposed roles of COX-2 and nNOS in the macula densa.

Atrial Natriuretic Peptide

If blood volume increases significantly, the resulting atrial stretch stimulates the release of atrial natriuretic peptide (ANP) from atrial myocytes. This hormone increases sodium excretion, through suppression of renin and aldosterone release and a direct inhibitory effect on sodium reabsorption in the medullary collecting duct. ANP may also increase GFR because high doses cause afferent arteriolar vasodilation and mesangial cell relaxation (thus increasing K_f; see Table 2-1).

Endothelins

Endothelins are potent vasoconstrictor peptides to which the renal vasculature is exquisitely sensitive.[41] Endothelins function primarily as autocrine or paracrine agents. The kidney is a rich source of endothelins, the predominant isoform being endothelin-1 (ET-1). ET-1 is generated throughout the renal vasculature, including afferent and efferent arterioles, where it causes vasoconstriction, possibly mediated by 20-HETE, and mesangial cells, where it causes contraction

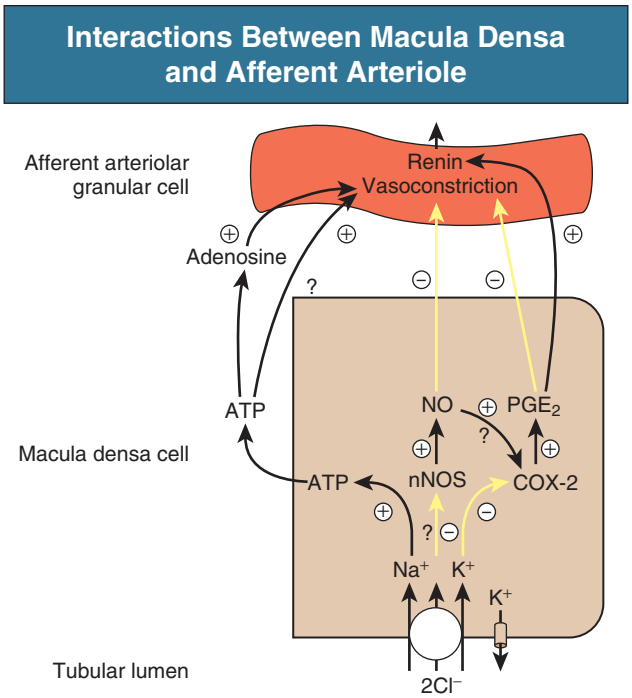

Figure 2-14 Interactions between macula densa and afferent arteriole: proposed mediators of renin secretion and tubuloglomerular feedback. Both cyclooxygenase-2 *(COX-2)* and neuronal nitric oxide synthase *(nNOS)* enzyme systems are present in macula densa cells. Increased NaCl delivery to the macula densa stimulates NaCl entry into the cells through the Na^+-K^+-$2Cl^-$ cotransporter. This causes afferent arteriolar constriction through adenosine or adenosine triphosphate *(ATP)* and also inhibits COX-2 activity; the latter effect might be mediated partly through inhibition of (nNOS-mediated) nitric oxide *(NO)* production. Generation of prostaglandin E_2 *(PGE_2)* by COX-2 stimulates renin release. PGE_2 also modulates vasoconstriction, as does NO.

(i.e., decreases K_f). Consequently, renal ET-1 can cause profound reductions in RBF and GFR (see Table 2-1).

In contrast to its effect on GFR, ET-1 can act on the renal tubule to increase urinary Na^+ and water excretion. ET-1 levels are highest in the renal medulla—in the TAL and, more prominently, the inner medullary collecting duct. The distribution of renal endothelin receptors (ET_A and ET_B) reflects the sites of production; the predominant receptor in the inner medulla is ET_B.[41] Mice with collecting duct–specific deletions of either ET-1 or ET_B receptors exhibit salt-sensitive hypertension, whereas duct-specific ET_A deletion results in no obvious renal phenotype. ET-1 knockout mice also show a greater sensitivity to vasopressin than do wild-type mice. There is mounting evidence that the natriuretic and diuretic effects of medullary ET_B stimulation are mediated by NO.[41] Taken together with evidence that ET-1 can inhibit Na^+ reabsorption in the medullary TAL (also likely mediated by NO),[33] these findings highlight the potential importance of ET-1/NO interactions in the control of Na^+ and water excretion.

Purines

Increasing evidence indicates that extracellular purines such as ATP, adenosine diphosphate (ADP), adenosine, and uric acid can act as autocrine or paracrine agents within the kidneys by activating specific cell surface receptors.[42] *Purinoceptors* are subdivided into P1 and P2 receptors. P1 receptors are responsive to adenosine and are more usually known as *adenosine receptors* (A_1, A_{2a}, A_{2b}, and A_3). P2 receptors are responsive to nucleotides (e.g., ATP, ADP) and are further subdivided into P2X (ligand-gated ion channel) and P2Y (metabotropic) receptors, each category having a number of subtypes. As indicated earlier, A_1 and $P2X_1$ receptors are found in afferent arterioles and mediate vasoconstriction. Purinoceptors are also found in the apical and basolateral membranes of renal tubular cells. Stimulation of A_1 receptors enhances proximal tubular reabsorption and inhibits collecting duct Na^+ reabsorption, whereas stimulation of P2 receptors generally has an inhibitory effect on tubular transport.[42] Thus luminally applied nucleotides, acting on a variety of P2 receptor subtypes, can inhibit Na^+ reabsorption in the proximal tubule, distal tubule, and collecting duct;[43] and stimulation of $P2Y_2$ receptors in the collecting duct inhibits vasopressin-sensitive water reabsorption.

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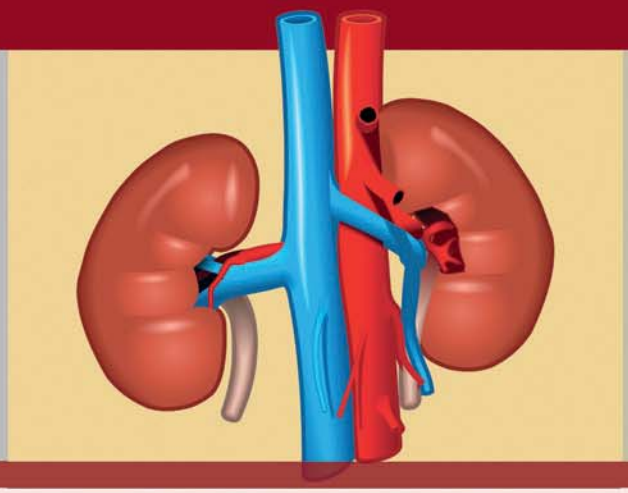

SECTION II

Investigation of Renal Disease

CHAPTER 3

Assessment of Renal Function

Lesley A. Inker, Li Fan, and Andrew S. Levey

GLOMERULAR FILTRATION RATE

Glomerular filtration rate (GFR) is a product of the average filtration rate of each nephron, the filtering unit of the kidneys, multiplied by the number of nephrons in both kidneys. The normal level for GFR is approximately 130 ml/min/1.73 m^2 for men and 120 ml/min/1.73 m^2 for women, with considerable variation among individuals according to age, gender, body size, physical activity, diet, pharmacotherapy, and physiologic states such as pregnancy. To standardize the function of the kidney for differences in kidney size, which is proportional to body size, GFR is adjusted for body surface area (BSA), computed from height and weight, and is expressed per 1.73 m^2 BSA, the mean BSA of young men and women. Even after adjustment for BSA, GFR is approximately 8% higher in young men than in women and declines with age; the mean rate of decline is approximately 0.75 ml/min/yr after age 40 years, but the variation is wide, and the sources of variation are poorly understood. During pregnancy, GFR increases by about 50% in the first trimester and returns to normal immediately after delivery. GFR has a diurnal variation and is 10% lower at midnight compared with the afternoon. Within an individual, GFR is relatively constant over time but varies considerably among people, even after adjustment for the known variables.

Reductions in GFR may result from a decline in the nephron number or in the single-nephron (SN) GFR from physiologic or hemodynamic alterations. An increase in SNGFR caused by increased glomerular capillary pressure or glomerular hypertrophy can compensate for a decrease in nephron number; therefore the level of GFR may not reflect the loss of nephrons. As a result, there may be substantial kidney damage before GFR decreases.

MEASUREMENT OF THE GLOMERULAR FILTRATION RATE

The GFR cannot be measured directly. Instead, it is measured as the urinary clearance of an ideal filtration marker.

Concept of Clearance

Clearance of a substance is defined as the volume of plasma cleared of a marker by excretion per unit of time. The clearance of substance x (C_x) can be calculated as $C_x = A_x/P_x$, where A_x is the amount of x eliminated from the plasma, P_x is the average plasma concentration, and C_x is expressed in units of volume per time. Clearance does not represent an actual volume; rather, it is a virtual volume of plasma that is completely cleared of the substance per unit of time. The value for clearance is related to the efficiency of elimination: the greater the rate of elimination, the higher the clearance. Clearance of substance x is the sum of the urinary and extrarenal clearance; for substances that are eliminated by renal and extrarenal routes, plasma clearance exceeds urinary clearance.

Urinary Clearance

The amount of substance x excreted in the urine can be calculated as the product of the urinary flow rate (V) and the urinary concentration (U_x). Therefore urinary clearance is defined as follows:

$$C_x = (U_x \times V)/P_x$$

Urinary excretion of a substance depends on filtration, tubular secretion, and tubular reabsorption. Substances that are filtered but not secreted or reabsorbed by the tubules are ideal filtration markers because their urinary clearance can be used as a measure of GFR. For substances that are filtered and secreted, urinary clearance exceeds GFR; and for substances that are filtered and reabsorbed, urinary clearance is less than GFR.

Measurement of urinary clearance requires a timed urine collection for measurement of urine volume, as well as urine and plasma concentrations of the filtration marker. Special care must be taken to avoid incomplete urine collections, which will limit the accuracy of the clearance calculation.

Plasma Clearance

Interest in measurement of plasma clearance continues because it avoids the need for a timed urine collection. GFR is calculated from plasma clearance (C_x) after a bolus intravenous injection of an exogenous filtration marker, with the clearance (C_x) computed from the amount of the marker administered (A_x) divided by the average plasma concentration (P_x), which can be computed from the area under the curve of plasma concentration versus time.

$$C_x = A_x/P_x$$

The decline in plasma levels is secondary to the immediate disappearance of the marker from the plasma into its volume of distribution (fast component) and to renal excretion (slow component). Plasma clearance is best estimated by use of a two-compartment model that requires blood sampling early (usually two or three time points until 60 minutes) and late (one to three time points from 120 minutes onward). As with urinary clearance, plasma clearance of a substance depends on filtration, tubular secretion, and tubular reabsorption, but in addition, extrarenal elimination.

Exogenous Filtration Markers

Inulin, an uncharged polymer of fructose with molecular weight of approximately 5000 daltons (d), was the first substance described as an ideal filtration marker and remains the reference (gold standard) against which other markers are evaluated. The classic protocol for inulin clearance requires a continuous intravenous (IV) infusion to achieve a steady state and bladder catheterization with multiple timed urine collections. Because this technique is cumbersome, and inulin measurement requires a difficult chemical assay, this method has not been used widely in clinical practice and remains a research

Exogenous Filtration Markers for Estimation of Glomerular Filtration Rate

Marker	Method of Administration	Comments
Inulin	Continuous IV infusion	Gold standard
Iothalamate	Bolus IV injection or subcutaneous injection	Can be administered as radioactive compound with iodine 125 (^{125}I) as the tracer or in nonradioactive form, with assay using HPLC methods. In radioactive form, potential problem of thyroid uptake of ^{125}I. Iothalamate is secreted, leading to overestimation of GFR
^{99m}Tc-DTPA	Bolus IV injection	Dissociation of ^{99m}Tc leads to plasma protein binding and underestimation of GFR
^{51}Cr-EDTA	Bolus IV injection	10% lower clearance than inulin
Iohexol	Bolus IV injection	Low incidence of adverse effects; comparable to inulin; expensive and difficult to perform assay

Table 3-1 Exogenous filtration markers for estimation of glomerular filtration rate. ^{51}*Cr-EDTA,* Chromium 51–labeled ethylenediaminetetraacetic acid; *GFR,* glomerular filtration rate; *HPLC,* high-performance liquid chromatography; *IV,* intravenous; ^{99m}*Tc-DTPA,* technetium 99m–labeled diethylenetriaminepentaacetic acid.

tool. Alternative exogenous substances include iothalamate, iohexol, ethylenediaminetetraacetic acid, and diethylenetriaminepentaacetic acid, often chelated to radioisotopes for ease of detection (Table 3-1). Alternative protocols to assess clearance have also been validated, including subcutaneous injection and spontaneous bladder emptying. There are advantages to alternative exogenous filtration markers and methods, but also limitations. Understanding the strengths and limitations of each alternative marker and each clearance method will facilitate interpretation of measured GFR.[1]

Endogenous Filtration Markers

Endogenous filtration markers are substances generated in the body at a relatively constant rate and eliminated largely by glomerular filtration. Therefore, the serum level correlates highly with measured GFR after accounting for factors other than GFR that influence the non-GFR determinants. Currently identified endogenous filtration markers include low-molecular-weight metabolites and serum proteins. Filtered metabolites may undergo reabsorption or secretion, which contribute to their urinary excretion. Comparison to urinary clearance of exogenous filtration markers enables inferences about the renal handling of endogenous filtration markers. By contrast, filtered serum proteins are reabsorbed and degraded within the tubule with minimal appearance in the urine. For filtration markers excreted in the urine, urinary clearance can be computed from a timed urine collection and a single measurement of serum concentration. If the serum level is not constant during the urine collection, as in acute kidney disease or when residual kidney function is assessed in dialysis patients, it is necessary to obtain additional blood samples during the urine collection to estimate the average serum concentration.

Creatinine is the most frequently used endogenous filtration marker in clinical practice. Urea was widely used in the past, and cystatin C presently shows great promise (Table 3-2).

Relationship of GFR and Non-GFR Determinants to Serum Levels

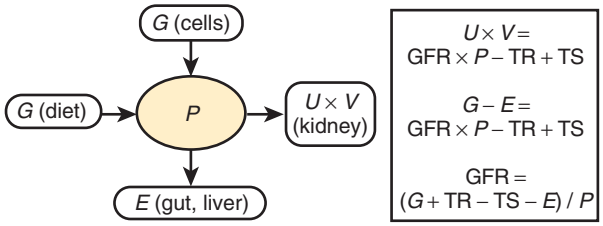

Figure 3-1 Relationship of glomerular filtration rate and non-GFR determinants to serum levels. *G,* Generation; *E,* extrarenal elimination; *P,* plasma; *TR,* tubular reabsorption; *TS,* tubular secretion. *(Modified from reference 1.)*

Estimated Glomerular Filtration Rate from Plasma Levels

Figure 3-1 shows the relationship of plasma concentration of substance x to its generation (G_x) by cells and dietary intake, urinary excretion ($U_x \times V$), and extrarenal elimination (E_x) by gut and liver. The plasma level is related to the reciprocal of the level of GFR, but it is also influenced by generation, tubular secretion and reabsorption, and extrarenal elimination, collectively termed *non-GFR determinants* of the plasma level.[1]

In the steady state, a constant plasma level of substance x is maintained because generation is equal to urinary excretion and extrarenal elimination. *Estimating equations* incorporate demographic and clinical variables as surrogates for the non-GFR determinants and provide a more accurate estimate of GFR than the reciprocal of the plasma level alone. Estimating equations are derived from regression of measured GFR on measured values of the filtration marker and observed values of the demographic and clinical variables. *Estimated* GFR (eGFR) may differ from measured GFR in a patient if a discrepancy exists between the true and average values for the relationship of the surrogate to the non-GFR determinants of the filtration marker. Other sources of errors include measurement error in the filtration marker (e.g., failure to calibrate assay for filtration marker to assay used in development of equation), measurement error in GFR in development of the equation, and regression to the mean. In principle, all these errors are likely to be greater at higher values for GFR.[2]

CREATININE

Metabolism and Excretion

Creatinine is a 113-d end product of muscle catabolism. Advantages of creatinine include its ease of measurement and the low cost and widespread availability of assays. Disadvantages include the large number of non-GFR determinants, leading to a wide range of GFR for a given serum creatinine level (see Table 3-2). For example, a serum creatinine level of 1.5 mg/dl (132 µmol/l) may correspond to a GFR from approximately 20 to 90 ml/min/1.73 m^2.

Creatinine is derived by the metabolism of phosphocreatine in muscle as well as from dietary meat intake or creatine supplements. Creatinine generation is proportional to muscle mass, which can be estimated from age, gender, race, and body size. Table 3-3 lists factors that can affect creatinine generation.[3]

Creatinine is released into the circulation at a constant rate during normal physiologic conditions. It is not protein bound and is freely

Comparison of Creatinine, Urea, and Cystatin C as Filtration Markers			
Variable	**Creatinine**	**Urea**	**Cystatin C**
Molecular Properties			
Weight (d)	113	60	13,000
Structure	Amino acid derivative	Organic molecular product of protein metabolism	Nonglycosylated basic protein
Physiologic Determinants of Serum Level			
Generation	Varies, according to muscle mass and dietary protein; lower in elderly persons, women, and whites	Varies, according to dietary protein intake and catabolism	Thought to be mostly constant by all nucleated cells; increases in hyperthyroid state and with steroid use; lower in elderly persons and women
Handling by kidney	Filtered, secreted, and excreted in urine	Filtered, reabsorbed, and excreted in urine	Filtered, reabsorbed, and catabolized
Extrarenal elimination	Yes; increases at reduced GFR	Yes; increases at reduced GFR	Preliminary evidence of increases at reduced GFR
Use In Estimating Equations for GFR			
Demographic and clinical variables as surrogates for physiologic determinants	Age, gender, and race; related to muscle mass	Not applicable	Age, gender
Accuracy	Accurate for GFR <60 ml/min/1.73 m^2	Not applicable	Unknown
Assay			
Method	Colorimetric or enzymatic	Direct measurement, enzymatic colorimetric and electrochemical	PENIA, PETIA, or ELISA
Assay precision	Very good except at low range	Precise throughout range	Precise throughout range
Clinical laboratory practice	Multiple assays; widely used nonstandard calibration	Multiple assays; enzymatic and colorimetric more common	Not on most autoanalyzers; not standardized
Standardized recommendation materials (SRMs)	SRM 967	SRM 912a	ERM-DA471/IFCC
Reference assay	IDMS	IDMS	PENIA, PETIA, or ELISA

Table 3-2 Comparison of creatinine, urea, and cystatin C as filtration markers. *ELISA,* Enzyme-linked immunosorbent assay; *GFR,* glomerular filtration rate; *IDMS,* isotope-dilution–mass spectroscopy; *PENIA,* particle-enhanced nephelometric immunoassay; *PETIA,* particle-enhanced turbidimetric immunoassay. *(Modified with permission from reference 2.)*

filtered across the glomerulus and secreted by the tubules. Several medications, such as cimetidine and trimethoprim, competitively inhibit creatinine secretion and reduce creatinine clearance. These medications thus lead to a rise in the serum creatinine concentration without an effect on GFR (Table 3-3).

In addition, creatinine is contained in intestinal secretions and can be degraded by bacteria. If GFR is reduced, the amount of creatinine eliminated through this extrarenal route is increased. Antibiotics can raise serum creatinine concentration by destroying intestinal flora, thereby interfering with extrarenal elimination, as well as by reducing the GFR. The rise in serum creatinine concentration after inhibition of tubular secretion and extrarenal elimination is greater in patients with a reduced GFR. Clinically, it can be difficult to distinguish a rise in serum creatinine concentration caused by inhibition of creatinine secretion or extrarenal elimination from a decline in GFR. However, processes other than a decrease in GFR should be suspected if serum urea concentration remains unchanged despite a significant change in serum creatinine concentration in a patient with an initially reduced GFR.

Creatinine clearance is usually computed from the creatinine excretion in a 24-hour urine collection and single measurement of serum creatinine in the steady state. Creatinine excretion rates vary with age, gender, and race and are approximately 20 to 25 mg/kg/day and 15 to 20 mg/kg/day in a complete collection in healthy young men and women, respectively. Equations are available to estimate the creatinine excretion from age, gender, weight, and other variables.[4] Deviations from these expected values can give some indication of errors in timing or completeness of urine collection. Creatinine clearance systematically overestimates GFR because of tubular creatinine secretion. In the past the amount of creatinine excreted by tubular secretion at normal levels of GFR was thought to be relatively small (10% to 15%), but with newer, more accurate assays for low values of serum creatinine, this difference may be substantially greater. At low values of GFR, the amount of creatinine excreted by tubular secretion may exceed the amount filtered.[2]

Creatinine Assay

Historically, the most common assay for measurement of serum creatinine was the alkaline picrate (Jaffe) assay that generates a color reaction. Chromogens other than creatinine are known to interfere with the assay, giving rise to errors of up to approximately 20% in normal individuals. Modern enzymatic assays do not detect noncreatinine chromogens and yield lower serum levels than with the alkaline picrate assays. Until recently, calibration of assays to adjust for this interference was not standardized across laboratories, thereby limiting the estimation of GFR from serum creatinine concentrations, especially at higher GFR.

To address the heterogeneity in creatinine assays, fresh-frozen serum pools with known creatinine levels traceable to an

Factors Affecting Serum Creatinine Concentration		
Factors	**Effect on Creatinine**	**Mechanism/Comment**
Age	Decrease	Reduced creatinine generation caused by age-related decline in muscle mass
Female gender	Decrease	Reduced creatinine generation caused by reduced muscle mass
Race		
African American	Increase	Higher creatinine generation caused by higher average muscle mass in African Americans; not known how muscle mass in other races compares with that of African Americans or Caucasians
Diet		
Vegetarian	Decrease	Decrease in creatinine generation
Ingestion of cooked meats and creatinine supplements	Increase	Transient increase in creatinine generation, although this may be blunted by transient increase in GFR
Body Habitus		
Muscular	Increase	Increased muscle generation caused by increased muscle mass and/or increased protein intake
Malnutrition, muscle wasting, amputation	Decrease	Reduced creatinine generation caused by reduced muscle mass and/or reduced protein intake
Obesity	No change	Excess mass is fat, not muscle mass, and does not contribute to increased creatinine generation.
Medications		
Trimethoprim, cimetidine, fibric acid derivatives other than gemfibrozil	Increase	Reduced tubular secretion of creatinine
Keto acids, some cephalosporins	Increase	Interference with alkaline picrate assay for creatinine

Table 3-3 Factors affecting serum creatinine concentration. *(Modified from reference 3.)*

isotope-dilution–mass spectrometry (IDMS) reference are available for instrument manufacturers to standardize creatinine measurements.[5] Use of standardized assays is recommended.[6] Standardization will reduce, but not completely eliminate, the error in estimating GFR at higher levels (Table 3-3).

Estimated Glomerular Filtration Rate from Serum Creatinine

Again, GFR can be estimated from serum creatinine by equations that use age, gender, race, and body size as surrogates for creatinine generation.[1] Despite substantial advances in the accuracy of estimating equations based on creatinine during the past several years, GFR estimates remain imprecise, and no equation is likely to overcome the limitations of creatinine as a filtration marker. None of the equations is expected to work as well in patients with extreme levels for creatinine generation, such as amputees, large or small individuals, patients with muscle-wasting conditions, or people with high or low levels of dietary meat intake (Table 3-3). Because of differences among racial and ethnic groups according to muscle mass and diet, equations developed in one racial or ethnic group are unlikely to be accurate in multiethnic populations. As discussed later, further improvements will probably require additional filtration markers.

Cockcroft-Gault Formula

The Cockcroft-Gault formula estimates creatinine clearance from age, gender, and body weight, in addition to serum creatinine (Box 3-1).[7] An adjustment factor for women is based on a theoretical assumption of 15% lower creatinine generation because of lower muscle mass. Comparison to normal values for creatinine clearance requires computation of BSA and adjustment to 1.73 m^2. Because of the inclusion of a term for "weight" in the numerator, this formula systematically overestimates creatinine clearance in edematous or obese patients.

The Cockcroft-Gault formula has three main limitations. First, it is not precise, in particular in the GFR range above 60 ml/min. Second, it estimates creatinine clearance rather than GFR and thus is expected to overestimate GFR, while normal values for creatinine secretion are not well known. Third, the formula was derived by older assay methods for serum creatinine, which cannot be calibrated to newer assay methods, which would be expected to lead to a systematic bias in estimating creatinine clearance.

Importantly, before standardization of creatinine assays, the Cockcroft-Gault formula was widely used to assess pharmacokinetic properties of drugs in patients with impaired kidney function. The accuracy of drug dosing recommendations based on the Cockcroft-Gault formula using creatinine values from modern assays remains controversial. One study suggested that drug dosage adjustment guided by the Cockcroft-Gault formula is slightly less accurate than adjustments based on more accurate estimating equations.[8]

Modification of Diet in Renal Disease Study

The Modification of Diet in Renal Disease (MDRD) study equation uses age, gender, and race (African American vs. Caucasian or other) and standardized serum creatinine to estimate GFR[9] (Box 3-1). It was derived from a study population with chronic kidney disease (CKD) and underestimates the measured GFR in populations with higher levels of GFR (Fig. 3-2). It has not been validated in children or pregnant women. The MDRD study equation had greater precision and greater overall accuracy than the Cockcroft-Gault formula. Modifications of the MDRD have now been reported in racial and ethnic populations other than African American and Caucasian, including those in China, Japan, Thailand, and South Africa.[10,11] In general, these modifications improve the accuracy of the MDRD equation in the study population but do not generalize well to other populations.

Organizations in several countries now recommend GFR estimates (eGFR) as the primary method of clinical assessment of

Equations for Estimating Glomerular Filtration Rate

Cockroft-Gault Formula[6]

Male

$$C_{cr}(\text{ml/min}) = \frac{(140 - \text{Age}) \times \text{Weight}}{72 \times S_{cr}(\text{mg/dl})} \quad \text{or} \quad C_{cr}(\text{ml/min}) = \frac{(140 - \text{Age}) \times \text{Weight}}{0.814 \times S_{cr}(\mu\text{mol/l})}$$

Female

$$C_{cr}(\text{ml/min}) = \frac{(140 - \text{Age}) \times \text{Weight} \times 0.85}{72 \times S_{cr}(\text{mg/dl})} \quad \text{or} \quad C_{Cr}(\text{ml/min}) = \frac{(140 - \text{Age}) \times \text{Weight} \times 0.85}{0.814 \times S_{cr}(\mu\text{mol/l})}$$

MDRD Study Equation for Use with Standardized Serum Creatinine (Four-Variable Equation)[8]

$$\text{GFR (ml/min/1.73 m}^2) = 175 \times \text{Standardized } S_{cr}(\text{mg/dl})^{-1.154} \times \text{Age}^{-0.203} \times 0.742 \text{ (if female)} \times 1.210 \text{ (if black)}$$

$$\text{GFR (ml/min/1.73 m}^2) = 30{,}849 \times \text{Standardized } S_{cr}(\mu\text{mol/l})^{-1.154} \times \text{Age}^{-0.203} \times 0.742 \text{ (if female)} \times 1.210 \text{ (if black)}$$

CKD-EPI Equation for Use with Standardized Serum Creatinine[11]

$$\text{GFR (ml/min/1.73 m}^2) = 141 \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{1.209} \times 0.993^{\text{Age}} \times 1.018 \text{ (if female)} \times 1.157 \text{ (if black)}$$

where κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, *min* indicates the minimum of S_{cr}/κ or 1, and *max* indicates the maximum of S_{cr}/κ or 1.

Female

$$\leq 0.7 \rightarrow \text{GFR} = 144 \times (S_{cr}/0.7)^{-0.329} \times (0.993)^{\text{Age}} \times 1.157 \text{ (if black)}$$

$$> 0.7 \rightarrow \text{GFR} = 144 \times (S_{cr}/0.7)^{-1.209}$$

Male

$$\leq 0.9 \rightarrow \text{GFR} = 141 \times (S_{cr}/0.9)^{-0.411}$$

$$> 0.9 \rightarrow \text{GFR} = 141 \times (S_{cr}/0.9)^{-1.209}$$

CKD-EPI Equation for Use with Standardized Serum Cystatin C[19]

$$\text{GFR (ml/min/1.73 m}^2) = 133 \times \min(S_{cys}/0.8, 1)^{-0.499} \times \max(S_{cys}/0.8, 1)^{-1.328} \times 0.996^{\text{Age}} \times 0.932 \text{ (if female)}$$

where *min* indicates the minimum of $S_{cys}/0.8$ or 1, and *max* indicates the maximum of $S_{cys}/0.8$ or 1.

$$\leq 0.8 \rightarrow \text{GFR} = 133 \times (S_{cys}/0.8)^{-0.499} \times 0.996^{\text{Age}} \times 0.932 \text{ (if female)}$$

$$> 0.8 \rightarrow \text{GFR} = 133 \times (S_{cys}/0.8)^{-1.328}$$

CKD-EPI Equation for Use with Standardized Serum Creatinine and Cystatin C[19]

$$\text{GFR (ml/min/1.73 m}^2) = 135 \times \min(\text{Scr}/\kappa, 1)^{\alpha} \times \max(\text{Scr}/\kappa, 1)^{-0.601} \times \min(S_{cys}/0.8, 1)^{-0.375} \times \max(S_{cys}/0.8, 1)^{-0.711} \times 0.995^{\text{Age}} \times 0.969 \text{ (if female)} \times 1.08 \text{ (if black)}$$

where κ is 0.7 for females and 0.9 for males; α is –0.248 for females and –0.207 for males; *min* indicates the minimum of S_{cr}/κ or 1, or of $S_{cys}/0.8$ or 1; and *max* indicates the maximum of Scr/κ or 1, or of $S_{cys}/0.8$ or 1.

Female

≤0.7	≤0.8	$\text{GFR} = 130 \times (S_{cr}/0.7)^{-0.248} \times (S_{cys}/0.8)^{-0.375}$	$\times 0.995^{\text{Age}}$	$\times 1.08$ (if black)
	>0.8	$\text{GFR} = 130 \times (S_{cr}/0.7)^{-0.248} \times (S_{cys}/0.8)^{-0.711}$		
>0.7	≤0.8	$\text{GFR} = 130 \times (S_{cr}/0.7)^{-0.601} \times (S_{cys}/0.8)^{-0.375}$		
	>0.8	$\text{GFR} = 130 \times (S_{cr}/0.7)^{-0.601} \times (S_{cys}/0.8)^{-0.711}$		

Male

≤0.9	≤0.8	$\text{GFR} = 135 \times (S_{cr}/0.9)^{-0.207} \times (S_{cys}/0.8)^{-0.375}$		
	>0.8	$\text{GFR} = 135 \times (S_{cr}/0.9)^{-0.207} \times (S_{cys}/0.8)^{-0.711}$		
>0.9	≤0.8	$\text{GFR} = 135 \times (S_{cr}/0.9)^{-0.601} \times (S_{cys}/0.8)^{-0.375}$		
	>0.8	$\text{GFR} = 135 \times (S_{cr}/0.9)^{-0.601} \times (S_{cys}/0.8)^{-0.711}$		

Box 3-1 Equations for estimating glomerular filtration rate. Age in years; weight in kg; S_{cr}, serum creatinine; S_{cys}, serum cystatin C. The Modification of Diet in Renal Disease (MDRD) study and Chronic Kidney Disease Epidemiology (CKD-EPI) equation calculator can also be found online at *http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm*.

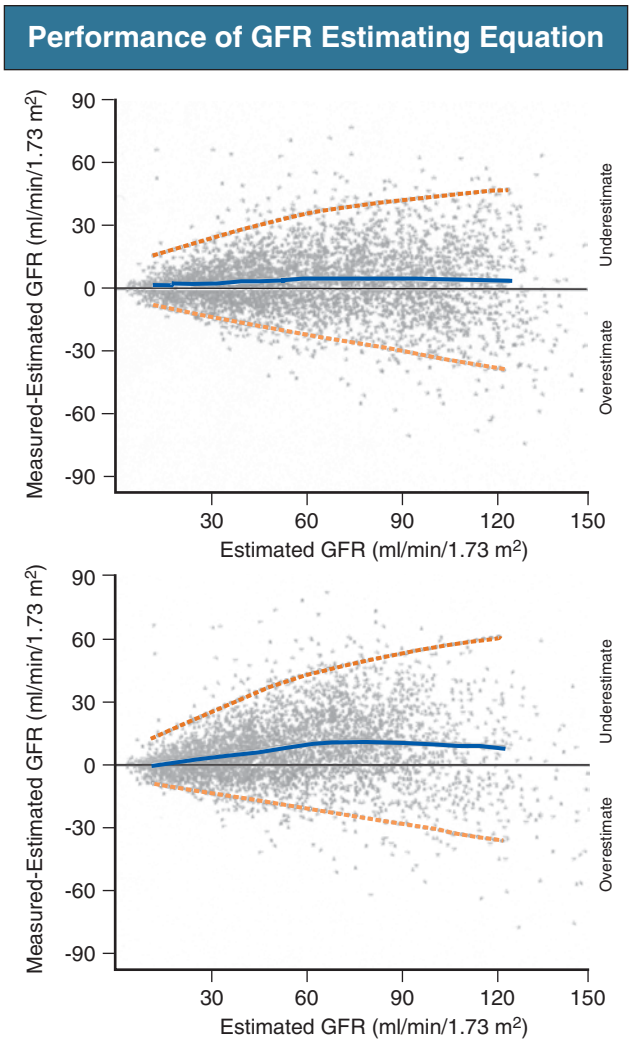

Figure 3-2 Comparison of performance of Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) study equations. Difference between measured GFR (mGFR) and estimated GFR (eGFR) versus eGFR for CKD-EPI equation *(top panel)* and MDRD equation *(bottom panel),* showing smoothed regression line and 95% confidence interval (CI, computed from lowest smoothing function in *R*) and using quantile regression, excluding lowest and highest 2.5% of eGFR values. For the two equations, median bias (percentage of estimates within 30% of measured GFR, P_{30}) is 2.5 (84) and 5.5 (81), respectively. To convert GFR from ml/min/1.73 m^2 to ml/s/m^2, multiply by 0.0167. *(Modified from reference 12.)*

kidney function.[6] Because of limitations in accuracy at higher levels, recommendations include reporting eGFR as a numerical value only if the GFR estimate is less than 60 ml/min/1.73 m^2 and reporting eGFR as "greater than 60 ml/min/1.73 m^2" for higher values.[6]

Chronic Kidney Disease Epidemiology Collaboration

The 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (Box 3-1) has been developed from a large database of participants in research studies and patients from clinical populations with diverse characteristics, including those with and without kidney disease, diabetes, and a history of organ transplantation, to overcome the limitations of the MDRD Study equation.[12] The CKD-EPI equation is based on the same four variables as the MDRD equation but uses a two-slope "spline" to model the relationship between GFR and serum creatinine, which partially corrects the underestimation of GFR at higher levels seen with the MDRD study equation. The CKD-EPI creatinine equation also incorporates slightly different relationships for age, gender, and race. As a result, the CKD-EPI equation is as accurate as the MDRD at eGFR of less than 60 ml/min/1.73 m^2 and is more accurate at higher levels (Fig. 3-2). The CKD-EPI is also more accurate across a wide range of characteristics, including age, gender, race, body mass index, and presence or absence of diabetes or history of organ transplantation. As with the MDRD, modifications of the CKD-EPI equations in Japan improve accuracy in these study populations.[11]

The CKD-EPI creatinine equation now allows reporting of eGFR across the entire range of values, without substantial bias. It is currently reported by the two major nationwide laboratories in the United States, as well as by laboratories in France. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that clinical laboratories report eGFR in all adults using CKD-EPI creatinine equations, or using other equations if shown to be superior to CKD-EPI equation in that population.[13]

UREA

The serum urea level has limited value as an index of GFR, in view of widely variable non-GFR determinants, primarily urea generation and tubular reabsorption (see Table 3-2).

Urea is a 60-d end product of protein catabolism by the liver. Factors associated with the increased generation of urea include protein loading from hyperalimentation and absorption of blood after a gastrointestinal hemorrhage. Catabolic states caused by infection, corticosteroid administration, or chemotherapy also increase urea generation. Decreased urea generation is seen in patients with severe malnutrition and liver disease.

Urea is freely filtered by the glomerulus and then passively reabsorbed in both proximal and distal nephrons. As a result of tubular reabsorption, urinary clearance of urea underestimates GFR. Reduced kidney perfusion in the patient with volume depletion and states of antidiuresis are associated with increased urea reabsorption. This leads to a greater decrease in urea clearance than the concomitant decrease in GFR. At GFR of less than about 20 ml/min/1.73 m^2, the overestimation of GFR by creatinine clearance resulting from creatinine secretion approximates the underestimation of GFR by urea clearance from urea reabsorption; thus the average of creatinine and urea clearance approximates the measured GFR.

CYSTATIN C

Metabolism and Excretion

Cystatin C is a 122–amino acid protein with molecular weight of 13 kd (see Table 3-2). Its multiple biologic functions include extracellular inhibition of cysteine proteases, modulation of the immune system, antibacterial and antiviral activities, and modification of the body's response to brain injury. The serum concentration of cystatin C remains constant from about 1 to 50 years of age. In analyses of the Third National Health and Nutrition Examination Survey (NHANES III), the median and upper 99th percentile levels of serum cystatin C for people age 20 to 39 without history of hypertension and diabetes were 0.85 mg/l and 1.12 mg/l, respectively, with levels lower in women than in men, higher in non-Hispanic whites than in blacks and Mexicans, and increasing steeply with age.[14]

Cystatin C has been thought to be produced at a constant rate by a "housekeeping" gene expressed in all nucleated cells. It is freely filtered at the glomerulus because of its small size and basic pH. Approximately 99% of the filtered cystatin C is reabsorbed by the

proximal tubular cells, where it is almost completely catabolized, with the remainder eliminated in the urine largely intact.[15] Some evidence suggests the existence of tubular secretion as well as extrarenal elimination, the latter estimated at 15% to 21% of renal clearance.[16]

Because cystatin C is not excreted in the urine, it is difficult to study its generation and renal handling. Thus, understanding non-GFR determinants of cystatin C relies on epidemiologic associations. Some suggest that inflammation, adiposity, thyroid diseases, certain malignant neoplasms, and use of glucocorticoids may increase cystatin C levels. Two studies found that key factors leading to higher cystatin C levels after adjustment for creatinine clearance or measured GFR were older age, male gender, fat mass, white race, diabetes, higher C-reactive protein level, increased white blood cell count, and lower serum albumin level.[17,18] Therefore factors other than GFR must be considered in interpreting cystatin C levels.

Cystatin C Assay

Available assays to analyze cystatin C all can result in different values. The International Federation of Clinical Chemists (IFCC) made a reference material for standardization of cystatin C, but international standardization of the assay is still in process.[19] The assays are considerably more expensive than those for creatinine determination.

Estimated Glomerular Filtration Rate from Serum Cystatin C

Numerous studies have found that serum cystatin C levels are a better estimate of GFR than serum creatinine concentration because cystatin C is less affected than creatinine by age, gender, or race. However, cystatin C or equations based on cystatin C are not more accurate than creatinine-based estimating equations, due to variation in non-GFR determinants of serum cystatin C.[20] Several studies, though, have demonstrated that equations combining both these filtration markers with age, gender, and race appear to be more precise than equations using either marker alone, probably because of smaller effects of the non-GFR determinants of both markers when used in combination. The 2012 CKD-EPI cystatin C and creatinine–cystatin C equations (see Box 3-1) are expressed for use with standardized serum creatinine and cystatin C and are recommended by the 2012 KDIGO guidelines (Fig. 3-3).[20] The equation

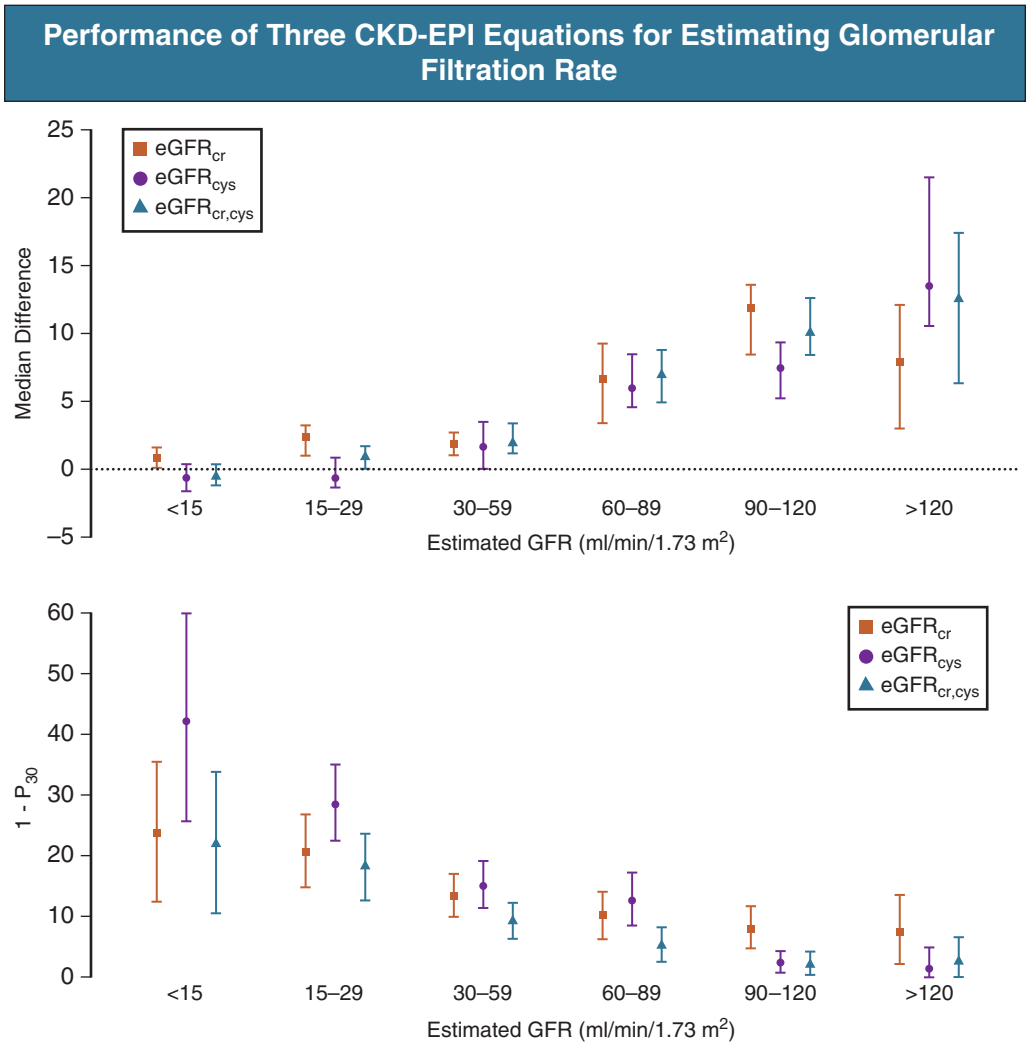

Figure 3-3 Performance of three equations for estimating GFR. GFR was estimated using the Chronic Kidney Disease Epidemiology estimating equations. *Top,* Median difference between measured GFR and estimated glomerular filtration rate *(eGFR).* The bias is similar with the equation using creatinine alone ($eGFR_{cr}$), that using cystatin C alone ($eGFR_{cys}$), and the combined creatinine–cystatin C equation ($eGFR_{cr,cys}$). *Bottom,* Accuracy of the three equations according to percentage of estimates greater than 30% of measured GFR ($1 - P_{30}$). *I bars* indicate 95% CI. *(Modified from reference 20.)*

using cystatin C without creatinine does not appear to require specification of race. Also, in patients with reduced muscle mass (e.g., neuromuscular or liver disease, low body mass index) or in patients with diabetes, cystatin C may result in more accurate GFR estimates than creatinine.

Some studies show that a lower eGFR based on serum cystatin C is a better predictor of the risk of cardiovascular disease and total mortality than is a lower eGFR based on serum creatinine concentration.[21] Whether this is caused by its superiority as a filtration marker or the confounding by non-GFR determinants of cystatin C and creatinine remains to be determined. In the future, GFR estimating equations using the combination of serum cystatin C and creatinine may be useful as a confirmatory test for CKD. However, this is feasible only after standardization, widespread availability, and cost reductions of cystatin C assays, as well as further investigation of non-GFR determinants of serum cystatin C.

OTHER FILTRATION MARKERS

β_2-Microglobulin (β_2M) and β-trace protein (βTP) are two other low-molecular-weight serum proteins being evaluated as filtration markers for estimating GFR and for their role in prognosis. However, β_2M and βTP are not recommended for use at this time. An 11.8-kd subunit of major histocompatibility complex (MHC) class I molecules, β_2M is present on all nucleated cells and plays a central role in cellular immunology. βTP, also known as lipocalin prostaglandin D_2 synthase, is a 168–amino acid glycoprotein of 23 to 29 kd. As with cystatin C, β_2M and βTP are freely filtered by the glomerulus and extensively reabsorbed and degraded by the proximal tubule, with only small amounts excreted in the urine under normal conditions.

In NHANES-III analyses, the median (upper 99th percentile) levels of serum β_2M and βTP for people age 20 to 39 without history of hypertension or diabetes were 0.52 mg/l (0.81 mg/l) and 1.59 mg/l (2.80 mg/l), respectively, with levels lower in women than in men and higher in non-Hispanic whites than in blacks and Mexicans;[22] levels were higher in older people. Several studies found correlations of serum β_2M and βTP levels with directly measured GFR that were better or similar to those observed with creatinine and that were similar to cystatin C.[23-26] In addition, studies have shown that β_2M and βTP are better predictors of adverse health outcomes than creatinine and are potentially as accurate as cystatin C in the general population and in patients with CKD.[23,27,28] However, some factors may limit their use as a filtration marker; serum β_2M concentration may be increased in several malignancies and inflammatory states, and corticosteroid administration may decrease serum βTP concentration.[28,29]

CLINICAL APPLICATION OF ESTIMATED GLOMERULAR FILTRATION RATE

Chronic Kidney Disease

Estimation of GFR is necessary for the detection, evaluation, and management of patients with CKD. Current guidelines recommend testing of patients at increased risk of CKD for albuminuria, as a marker of kidney damage, or a reduced eGFR to assess kidney function and staging of disease severity by eGFR level. Use of serum creatinine alone as an index of GFR is unsatisfactory and can lead to delays in detection of CKD and misclassification of the severity of CKD. Use of estimating equations allows direct reporting of eGFR by clinical laboratories whenever serum creatinine is measured. Current estimating equations will be less accurate in people with factors affecting serum creatinine concentration other than GFR (see Table 3-3). In these patients, more accurate GFR estimates require additional testing, such as measurement with an endogenous filtration marker (e.g., cystatin C, β_2M, βTP), a timed urine creatinine clearance measurement, or clearance measurement using an exogenous marker.

Acute Kidney Injury

In the nonsteady state, there is a lag before the rise in serum level because of the time required for retention of an endogenous filtration marker (Fig. 3-4). Conversely, after recovery of GFR, there is a lag before the excretion of the retained marker. During this time, neither the serum level nor the GFR estimated from the serum level accurately reflects the measured GFR. Nonetheless, a change in the eGFR in the nonsteady state can be a useful indication of the magnitude and direction of the change in measured GFR. If the eGFR is decreasing, the decline in eGFR is less than the decline in measured GFR. Conversely, if the eGFR is increasing, the rise in eGFR is greater than the rise in measured GFR. The more rapid the change in eGFR, the greater is the change in measured GFR. When eGFR reaches a new steady state, it more accurately reflects measured GFR. In patients with acute kidney injury, serum cystatin C appears to increase more rapidly than serum creatinine.[30] More data are required to establish whether changes in serum cystatin C are a more sensitive indicator of rapidly changing kidney function than changes in serum creatinine.

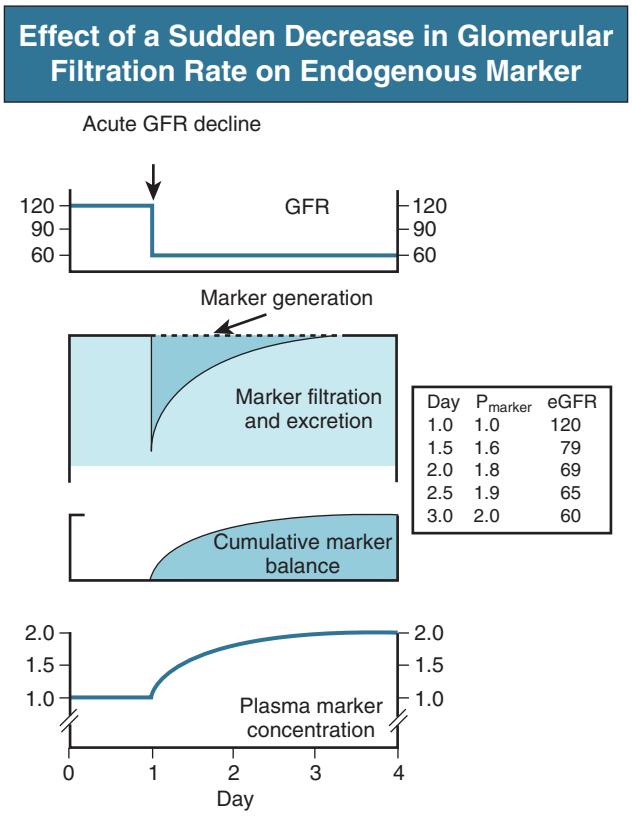

Figure 3-4 Sudden decrease in glomerular filtration rate. Graphs show effect of acute GFR decline *(top)* on generation, filtration/excretion, and balance of endogenous marker *(middle)* and concentration of plasma marker *(bottom). (Modified from reference 1.)*

MARKERS OF TUBULAR DAMAGE

The urinary excretion of low-molecular-weight serum proteins may increase when proximal tubular reabsorption is impaired, which may serve as a marker of proximal tubular damage. Examples include cystatin C and β_2M, as previously described, as well as interleukin-18 (18,000 d), retinol-binding protein (21,000 d) and α_1-macroglobulin (33,000 d). In contrast, other markers of tubular damage are produced in the kidney in response to injury, such as *N*-acetyl-β-glucosaminidase (NAG) and urinary kidney injury molecule 1 (KIM-1). Increased excretion of neutrophil gelatinase–associated lipocalin (NGAL), a 25,000-d protein in kidney disease, may reflect impaired reabsorption of filtered NGAL or increased production by the kidney. These and other urinary markers of tubular damage under investigation are discussed further in Chapter 71.

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CHAPTER 4

Urinalysis

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DEFINITION

Urinalysis is one of the key tests to evaluate kidney and urinary tract disease. When a patient is first seen by a nephrologist, urinalysis should always be performed. Dipsticks are the most widely used method for urinalysis, but the nephrologist should be aware of their limitations. Urine sediment examination is an integral part of urinalysis, which is performed routinely in general clinical laboratories. Ideally, however, urine microscopy should be performed by trained nephrologists rather than clinical laboratory personnel, who are at times unable to identify important elements,[1] and who are not always aware of the clinical correlates of the findings.[2]

This chapter describes the main aspects of urinalysis, including urine collection, evaluation of physical and chemical features of urine, and urine microscopy.

URINE COLLECTION

The way urine is collected and handled can greatly influence the results (Box 4-1). Written instructions for performing a urine collection should be given to the patient. First, strenuous physical exercise (e.g., running, soccer) should be avoided for at least 24 hours before the collection to avoid exercise-induced proteinuria and hematuria or cylindruria. In women, urinalysis should also be avoided during menstruation because blood contamination can easily occur.

If a midstream sample of the first morning urine is used, lysis of cells and casts may occur in the bladder overnight, which may lead to false-negative results at urine sediment examination. For this reason, for renal patients, we suggest performing a combined dipstick and urine microscopy on the second morning urine.

For the measurement of 24-hour protein excretion, a 24-hour urine collection is needed. Errors caused by improper timing and missed samples can lead to overcollection or undercollection of urine. Errors can be minimized by giving the patient simple written instructions. Written instructions should also be provided for other types of urine collection, such as that needed for the evaluation of orthostatic proteinuria, which implies the collection of one sample produced while the patient has been recumbent for some hours, and another sample produced while the patient has been standing.

Spot urine samples are widely recommended[3] because they are easy to obtain, although timed urines are still recommended by some authorities (see Chapter 80).

After the washing of hands, women should spread the labia of the vagina and men withdraw the foreskin of the glans. The external genitalia are washed and wiped dry with a paper towel, and the "midstream" urine is collected after the first portion is discarded. The same procedures can also be used for children. For small infants, bags for urine are often used, even though these carry a high probability of contamination. A suprapubic bladder puncture may occasionally be necessary. In special situations, urine can also be collected through a bladder catheter, although the catheter may cause hematuria. Permanent indwelling catheters are often associated with bacteriuria, leukocyturia, hematuria, and candiduria.

The container for urine should be provided by the laboratory or bought in a pharmacy. It should be clean, have a capacity of at least 50 to 100 ml, and have a diameter opening of at least 5 cm to allow easy collection. It should have a wide base to avoid accidental spillage and should be capped. The label should identify the patient as well as the hour of urine collection.

Several elements (but especially leukocytes) can lyse rapidly after collection, thus ideally the sample should be handled and examined as soon as possible. In everyday practice, we suggest the samples be analyzed within 3 hours from collection. If this is not possible, refrigeration of specimens at +4° to +8°C assists preservation but may cause precipitation of phosphates or urates, which can hamper examination. Alternatively, chemical preservatives such as formaldehyde or glutaraldehyde can be used.

PHYSICAL CHARACTERISTICS

Color

The color of normal urine ranges from pale to dark yellow and amber, depending on the concentration of the urochrome. Abnormal changes in color can be caused by pathologic conditions, drugs, or foods.

The most frequent pathologic conditions that can cause color changes of the urine are gross hematuria, hemoglobinuria, or myoglobinuria (pink, red, brown, or black urine); bilirubinuria (dark-yellow to brown urine); and massive uric acid crystalluria (pink urine). Less frequent causes are urinary infection, mainly from *Klebsiella* spp., *Proteus mirabilis, Escherichia coli, Providencia stuartii,* or *Enterococcus* spp. in patients with permanent bladder catheter (purple urine, sometimes called "purple urine bag syndrome")[4]; chyluria (white milky urine); and porphyrinuria (associated with the excretion in the urine of porphobilinogen) and alkaptonuria (red urine turning black on standing).

The main drugs responsible for abnormal urine color are rifampin (yellow-orange to red urine); desferrioxamine (pinkish urine); phenytoin (red urine); chloroquine and nitrofurantoin (brown urine); triamterene, propofol, and blue dyes of enteral feeds (green urine); methylene blue (blue urine); and metronidazole, methyldopa, and imipenem-cilastatin (darkening on standing).

Among foods are beetroot (red urine), senna and rhubarb (yellow to brown or red urine), and carotene (brown urine).

Turbidity

Normal urine is transparent. Urine can be turbid because of a high concentration of any urine particle, especially cells, crystals, and

Procedures for Preparation and Examination of Urine Sediment

- Written instructions to the patients for urine collection.
- Collection in disposable containers of the second urine of the morning after discarding the first few milliliters of urine (i.e., midstream urine).
- Sample handling and examination within 3 hours of collection.
- Centrifugation of a 10-ml aliquot of urine at 400 g for 10 minutes.
- Removal by suction of 9.5 ml of supernatant urine.
- Gentle but thorough resuspension with a Pasteur pipette of sediment in remaining 0.5 ml of urine.
- Transfer by a precision pipette of 50 µl of resuspended urine to a slide.
- Covering of sample with a 24 × 32–mm coverslip.
- Examination of the urine sediment by a phase contrast microscope at ×160 and ×400.
- Use of polarized light to identify suspected lipids and crystals.
- Matching of the microscopic findings with dipstick for pH, specific gravity, hemoglobin, leukocyte esterase, nitrites, and albumin (presence of albumin orients examination of sample toward a glomerular disease).
- Cells expressed as lowest/highest number seen per high-power field (hpf), casts as number per low-power field (lpf), and all other elements (e.g., bacteria, crystals) on scale from 0 to ++++.

Box 4-1 Preparation and examination of urine sediment. Procedures used in the authors' laboratory.

bacteria. The most frequent causes of turbidity are urinary tract infection, heavy hematuria, and contamination of urine from genital secretions. The absence of turbidity is not a reliable criterion by which to judge a urine sample because pathologic urine can be transparent.

Odor

A change in urine odor may be caused by the ingestion of some foods, such as asparagus. A pungent odor, caused by the production of ammonia, is typical of most bacterial urinary tract infection, whereas there is often a sweet or fruity odor with ketones in the urine. Some rare conditions confer a characteristic odor to the urine. These include maple syrup urine disease (maple syrup odor), phenylketonuria (musty or mousy odor), isovaleric acidemia (sweaty feet odor), and hypermethioninemia (rancid butter or fishy odor).

Relative Density

The relative density parameter can be measured by specific gravity or osmolality. *Specific gravity* (SG) refers to the weight of a volume of urine compared with the weight of the same volume of distilled water and depends on the mass and number of the dissolved particles. SG is most frequently evaluated by dipstick, which measures the ionic concentration of urine. In the presence of ions, protons are released by a complexing agent and produce a color change in the indicator bromthymol blue from blue to blue-green to yellow. Underestimation occurs with urine pH above 6.5, whereas overestimation is found with urine protein concentration above 7.0 g/L. Because nonionized molecules, such as glucose and urea, are not detected by dipstick, this method does not strictly correlate with the results obtained by refractometry and osmolality.

Refractometry measures SG through the refraction of light while it passes through a drop of urine on a glass plate. This measures the number of solutes per unit volume and measures all solutes rather than just ionic substances. Therefore, refractometry is more accurate than dipstick, despite being influenced by urine temperature, although temperature-compensated refractometers are available. Refractometers are inexpensive, simple to use, and have the major advantage of requiring only 1 drop of urine. For these reasons, we suggest the use of refractometry for everyday practice.

An SG of 1.000 to 1.003 is consistent with marked urinary dilution, as observed in patients with diabetes insipidus or water intoxication. SG of 1.010 is often called *isosthenuric* urine because it is of similar SG (and osmolality) to plasma, so it is often observed in conditions in which urinary concentration is impaired, such as acute tubular necrosis (ATN) and chronic kidney disease. SG above 1.040 almost always indicates the presence of some extrinsic osmotic agent, such as radiocontrast.

Osmolality is measured by an osmometer, which evaluates the freezing-point depression of a solution and supplies results as milliosmoles per kilogram (mOsm/kg) of water. Osmolality depends only on the number of particles present and is not influenced by urine temperature or protein concentrations. However, high glucose concentrations significantly increase osmolality (10 g/l of glucose = 55.5 mOsm/l). The measurement of osmolality is more reliable than SG by either dipstick or refractometry for the evaluation of pathologic urine.

CHEMICAL CHARACTERISTICS

Chemical characteristics of urine are most frequently evaluated by dipstick. Dipsticks have the advantages of simplicity, low cost, and stability. Disadvantages include qualitative or semiquantitative results only, susceptibility to interference by substances, and urine discoloration. When the reading is visual and not by automated instruments, the interval between removal of the dipstick from urine and the reading of results indicated by the manufacturer must be respected to avoid false results.

Sensitivity and specificity of dipsticks greatly differ among studies and depend on the brand used and different clinical conditions and patient populations investigated. False results can also be caused by the use of time-expired dipsticks. Table 4-1 summarizes the main false-negative and false-positive results that can occur with urine dipstick testing.

pH

The pH is determined by dipsticks that cover the pH range of 5.0 to 8.5 or to 9.0. With use of dipsticks, significant deviations from true pH are observed for values below 5.5 and above 7.5. Therefore, a pH meter with a glass electrode is mandatory if an accurate measurement is necessary.

Urine pH reflects the presence of hydrogen ions (H^+), but this does not necessarily reflect the overall acid load in the urine because most of the acid is excreted as ammonia. A low pH is often observed with metabolic acidosis (in which acid is secreted), with high-protein meals (which generate more acid and ammonia), and with volume depletion (in which aldosterone is stimulated, resulting in an acid urine). Indeed, low urine pH may help distinguish pre-renal acute kidney injury (AKI) from ATN, which is typically associated with a higher pH. High pH is often observed with renal tubular acidosis (especially distal, type 1; see Chapter 12), with vegetarian diets (caused by minimal nitrogen and acid generation), and with infection with urease-positive organisms (e.g., *Proteus*) that generate ammonia from urea.

Urine Dipstick Testing		
Constituent	**False-negative Results**	**False-positive Results**
Specific gravity (SG)	Urine pH >6.5	Urine protein >7.0 g/l
pH	Reduced values in presence of formaldehyde	—
Hemoglobin	Ascorbic acid High SG of urine Formaldehyde (0.5 g/l) used to preserve samples	Myoglobin Microbial peroxidases
Glucose	Ascorbic acid Bacteria	Oxidizing detergents
Albumin	Immunoglobulin light chains Tubular proteins Globulins	Urine pH ≥9.0 Quaternary ammonium detergents Chlorhexidine Polyvinylpyrrolidone
Leukocyte esterase	Glucose ≥20.0 g/l Protein >5.0 g/l Cephalothin (+++) Tetracycline (+++) Cephalexin (++) Tobramycin (+) High SG of urine	Formaldehyde (0.4 g/l) ?Imipenem ?Meropenem ?Clavulanate Abnormally colored urine
Nitrites	Bacteria that do not reduce nitrates to nitrites No vegetables in diet Short bladder incubation time	Abnormally colored urine
Ketones	Improper storage	Free sulfhydryl groups (e.g., captopril) Levodopa Abnormally colored urine

Table 4-1 Urine dipstick testing. Main false-negative and false-positive results of urine dipsticks. False results may also occur when time-expired dipsticks are used.

Measurement of urine pH is also needed for the interpretation of urinalysis (see Leukocyte Esterase and Urine Microscopy).

Hemoglobin

Hemoglobin is detected by a dipstick on the basis of the pseudoperoxidase activity of the heme moiety of hemoglobin, which catalyzes the reaction of a peroxide and a chromogen to form a colored product. The presence of hemoglobin is shown as green spots, which result from intact erythrocytes, or as a homogeneous, diffuse green pattern. This can result from marked hematuria because of the high number of erythrocytes that cover the whole pad surface; from lysis of erythrocytes favored by delayed examination, alkaline urine pH, or low SG; or from hemoglobinuria secondary to intravascular hemolysis.

False-negative results are mainly caused by (1) ascorbic acid, a strong reducing agent, which can result in low-grade microscopic hematuria being completely missed,[5] and (2) high SG.

The most important causes of false-positive results are myoglobinuria, resulting from rhabdomyolysis, and a high concentration of bacteria with pseudoperoxidase activity (Enterobacteriaceae, staphylococci, and streptococci).[6]

Glucose

Glucose is also often detected by dipstick. With glucose oxidase as catalyst, glucose is first oxidized to gluconic acid and hydrogen peroxide. Through the catalyzing activity of a peroxidase, hydrogen peroxide then reacts with a reduced colorless chromogen to form a colored product. This test detects concentrations of 0.5 to 20 g/l. When more precise quantification of urine glucose is needed, enzymatic methods such as hexokinase must be used.

False-negative results with glucose detection occur in the presence of ascorbic acid and bacteria. False-positive findings may be observed in the presence of oxidizing detergents.

Protein

Although there is no consistent definition of proteinuria,[7] it is accepted that physiologic proteinuria does not exceed 150 mg/24 h for adults and 140 mg/m^2 for children. Three different approaches can be used for the evaluation of proteinuria, as described next.

Albumin Dipstick

The albumin dipstick test is based on the presence of protein in a buffer causing a change in pH proportional to the concentration of protein itself. The dipstick changes its color, from pale green to green and blue, according to the pH changes induced by the protein. The dipstick for protein is sensitive to albumin but has a very low sensitivity to other proteins, such as tubular proteins and light-chain immunoglobulins; thus the dipstick will not detect the overflow proteinuria that can occur in myeloma. Moreover, the detection limit is 0.25 to 0.3 g/l, which may be too high to identify the early phases of kidney disease (i.e., microalbuminuria) and is influenced by hydration status (false-negative results may occur at low urine SG, and vice versa) and urine pH (false-positive results at strongly alkaline pH). Also, dipstick supplies only a semiquantitative measurement of urine albumin, which is expressed on a scale from 0 to +++ or ++++.[7] Some manufacturers also supply numerical results, although these represent only approximate quantitative measurements. Thus, for accurate quantification, other methods are needed. Recently, a creatinine test pad has been added to some dipsticks, which supplies a protein-creatinine ratio (PCR) and reduces the variability caused by changing diuresis and urine dilution.[8]

24-Hour Protein Excretion

The 24-hour urine collection for protein excretion remains the reference (gold standard) method. It is based on chemical assay (e.g., biuret or Folin-Lowry reaction), turbidimetric technique (e.g., trichloroacetic acid, benzethonium chloride, ammonium chloride), or dye-binding technique (e.g., ponceau S, Coomassie brilliant blue G-250, pyrogallol red molybdate), which quantify total proteins rather than simply albumin. The 24-hour protein excretion averages the variation of proteinuria caused by the circadian rhythm and is the most accurate for monitoring of proteinuria during treatment. However, it can be impractical in some settings (e.g., children, outpatients, elderly patients) and is subject to error from overcollection or undercollection. For this reason, we give our patients written, simple but definitive instructions on how to collect urine (see earlier discussion).

Protein-Creatinine Ratio on Random Urine Sample

This PCR is obtained by the ratio between urine protein excretion (measured by methods in 24-Hour Protein Excretion) and creatinine excretion, expressed as mg/mg or mg/mmol. PCR represents a practical alternative to the 24-hour urine collection because it is easy to obtain and is not influenced by variation in water intake or rate of

diuresis.[3] Also, the same sample can also be used for microscopic investigation.

A close correlation between the PCR in a random urine sample and the 24-hour protein excretion has been demonstrated in a wide range of patients,[7,9] including those with different types of glomerulonephritis (GN) evaluated longitudinally during treatment.[10] However, the results may be influenced by a reduced creatinine excretion because of reduced muscle mass. Thus, in elderly and female patients, PCR values can be higher than in young men. Another factor to be considered is the timing of the sample, which is influenced by the daily circadian fluctuation of protein excretion in the presence of minimal corresponding variation of creatinine excretion. Thus, the best estimates are probably obtained with morning samples, but not the first void.[11]

Some consider that a normal PCR is sufficient to rule out pathologic proteinuria, but that an elevated PCR should be confirmed and quantified with a 24-hour collection.[12] Other investigators have found poor correlation between PCR and 24-hour proteinuria at high levels of protein excretion,[10] or that PCR is an unreliable method to monitor some patients with lupus nephritis[13,14] (see also Chapter 80).

A possible alternative to PCR is the measurement of albumin-creatinine ratio (ACR), especially to screen and monitor diabetic patients.[9] However, with ACR false-negative results may occur,[15] as a consequence of the variable proportion of albumin present in the urine, which may depend on the underlying renal disease. An elevated PCR with a negative ACR for example suggests the diagnosis of myeloma.

The ratio of urinary albumin to total protein excretion (urine albumin/protein ratio, uAPR) has recently been proposed as a method to distinguish proteinuric patients with a pure glomerular disease from patients with a glomerular disease associated with tubulointerstitial damage or with a tubulointerstitial nephropathy. However, uAPR is not yet validated for routine clinical practice.[16,17]

Specific Proteins

Microalbuminuria Defined as the presence of albumin in the urine in a range of 30 to 299 mg/24 h, microalbuminuria identifies diabetic patients at increased risk of developing overt diabetic nephropathy. Also, in the general population, microalbuminuria identifies patients at increased risk of chronic kidney disease, cardiovascular morbidity, and overall mortality. The 24-hour urine collection, initially considered the gold standard method for the detection of microalbuminuria, currently has been replaced by the use of early-morning urine, which minimizes the changes caused by diurnal volume variations. A number of semiquantitative dipstick tests are available to screen for microalbuminuria.

Once microalbuminuria is found by dipstick, a standard quantitative method is then used for confirmation, usually immunoassay.[18] Because of its great simplicity, immunoturbidometry is the method most frequently used.

Tubular Proteins Low-molecular-weight tubular proteins such as α_1-microglobulin, retinol-binding protein, and β_2-microglobulin are identified by a qualitative analysis of urine proteins, using electrophoresis on cellulose acetate or agarose after protein concentration or using very sensitive stains such as silver and gold. Sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) can be used to identify tubular proteins in the urine of patients with glomerular diseases, which may have therapeutic and prognostic implications.[19]

Bence Jones Proteinuria The Bence Jones protein indicates the presence in the urine of free immunoglobulin light chains, as occurs in patients with monoclonal gammopathies. Bence Jones proteinuria is revealed by urine electrophoresis, whereas light-chain identification requires urine immunofixation.[20]

Selectivity of Proteinuria Selectivity can be assessed in nephrotic patients by the ratio of the clearance of IgG (molecular weight of 160,000 d) to the clearance of transferrin (88,000 d).[21] Although now used infrequently, highly selective proteinuria (ratio <0.1) in nephrotic children suggests the diagnosis of minimal change disease and predicts corticosteroid responsiveness.

Leukocyte Esterase

The leukocyte esterase dipstick test evaluates the presence of leukocytes based on the activity of an indoxyl esterase released from lysed neutrophil granulocytes. Leukocyte esterase may be positive when microscopy is negative and when leukocytes are lysed, because of low relative density, alkaline pH, or a delay in sample handling and examination.

False-negative results derive from high glucose (≥20 g/l) or high protein (≥5 g/l) concentration or from the presence of antibiotics such as cephalothin and tetracycline (strong inhibition), cephalexin (moderate inhibition), or tobramycin (mild inhibition). The sensitivity is also reduced by high SG because this prevents leukocyte lysis. False-positive results may occur when formaldehyde is used as a urine preservative and, according to one report, from the presence in the urine of imipenem, meropenem, or clavulanate.[22]

Nitrites

The dipstick nitrites test detects bacteria that reduce nitrates to nitrites by nitrate reductase activity. This includes most gram-negative uropathogenic bacteria, but not *Pseudomonas*, *Staphylococcus albus*, or *Enterococcus*. A positive test result also occurs with a diet rich in nitrates (vegetables), which form the substrate for nitrite production, and sufficient bladder incubation time. Thus, not surprisingly, the sensitivity of the dipstick nitrites test is low, but specificity is high.[23]

Bile Pigments

Measurement of urinary urobilinogen and bilirubin concentrations has lost its clinical value in the detection of liver disease after the introduction of serum tests of liver enzyme function.

Ketones

The ketone dipstick tests for acetoacetate and acetone (but not β-hydroxybutyrate), which are excreted into urine during diabetic acidosis or during fasting, vomiting, or strenuous exercise. It is based on the reaction of the ketones with nitroprusside.

URINE MICROSCOPY

Methods

The second urine specimen of the morning should be collected because it avoids the lysis of particles that can occur in the bladder overnight (see Urine Collection and Box 4-1). We centrifuge an aliquot of urine within 3 hours from collection and concentrate it by removal of a fixed aliquot of supernatant urine. After this, the sediment is resuspended with a Pasteur pipette, and a fixed aliquot is transferred to the slide and prepared using a coverslip with a fixed surface.

Phase contrast microscopy is recommended because it improves the identification of almost all particles, whereas polarized light is mandatory for the correct identification of some lipids and crystals.[24] At least 20 microscopic fields, in different areas of the sample, should be examined at both low magnification (e.g., ×100 or ×200) and high magnification (e.g., ×400). More extensive examination may be required in certain clinical settings, such as isolated microhematuria of unknown origin, for which we suggest examination of 50 low-power fields (lpf) to look for erythrocyte casts.

For correct examination, both pH and SG of the sample should be known. Both alkaline pH (≥7.0) and low SG (especially <1.010) favor the lysis of erythrocytes and leukocytes, which can cause discrepancies between dipstick readings and the microscopic examination (see earlier discussion). Alkaline pH also impairs the formation of casts and favors the precipitation of phosphates.

The various elements observed are quantified as number per microscopic field, and if counting chambers are used, the elements are quantified as number per milliliter. Counting chambers allow a precise quantitation but are rarely used in everyday practice.

Cells

Erythrocytes

Urinary erythrocytes have a diameter of 4 to 10 µm. In the urine, there are two main types of erythrocytes: *isomorphic,* with regular shapes and contours, derived from the urinary excretory system; and *dysmorphic,* with irregular shapes and contours, which are of glomerular origin (Fig. 4-1, *A* and *B*).[25] Thus, according to the proportion of isomorphic and dysmorphic erythrocytes found in the sample, hematuria is defined as nonglomerular or glomerular. Unfortunately, there is no agreement on the criteria to use for such classification. Some authors define glomerular hematuria as more than 80% of erythrocytes being dysmorphic; others define the discriminating cutoff as being as low as 10% or 14%.[24] Still others define hematuria as glomerular when at least 5% of erythrocytes examined are *acanthocytes,*[26] a subtype of dysmorphic erythrocytes with a distinguishing appearance easily identifiable by the presence of one or more blebs of different size and shape protruding from a ring-shaped body (Fig. 4-1, *B, inset*).

In our laboratory, glomerular hematuria is diagnosed when there are 40% or more dysmorphic erythrocytes and/or 5% or more acanthocytes and/or one or more red blood cell casts/50 lpf (×160). With this criterion, a good correlation was found between urinary sediment and renal biopsy findings in 16 patients with longstanding isolated microhematuria.[27]

Erythrocyte dysmorphism is thought to result from deformation of the erythrocytes as they pass through gaps in the glomerular basement membrane, followed by physicochemical insults occurring while the erythrocytes pass through the tubular system.[28]

The distinction between glomerular and nonglomerular hematuria is of special value in the evaluation of patients with isolated microhematuria. In these patients, it is important to decide from the early phases of the diagnostic workup whether nephrologic or urologic investigation is needed.

Leukocytes

Urinary *neutrophils* range from 7 to 15 µm in diameter and are the most frequently found leukocytes in the urine. Neutrophils are identified by their granular cytoplasm and lobulated nucleus (Fig. 4-1, *C*). In most patients, neutrophils indicate lower or upper urinary tract infection, but they may also result from urine contamination caused by genital secretions, especially in young women. Variable numbers of neutrophils are often, but not always, found in acute interstitial nephritis. Neutrophils can be found in low numbers in chronic interstitial nephritis and in proliferative GN, intermingled with high numbers of erythrocytes.[29]

Eosinophils, which can be identified only by the use of stains (e.g., Hansel), were once considered a marker of acute allergic interstitial nephritis. Currently, however, eosinophils are seen as nonspecific because they may be present in various types of GN, prostatitis, chronic pyelonephritis, urinary schistosomiasis, and cholesterol embolism (see Chapter 66).[30,31]

Lymphocytes, whose identification also requires staining of the sample, may indicate acute cellular rejection in renal allograft recipients. However, finding lymphocytes in the urine cannot replace more reliable diagnostic tools such as renal biopsy. Lymphocytes are also a typical finding in patients with chyluria.

Macrophages are mononucleated or multinucleated cells of variable size (13 to 95 µm in diameter) and variable appearance: granular (Fig. 4-1, *D*), vacuolar, phagocytic (when cytoplasm contains bacterial debris, cell fragments, destroyed erythrocytes, crystals, etc.), or homogeneous (when cytoplasm does not contain granules or other particles). In patients with the nephrotic syndrome, macrophages may be engorged with lipid droplets, appearing as "oval fat bodies."[32] Macrophages have been found in the urine of patients with active GN. In our experience, macrophages are frequently seen in the urine of kidney transplant recipients with BK virus infection (see later discussion). However, urinary macrophages are not yet considered diagnostic of any specific condition.

Renal Tubular Epithelial Cells

The renal tubular epithelial cells (RTECs) derive from the exfoliation of the tubular epithelium. In the urine, RTECs can differ in size (diameter ~9 to 25 µm) and shape, from roundish to rectangular or columnar, with a central or peripheral large nucleus (Fig. 4-1, *E*). RTECs are not found in the normal individual but can be found in all patients with conditions associated with acute tubular damage, such as ATN,[33] acute interstitial nephritis, and acute cellular rejection of a renal allograft. In smaller numbers, RTECs can also be found in glomerular diseases.[29] In ATN, these cells are frequently damaged and necrotic and may be present in casts (so-called epithelial casts).

Transitional Epithelial Cells

The transitional epithelial cells derive from the exfoliation of the uroepithelium, which lines the urinary tract from calyces to the bladder in women and to the proximal urethra in men. This multilayered epithelium has small cells in the deep layers and larger cells in the superficial layers. When present in large numbers (e.g., ≥1/high-power field [hpf]), cells of the deep epithelial layers (diameter ~10 to 38 µm; Fig. 4-1, *F*) suggest severe damage of uroepithelium, as caused by neoplasia, stones, obstruction, or longstanding bladder catheters or ureteral stents.[24] Transitional cells of the superficial layers (diameter ~17 to 43 µm; Fig. 4-1, *G*) are a common finding, being associated with mild damage of uroepithelium, as may occur in cystitis.

Squamous Epithelial Cells

The squamous epithelial cells (diameter, 17 to 118 µm; Fig. 4-1, *H*) derive from the urethra or from the external genitalia. In small numbers, squamous cells are a normal finding, but in large numbers, they indicate urine contamination from genital secretions.

Lipids

Lipids are found in the urine as *drops,* which are spherical, translucent, yellowish particles of different size that can be isolated or in

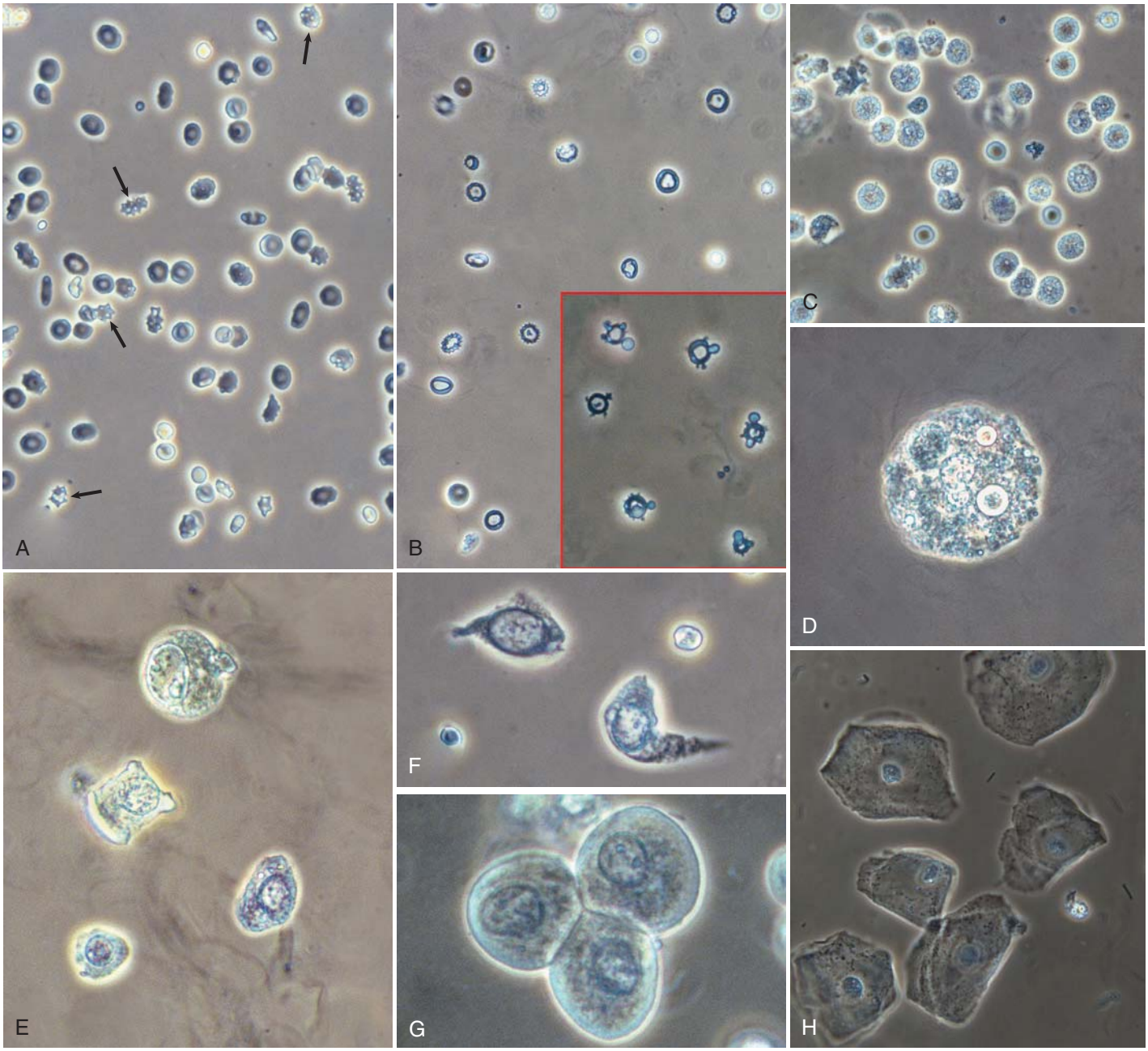

Figure 4-1 Urinary sediment cells. A, Isomorphic nonglomerular erythrocytes. The *arrows* indicate the so-called crenated erythrocytes, which are a finding in nonglomerular hematuria. **B,** Dysmorphic glomerular erythrocytes. The dysmorphism consists mainly of irregularities of the cell membrane. *Inset,* Acanthocytes, with their typical ring-formed cell bodies with one or more blebs of different sizes and shapes. **C,** Neutrophils. Note their typical lobulated nucleus and granular cytoplasm. **D,** Granular phagocytic macrophage (diameter ~60 µm). **E,** Different types of renal tubular epithelial cells. **F,** Two cells from deep layers of uroepithelium. **G,** Three cells from superficial layers of uroepithelium. Note the difference in shape, size, and ratio of nucleus to cytoplasm between the two types of uroepithelial cells. **H,** Squamous epithelial cells. (All images by phase contrast microscopy; original magnification ×400.)

clusters (Fig. 4-2, *A*); as *oval fat bodies,* which are RTECs or macrophages gorged with lipid droplets[32]; as *fatty casts,* cylindrical structures containing variable amounts of fatty droplets or even oval fat bodies; and cholesterol crystals (see Crystals). All these particles contain mainly cholesterol esters and free cholesterol and under polarized light have the appearance of Maltese crosses with symmetric arms (Fig. 4-2, *B*).

These lipids are typical of glomerular diseases associated with marked proteinuria, usually but not invariably in the nephrotic range.

In Fabry disease, urine sediment contains fatty particles even in the absence of proteinuria (see Chapter 48). These particles differ from those previously described because they contain *glycosphingolipids* (especially globotriaosylceramide-3) and have irregular shape and size, variable protrusions or an internal lamellar structure, and irregular or truncated Maltese crosses under polarized light (Fig. 4-2, *C*). It has recently been demonstrated that these fatty particles are of diagnostic importance.[34]

Casts

Casts are cylindrical structures that form in the lumen of distal renal tubules and collecting ducts. Their matrix is made of Tamm-Horsfall glycoprotein, also called uromodulin, which is secreted by

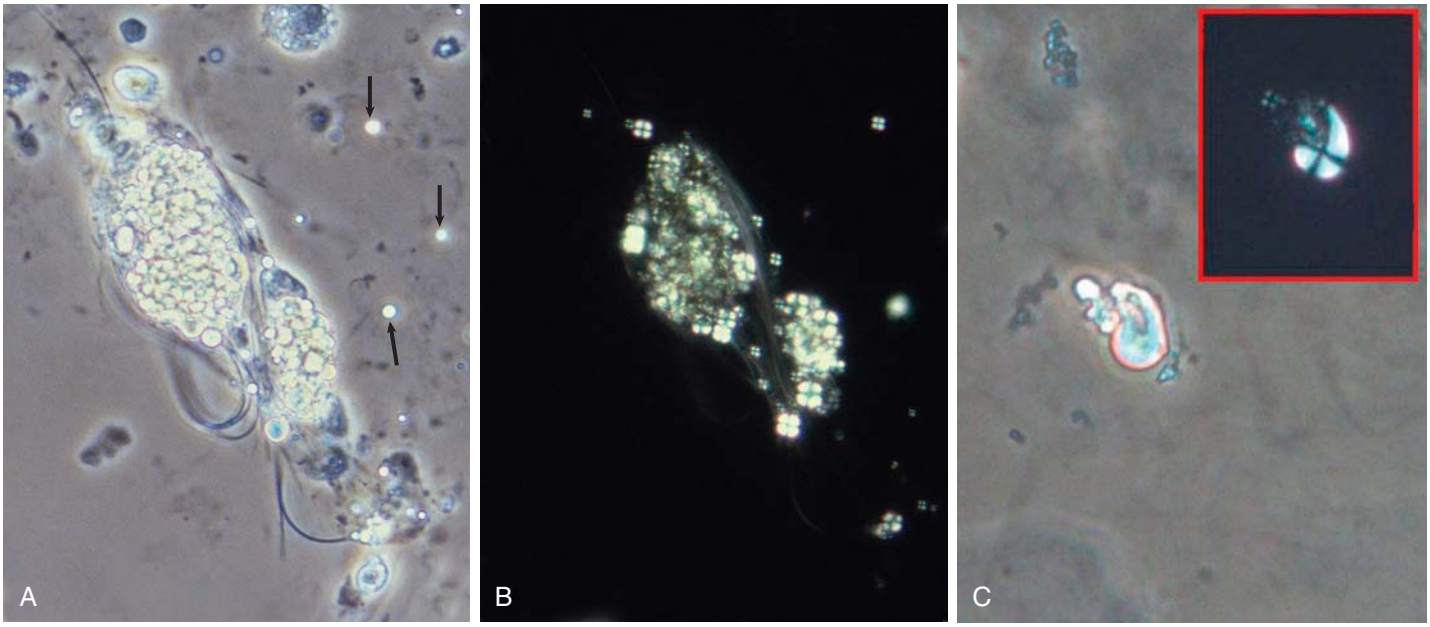

Figure 4-2 Fatty particles. A, Aggregated and isolated *(arrows)* round lipid droplets by phase contrast microscopy. **B,** Same lipid droplets in *A* under polarized light, showing typical Maltese crosses with symmetric arms. **C,** Fatty particle with protrusions, as found in Fabry disease (phase contrast microscopy). *Inset*, Same particle under polarized light. Note the truncated Maltese cross. (Original magnification ×400.)

Clinical Significance of Urinary Casts

Cast	Main Clinical Associations
Hyaline	Normal individual; renal disease
Hyaline-granular	Normal individual; renal disease
Granular	Renal disease; acute tubular necrosis
Waxy	Renal disease with function impairment
Fatty	Proteinuria; nephrotic syndrome
Erythrocyte	Glomerular hematuria; proliferative/ necrotizing GN
Leukocyte	Acute interstitial nephritis; acute pyelonephritis; proliferative GN
Renal tubular epithelial cell (so-called epithelial casts)	Acute tubular necrosis; acute interstitial nephritis; proliferative GN; nephrotic syndrome
Hemoglobin	Same as for erythrocyte cast; hemoglobinuria caused by intravascular hemolysis
Myoglobin	Rhabdomyolysis
Bilirubin	Jaundice caused by increased direct bilirubin
Bacterial, fungal	Bacterial or fungal infection in the kidney
Containing crystals	Normal individual; renal stone disease; crystalluric AKI
Mixed	According to components present in the cast

Table 4-2 Types of casts and their main clinical associations. *GN,* Glomerulonephritis; *AKI,* acute kidney injury.

the cells of the thick ascending limb of Henle loop. Trapping of particles within the cast matrix results in casts with different appearances, each of which may have specific clinical significance (Table 4-2). Because casts form in the renal tubules, whatever particle is contained in a cast derives from the kidneys. Specific casts include the following:

- *Hyaline casts* are colorless with a low refractive index (Fig. 4-3, *A*). They are easily seen with phase contrast microscopy but can be overlooked when bright-field microscopy is used. Hyaline casts may occur in normal urine, especially when it is concentrated and acid (both conditions favoring precipitation of Tamm-Horsfall protein). In patients with renal disease, hyaline casts are usually associated with other types of casts.
- *Hyaline-granular casts* contain variable amounts of granules within the hyaline matrix (Fig. 4-3, *B*) and are the most common mixed casts (described later). Hyaline-granular casts are rare in normal individuals but are common in patients with renal diseases such as GN[29] and acute interstitial nephritis.[35]
- *Granular casts* can be finely granular (Fig. 4-3, *C*) or coarsely granular. Both types are typical of renal disease. Recent studies have demonstrated that granular casts together with RTECs[33,36] or with epithelial casts[37] are a sensitive marker of ATN.
- *Waxy casts* derive their name from their appearance, which is similar to that of melted wax (Fig. 4-3, *D*). They are typically found in patients with renal disease associated with renal impairment, whether acute, rapidly progressive, or chronic.
- *Fatty casts* contain variable amounts of lipid droplets, isolated, in clumps, or packed, or even oval fat bodies or cholesterol crystals. Fatty casts are typical of glomerular diseases associated with marked proteinuria or the nephrotic syndrome.
- *Erythrocyte casts* may contain a few erythrocytes (Fig. 4-3, *E*) or so many that the matrix of the cast cannot be identified. Erythrocyte casts are usually considered a marker of glomerular bleeding, even though a recent report found them in 28% of patients with acute interstitial nephritis.[35]
- *Hemoglobin casts* have a brownish hue and usually a coarsely granular appearance, which derives from the degradation of erythrocytes entrapped within the cast matrix (Fig. 4-3, *F*). Therefore, hemoglobin casts have the same clinical significance as erythrocyte casts. Hemoglobin casts may also derive from hemoglobinuria, as may occur in intravascular hemolysis from any cause. In these patients, hemoglobin casts have a smooth surface.

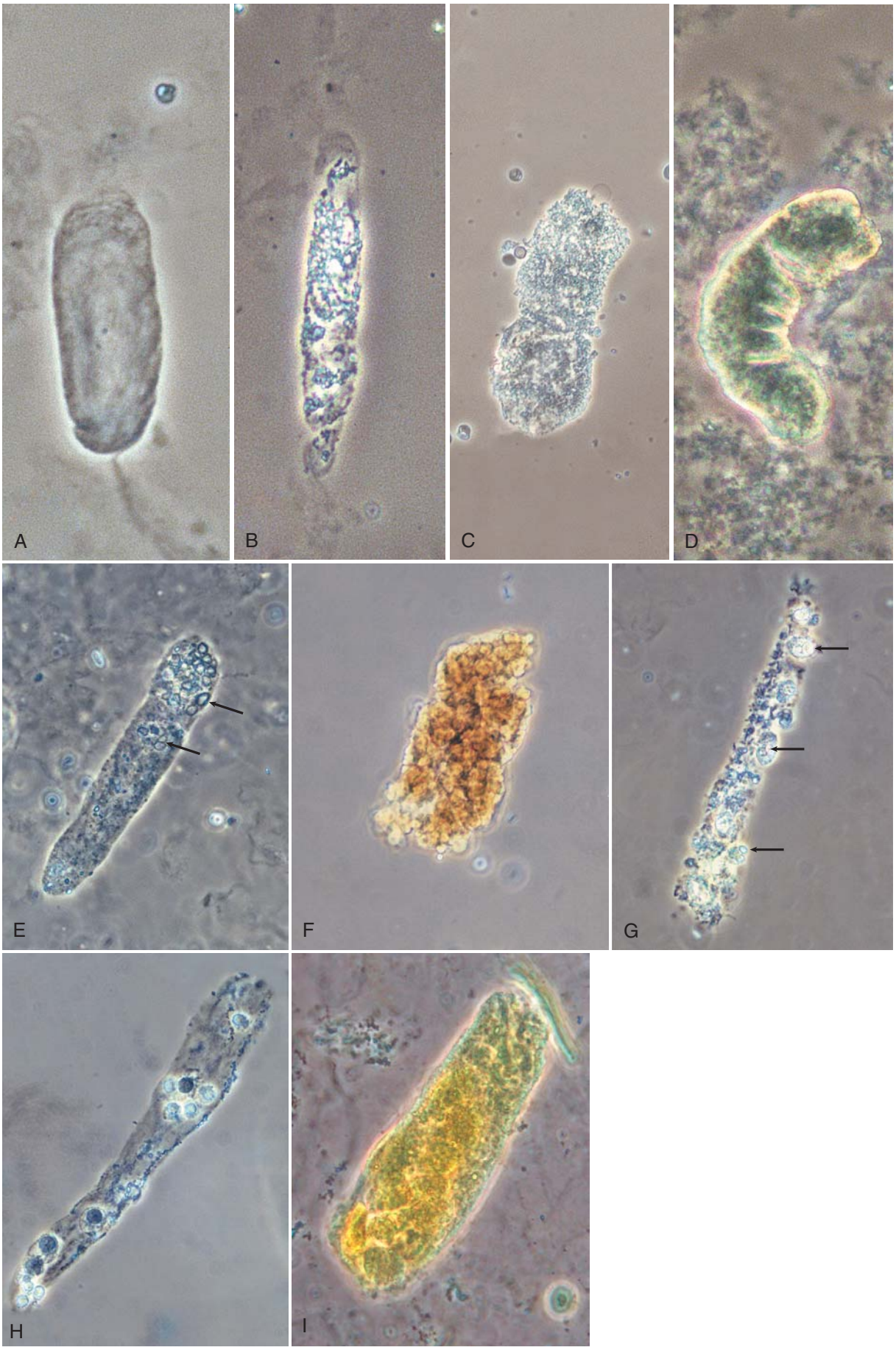

Figure 4-3 **Casts. A,** Hyaline cast. **B,** Hyaline-granular cast. **C,** Finely granular cast. **D,** Waxy cast. **E,** Erythrocyte cast, with erythrocytes *(arrows)* plunged into the cast matrix. **F,** Hemoglobin cast with a coarsely granular appearance and typical brownish hue. **G,** Leukocyte cast. Note the lobulated nucleus of polymorphonuclear leukocytes *(arrows)*. **H,** Epithelial cell cast. Note the large nucleus of the renal tubular epithelial cells. **I,** Bilirubin cast with a coarsely granular appearance and typical yellow color. (All images by phase contrast microscopy; original magnification ×400.)

- *Leukocyte casts* contain variable amounts of polymorphonuclear leukocytes (Fig. 4-3, *G*). They can be found in patients with acute pyelonephritis and acute interstitial nephritis, but are rare in GN.[29]
- *Renal tubular epithelial cell casts* (so-called epithelial casts) contain variable numbers of RTECs, which can be identified by their prominent nucleus (Fig. 4-3, *H*). Epithelial casts indicate damage of the renal tubular epithelium and can therefore be found in the urine of patients with ATN,[37] acute interstitial nephritis, and even glomerular disease.[29]
- *Myoglobin casts* are pigmented cylinders, with the myoglobin providing their color. They may be similar to hemoglobin casts (Fig. 4-3, *F*), from which myoglobin casts can be distinguished by the clinical setting. Myoglobin casts are observed in the urine of patients with AKI associated with rhabdomyolysis.
- *Bilirubin casts* are cylinders pigmented with bilirubin, which can stain any particle contained in the cast (Fig. 4-3, *I*). They are observed in the urine of patients with jaundice associated with increased direct (conjugated) bilirubin.
- Casts containing microorganisms (bacteria and yeasts) indicate renal infection.
- Casts containing crystals indicate that crystals derive from the renal tubules. Crystal casts are an important diagnostic element in crystalluric forms of AKI, such as acute urate nephropathy.
- *Mixed casts* contain components of different nature, such as granules, cells, and lipids. This causes the appearance of pleomorphic cylinders, whose clinical significance is the same as that for the pure types of casts, of which mixed casts contain some components.

Crystals

Correct identification of urine crystals requires knowledge of crystal morphology, urine pH, and appearance under polarizing light. Examination of the urine for crystals is informative in the assessment of patients with stone disease, with some rare inherited metabolic disorders (e.g., cystinuria, oxalosis, phosphoribosyltransferase deficiency), and with suspected drug nephrotoxicity.[24] Crystals can be classified in four categories: common, pathologic, caused by drugs, and other crystals.

Common Crystals

Uric Acid Crystals and Amorphous Urates Uric acid crystals have an amber color and a wide spectrum of appearances, including rhomboids and barrels (Fig. 4-4, *A*). These crystals are found only in acid urine (pH 5.0 to 5.8) and are polychromatic under polarizing light.

Amorphous urates are tiny granules of irregular shape that also precipitate in acid urine. They are identical to amorphous phosphates, which, however, precipitate in alkaline urine. In addition, whereas uric acid crystals polarize light, phosphates do not.

Calcium Oxalate Crystals There are two types of calcium oxalate crystals: bihydrated (or weddellite) crystals, which most often have a bipyramidal appearance (Fig. 4-4, *B*), and monohydrated (or whewellite) crystals, which are ovoid, dumbbell shaped, or biconcave disks (Fig. 4-4, *C*). Both types of calcium oxalate crystals precipitate at pH 5.4 to 6.7. Monohydrated crystals always polarize light, whereas bihydrated crystals usually do not.

Brushite (Calcium Phosphate Crystals) and Amorphous Phosphates Brushite crystals are pleomorphic, appearing as prisms, star-like particles, or needles of various sizes and shapes (Fig. 4-4, *D*). Brushite crystals can also appear as plates with a granular surface. Calcium phosphate crystals precipitate in alkaline urine (pH ≥7.0) and, with the exception of plates, polarize light intensely.

Amorphous phosphates are tiny particles identical to amorphous urates, but these phosphates precipitate at a pH of 7.0 or higher and do not polarize light.

Struvite (Triple Phosphate) Crystals Struvite crystals contain magnesium ammonium phosphate and typically have the appearance of "coffin lids" (Fig. 4-4, *E*). Triple phosphate crystals are found in alkaline urine (pH ≥7.0) and almost always polarize light strongly.

Pathologic Crystals

Cholesterol Crystals Cholesterol crystals are thin, transparent plates, often clumped together, with sharp edges (Fig. 4-4, *F*).

Cystine Crystals Cystine crystals occur in patients with cystinuria and are hexagonal plates with irregular sides that are often heaped on one another (Fig. 4-4, *G*). They precipitate in acid urine. Evaluation of their size can be used to predict the recurrence of cystine stones.[38]

2,8-Dihydroxyadenine Crystals These spherical, brownish crystals have a central umbilicus and a birefringent cross-like appearance under polarized light (Fig. 4-4, *H*).[39] 2,8-Dihydroxyadenine crystals are a marker of homozygotic deficiency of the enzyme adenine phosphoribosyltransferase. This rare condition causes crystalluria in about 96% of untreated patients, who frequently also have radiolucent urinary stone formation, AKI, or chronic kidney disease.[39,40]

Other rare pathologic crystals are *tyrosine,* found in patients with acute liver disease and the rare hereditary disease tyrosinemia, and *leucine,* found in acute liver disease.

Crystals Caused by Drugs

Many drugs can cause crystalluria, especially in a setting of drug overdose, dehydration, or hypoalbuminemia in the presence of a specific urinary pH favoring drug crystallization. Examples include the antibiotics sulfadiazine, amoxicillin (Fig. 4-4, *I*), and ciprofloxacin (Fig. 4-4, *J*)[24]; the antiviral agents acyclovir and indinavir (Fig. 4-4, *K*); the vasodilators pyridoxylate and naftidrofuryl oxalate; the barbiturate primidone; the antiepileptic felbamate; the inhibitor of gastroenteric lipase orlistat; and intravenous vitamin C.[24] Most of these drugs cause crystals that are made of the drug itself, with unusual morphologies that differ from those of the crystals previously described. However, naftidrofuryl oxalate, orlistat, and vitamin C cause calcium oxalate crystals, which are indistinguishable from calcium oxalate crystals resulting from other causes.

Other Crystals

Hippuric acid crystals, calcium carbonate crystals, and ammonium biurate crystals are rare and devoid of clinical significance.

Clinical Significance of Crystals

Uric acid, calcium oxalate, and calcium phosphate (brushite) crystals may have no clinical significance because they can reflect transient supersaturation of the urine caused by ingestion of some foods (e.g., meat for uric acid, spinach or chocolate for calcium oxalate, milk or cheese for calcium phosphate) or mild dehydration. However, the persistence of calcium oxalate or uric acid crystalluria may reflect hypercalciuria, hyperoxaluria, or hyperuricosuria. In calcium stone formers, the evaluation of crystalluria may be used to assess calcium stone disease activity.[41]

Large numbers of uric acid crystals may be associated with AKI caused by acute urate nephropathy, whereas large numbers of monohydrated calcium oxalate crystals, especially with a spindle shape, may be associated with AKI from ethylene glycol intoxication.

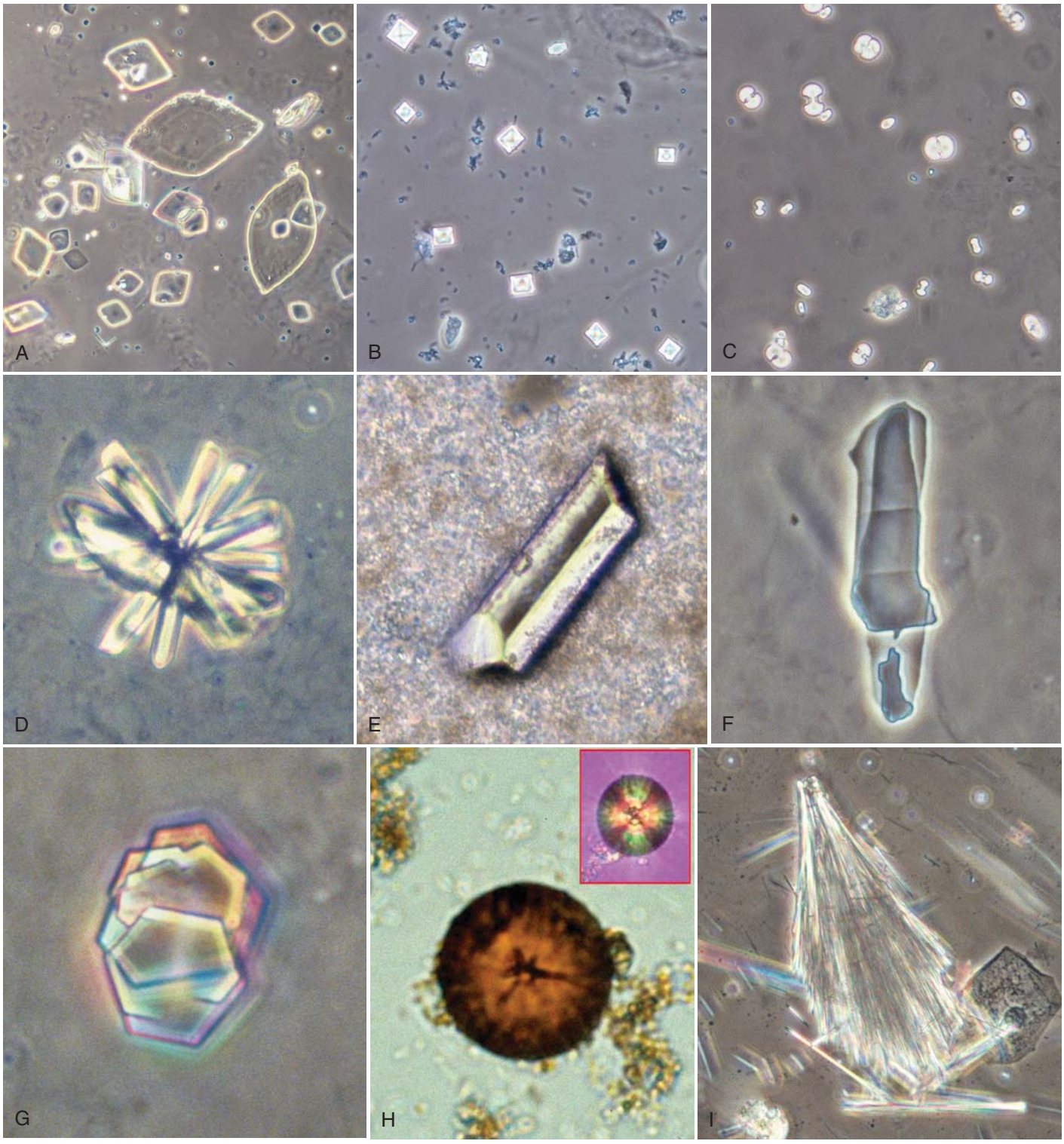

Figure 4-4 **Crystals. A,** Uric acid crystals. This rhomboid shape is the most common. **B,** Bihydrated calcium oxalate crystals with typical "letter envelope" appearance. **C,** Different types of monohydrated calcium oxalate crystals. **D,** Star-like brushite (calcium phosphate) crystal. **E,** Struvite (triple phosphate) crystal, on the background of a massive amount of amorphous phosphate particles. **F,** Cholesterol crystal. **G,** Cystine crystals heaped one on the other. **H,** 2,8-Dihydroxyadenine crystal by bright-field microscopy; *inset*, by polarized light. **I,** Amoxicillin crystal resembling a branch of a broom bush.

Figure 4-4, cont'd **J,** Star-like ciprofloxacin crystals as seen by polarized light. **K,** Large crystal of indinavir. (All images but 4-4.H and 4-4.J by phase contrast microscopy; original magnification ×400.) *(**H** courtesy Prof. Michel Daudon, Paris.)*

Struvite crystals are often associated with urinary tract infection caused by urea-splitting microorganisms such as *Ureaplasma urealyticum* and *Corynebacterium urealyticum.*

Cholesterol crystals are found in association with other fatty particles in patients with marked proteinuria. Again, cystine crystals are a marker of cystinuria, and 2,8-dihydroxyadenine crystals are associated with phosphoribosyltransferase enzyme deficiency. Crystalluria resulting from drugs must be suspected whenever crystals with unusual morphology are seen. In this setting, crystalluria may be isolated and asymptomatic or associated with hematuria, obstructive uropathy, or AKI caused by the precipitation of crystals within the renal tubules.[24]

Organisms

Bacteria are a frequent finding because urine is usually collected and handled under nonsterile conditions and examination is often delayed. Urine infection should be suspected only if bacteria are found in noncontaminated, freshly voided midstream urine and especially if leukocytes are also present. *Candida* (yeasts), *Trichomonas vaginalis* (protozoon), and *Enterobius vermicularis* (parasite) are usually present as contaminants derived from genital secretions.

The parasite *Schistosoma haematobium* is responsible for urinary schistosomiasis (see Chapter 56). The examination of the urinary sediment is the most widely used method for diagnosis of schistosomiasis, which causes microhematuria with recurrent bouts of macrohematuria and obstructive uropathy. The diagnosis is based on the finding of the parasite eggs, with their typical terminal spike (Fig. 4-5). The eggs are especially found between 10 AM and 2 PM and after physical exercise, which favors the detachment of the eggs from the bladder mucosa.

Contaminants

A large number of particles can contaminate urine. These particles may come from the patient (e.g., spermatozoa; erythrocytes from menstruation; leukocytes from vaginitis, cloth or synthetic fibers, creams or talcum), the laboratory (e.g., starch particles, glass fragments from coverslips), or the environment (e.g., pollens, plant cells, fungal spores).[24] Correct identification of these particles is important to avoid misinterpretation and false results (e.g., misdiagnosis of hematuria due to urine contamination from menstrual blood).

Figure 4-5 **Egg of *Schistosoma haematobium.*** Note the typical terminal spike *(arrow)*. (Phase contrast microscopy; original magnification ×400.)

INTERPRETATION OF URINE SEDIMENT FINDINGS

Examination of the urine sediment, coupled with the quantity of proteinuria and other urine and blood findings, results in urine sediment profiles that aid in the diagnosis of urinary tract diseases (Table 4-3).

Nephrotic Syndrome

The typical nephrotic sediment contains lipids, casts, and renal tubular epithelial cell. Fatty, epithelial, granular, hyaline, and hyaline-granular casts are seen, and erythrocyte or hemoglobin casts, leukocyte casts, and waxy casts are absent or few. Erythrocytes may be totally absent, especially in minimal change disease, or may be in low to moderate numbers (e.g., 3-5/hpf to 20-30/hpf), which is seen especially in membranous nephropathy and focal segmental glomerulosclerosis. Leukocytes are usually not found.

Nephritic Syndrome

Erythrocytes with erythrocyte and hemoglobin casts are the hallmark of the nephritic sediment. Usually, the number of erythrocytes ranges from 30 to 40 cells/hpf to more than 100 cells/hpf, with the

Main Urinary Sediment Profiles

Renal Disease	Hallmark	Associated Findings
Nephrotic syndrome (proteinuria: ++++)	Fatty particles	Renal tubular epithelial cells (RTECs) RTEC casts Erythrocytes (absent to moderate number)
Nephritic syndrome (proteinuria: + → ++++)	Erythrocytes (moderate to high number) Erythrocyte/hemoglobin casts	Leukocytes (low number) RTECs (low number) RTEC casts Waxy casts
Acute tubular necrosis (ATN; proteinuria: absent to trace)	RTECs RTEC casts Granular casts	Variable according to cause of ATN (e.g., myoglobin casts in rhabdomyolysis; uric acid crystals in acute urate nephropathy; erythrocytes in proliferative/active glomerulonephritis)
Urinary tract infection (proteinuria: absent)	Bacteria Leukocytes	Isomorphic erythrocytes Superficial transitional epithelial cells Struvite crystals (for infections caused by urease-producing bacteria) Leukocyte casts (in renal infection)
Urologic diseases (proteinuria: absent)	Isomorphic erythrocytes (low to high number) Leukocytes	Transitional cells (deep, superficial, atypical)
Polyomavirus BK infection (proteinuria: absent)	Decoy cells	Decoy cell casts (in BK virus nephropathy)

Table 4-3 **Main urinary sediment profiles.**

higher figure found especially in patients with extracapillary or necrotizing glomerular lesions. Leukocyturia is also common and is mild (e.g., 3-5/hpf) in most patients, but in those with acute postinfectious GN or active proliferative lupus nephritis, we have seen samples with up to 30 to 40 leukocytes/hpf. Leukocyte casts and waxy casts also may be observed.

The nephritic sediment may clear with treatment, but its reappearance usually indicates relapse of the disease, such as lupus nephritis[42] or systemic vasculitis.[43] Rarely, patients may have an active proliferative GN without nephritic sediment.

Acute Tubular Necrosis

RTECs associated with epithelial casts and granular casts are the hallmark of the sediment of ATN but are not found in functional pre-renal AKI.[33,36,37] In addition to RTECs, depending on the cause of the tubular damage, other elements can be seen. These include myoglobin-pigmented casts in rhabdomyolysis, uric acid crystals (usually in massive amounts) in acute uric acid nephropathy, and erythrocytes (high numbers) and erythrocyte casts in active proliferative glomerular diseases.

Urinary Tract Infection

Bacteria and leukocytes are the hallmarks of urinary tract infection, in association with superficial transitional epithelial cells and isomorphic erythrocytes. Struvite crystals can also be present when the infection is caused by urease-producing bacteria, such as *U. urealyticum* and *C. urealyticum.* In patients with renal infection, leukocyte casts and casts containing microorganisms may be found.

The correlation between the urine sediment findings and the urine culture is usually good. False-positive results may be caused by urine contamination from genital secretions or bacterial overgrowth on standing. False-negative results may be caused by the lysis of leukocytes or misinterpretation of bacteria, especially with cocci.

BK Virus Infection

The serial examination of the urinary sediment, coupled with the measurement of viremia, is useful to diagnose and monitor the reactivation of BK virus (BKV) in kidney transplant recipients,[44] an event which may lead to BKV nephropathy and graft loss (see Chapter 105). In BKV infection, the urine sediment contains variable numbers of "decoy cells," which are cells with nuclear changes caused by virus invasion. The four decoy phenotypes identified[45] are (1) nuclear ground-glass or gelatinous appearance; (2) intranuclear inclusion surrounded by a clear halo (cytomegalovirus-like); (3) multinucleated cells; and (4) vesicular nuclei with clumped chromatin and nucleoli. In addition, cells with eccentric nucleus and comet-like appearance are frequently seen in BKV infection, as well as hybrid forms that represent transitions between the different phenotypes.

Decoy cells are best identified by Papanicolaou stain performed on cytocentrifuged or smeared samples[45] (Fig. 4-6, *A*). In our experience, decoy cells can easily be seen also by phase contrast microscopy in unstained samples[46] (Fig. 4-6, *B*).

The finding of decoy cells may indicate reactivation of BKV only or BKV nephropathy. Nephropathy is suspected when the number of decoy cells is high and persistent over time or casts containing decoy cells are found, in the presence of BK viremia and renal dysfunction.[44,45,47] However, a definite diagnosis of BKV nephropathy can be obtained only with renal biopsy.

Urologic Diseases

Urinary tract disorders such as cancer, urolithiasis, and hydronephrosis are associated with the finding in the urine sediment of variable numbers of isomorphic erythrocytes, which are often associated with leukocytes or transitional epithelial cells (from deep or superficial layers of uroepithelium). In addition, in uroepithelial cancer, malignant transitional cells can be found, with abnormal size and shape, increased number and size of nuclei, and enlarged nucleoli. These cells can also be identified in unstained samples by phase contrast microscopy.

Nonspecific Urinary Abnormalities

Some urine sediment findings are nonspecific. This occurs when variable numbers of hyaline or hyaline-granular casts are found with or without low numbers of erythrocytes, leukocytes, common crystals, or small numbers of superficial transitional epithelial cells. In such patients, especially if the findings persist over time, the correct interpretation of the urinary findings requires adequate clinical information and the knowledge of other laboratory tests.

AUTOMATED ANALYSIS OF URINE SEDIMENT

Instruments for the automated analysis of the urinary sediment are based on flow cytometry or digital imaging. Flow cytometry uses

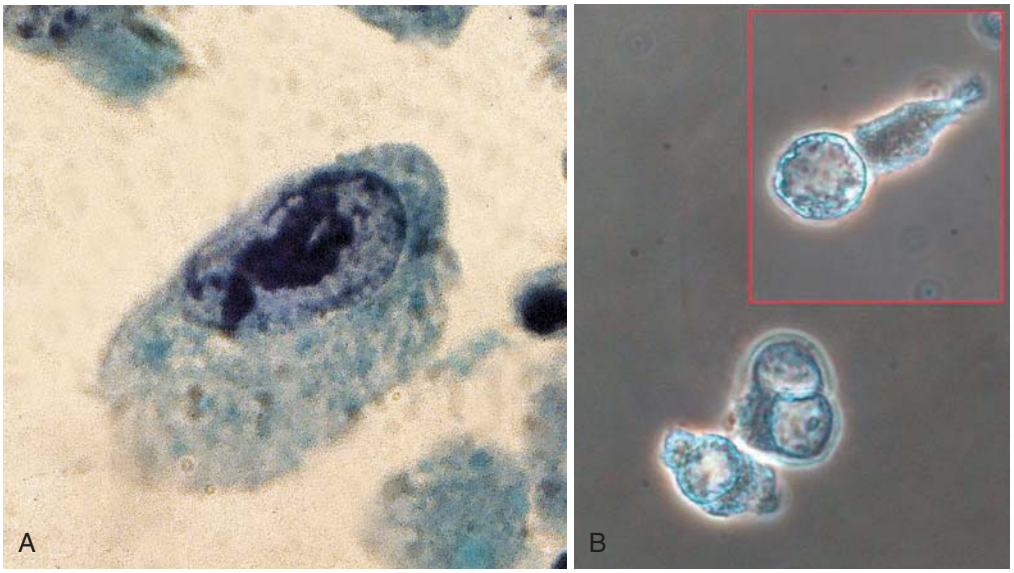

Figure 4-6 Decoy cells resulting from polyomavirus BK infection. A, Decoy cell with coarse, clumped chromatin, as seen by Papanicolaou stain. **B,** Decoy cells with the nuclear ground-glass phenotype as seen by phase contrast microscopy. *Inset*, Decoy cell with comet-like appearance. (Original magnification: **A,** ×1000; **B,** ×400.)

stains for nucleic acid and cell membranes in uncentrifuged urine samples to identify cells, bacteria, and casts.[48] Accuracy is good for leukocytes and erythrocytes, even though the erythrocytes can be overestimated because of the interference from bacteria, crystals, and yeasts. False-negative results for casts are common, ranging from about 13% to 43%.

Digital imaging systems supply quantitative results and black-and-white images of urine particles, which can be used to review the results. Currently, two main instruments are based on this technology. The first shows the particles identified on the screen by categories (e.g., all epithelial squamous cells, all crystals), with a good precision and accuracy for erythrocytes and leukocytes but rather low sensitivity for casts.[49] The other instrument supplies whole-field images, similar to those obtained by bright-field manual microscopy, and has good sensitivity for casts and epithelial cells as well.[50]

Automated instruments are now used in large laboratories to screen large numbers of samples in a short time and to identify the samples that are normal or that contain only minor changes. This approach greatly reduces the number of samples that require manual microscopy. As yet, however, these instruments do not recognize a number of particles of clinical importance, such as lipids, cellular casts, deep epithelial transitional cells, RTECs, and various types of crystals. Therefore, for the proper evaluation of the renal patient, manual microscopy with phase contrast and polarized-light devices is still the recommended approach.

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CHAPTER 5

Imaging

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Imaging evaluation of patients with renal disease has changed significantly in recent years. Intravenous urography is infrequently used and has mostly been replaced by ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine scanning. Rapidly changing computer-based data manipulation has resulted in major technologic advances in each of these modalities. Three-dimensional or even four-dimensional (time-sensitive) image analysis is now available. *Molecular imaging,* which visualizes cellular function using biomarkers, is providing functional as well as anatomic information.

The American College of Radiology (ACR) has published Appropriateness Criteria,[1] guidelines that suggest the choice of imaging to provide a rapid answer to the clinical question while minimizing cost and potential adverse effects to the patient, such as contrast-induced nephrotoxicity and radiation exposure. Tables 5-1, 5-2, and 5-3 list relative radiation exposures, first-choice imaging modalities in renal disease, and risk estimates, respectively. Risks of imaging and cost need to be balanced against benefits.

ULTRASOUND

Ultrasound is relatively inexpensive and provides a rapid way to assess renal location, contour, and size without radiation exposure. Nephrologists are increasingly undertaking straightforward ultrasound examination; the practical techniques as well as the appropriate interpretative skills are discussed in Chapter 92. Portable ultrasound is available and is essential in the pediatric or emergency setting. Obstructing renal calculi can be readily detected, and renal masses can be identified as cystic or solid. In cases of suspected obstruction, the progression or regression of hydronephrosis is readily evaluated. Color Doppler imaging permits assessment of renal vascularity and perfusion. Unlike the other imaging modalities, ultrasound is highly dependent on operator skills. Limitations of ultrasound include lack of an acoustic window, body habitus, and poor patient cooperation.

Kidney Size

The kidney is imaged in transverse and sagittal planes and is normally 9 to 12 cm in length in adults. Differences in kidney size can be detected with all imaging modalities. Figure 5-1 diagrams the common causes of enlarged and shrunken kidneys.

Renal Echo Pattern

The normal renal cortex is hypoechoic compared with the fat-containing echogenic renal sinus (Fig. 5-2, *A*). The cortical echotexture is defined as isoechoic or hypoechoic compared with the liver or spleen. In children, the renal pyramids are hypoechoic (Fig. 5-2, *B*), and the cortex is characteristically hyperechoic compared with the liver and the spleen.[2] In adults, an increase in cortical echogenicity is a sensitive marker for parenchymal renal disease but is nonspecific (Fig. 5-3). Decreased cortical echogenicity can be found in acute pyelonephritis and acute renal vein thrombosis.

The normal renal contour is smooth, and the cortical mantle should be uniform and slightly thicker toward the poles. Two common benign pseudomasses that can be seen with ultrasound are the dromedary hump and the column of Bertin. The column of Bertin results from bulging of cortical tissue into the medulla; it is seen as a mass with an echotexture similar to that of the cortex, but it is found within the central renal sinus (Fig. 5-4). The renal pelvis and proximal ureter are anechoic. An *extrarenal pelvis* refers to the renal pelvis location outside the renal hilum. The ureter is not identified beyond the pelvis in nonobstructed patients.

Obstruction can be identified by the presence of hydronephrosis (Fig. 5-5). Parenchymal and pelvicalyceal nonobstructing renal calculi as well as ureteral obstructing calculi can be readily detected (Fig. 5-6). The upper ureter will also be dilated if obstruction is distal to the pelviureteral junction (see Fig. 5-5, *C*). False-negative ultrasound examination findings with no hydronephrosis occasionally occur in early obstruction. Obstruction without ureteral dilation may also occur in retroperitoneal fibrosis and in transplanted kidneys as a result of periureteral fibrosis.

Renal Cysts

Cysts can be identified as anechoic lesions and are a frequent coincidental finding during renal imaging. Ultrasound usually readily identifies renal masses as cystic or solid (Figs. 5-7 and 5-8). However, hemorrhagic cysts may be mistakenly called solid because of increased echogenicity. Differentiation of cysts as simple or complex is required to plan intervention.

Simple Cysts

A simple cyst on ultrasound is anechoic, has a thin or imperceptible wall, and demonstrates through-transmission because of the relatively rapid progression of the sound wave through fluid compared with adjacent soft tissue.

Complex Cysts

Complex cysts contain calcifications, septations, and mural nodules. Instead of being anechoic, these masses may contain internal echoes representing hemorrhage, pus, or protein. Complex cysts may be benign or malignant; cyst wall nodularity, septations, and vascularity strongly suggest malignancy. The Bosniak classification of cystic renal masses is widely used (see Table 61-5). Complex cysts identified by ultrasound require further evaluation by contrast-enhanced CT (or MRI) to identify abnormal contrast enhancement of the cyst wall, mural nodule, or septum.

Relative Radiation Doses of Imaging Examinations	
Examination	**Effective Dose (mSv)**
Chest: PA x-ray film	0.02
Lumbar spine	1.8
KUB abdomen	0.53
CT abdomen	10
CT chest	20-40
PET-CT	25
Ultrasound or MRI	0

Table 5-1 Relative radiation doses of imaging examinations. *PA,* Posteroanterior; *mSv,* millisieverts; *KUB,* kidney, ureter, bladder (plain film); *CT,* computed tomography; *PET,* positron emission tomography; *MRI,* magnetic resonance imaging.

Recommended Imaging in Renal Disease	
Renal Pathology	**First-Choice Imaging**
Acute kidney injury, chronic kidney disease	Ultrasound
Hematuria	Ultrasound or CT
Proteinuria, nephrotic syndrome	Ultrasound CT urography
Hypertension with normal renal function	Ultrasound Consider CTA or MRA
Hypertension with impaired renal function	Ultrasound with Doppler
Renal infection	Contrast-enhanced CT
Hydronephrosis identified on ultrasound	Nuclear renogram
Retroperitoneal fibrosis	Contrast-enhanced CT
Papillary or cortical necrosis	Contrast-enhanced CT
Renal vein thrombosis	Contrast-enhanced CT
Renal infarction	Contrast-enhanced CT
Nephrocalcinosis	CT

Table 5-2 Suggested imaging in renal disease. These recommendations assume availability of all common imaging modalities. *CT,* Computed tomography; *CTA,* computed tomographic angiography; *MRA,* magnetic resonance angiography. *(Modified from reference 1.)*

Risk Estimates in Diagnostic Imaging	
Imaging Risk	**Estimated Risk**
Cancer from 10 mSv of radiation (1 body CT)[3]	1 in 1000
Contrast-induced nephropathy in patient with renal impairment[4]	1 in 5
Nephrogenic systemic fibrosis[5,6]	1 in 25,000 to 1 in 30,000 (depends on gadolinium agent) 1 in 5 if GFR <30/ml
Death from iodine contrast anaphylaxis[7]	1 in 130,000
Death from gadolinium contrast anaphylaxis[8]	1 in 280,000

Table 5-3 Risk estimates in diagnostic imaging.

Bladder

Real-time imaging can be used to evaluate for bladder wall tumors and bladder stones. Color flow Doppler evaluation of the bladder in well-hydrated patients can be used to identify a ureteral jet, produced when peristalsis propels urine into the bladder. The incoming urine has a higher specific gravity relative to the urine already in the bladder (Fig. 5-9). Absence of the ureteral jet can indicate total ureteral obstruction.

Renal Vasculature

Color Doppler investigation of the kidneys provides a detailed evaluation of the renal vascular anatomy. The main renal arteries can be identified in most patients (Fig. 5-10). Power Doppler imaging is a more sensitive indicator of flow, but unlike color Doppler imaging, power Doppler provides no information about flow direction and cannot be used to assess vascular waveforms. However, power Doppler imaging is exquisitely sensitive for detection of renal parenchymal flow and has been used to identify cortical infarction.

Renal Artery Duplex Scanning

The role of gray-scale and color Doppler sonography in screening for renal artery stenosis is controversial. The principle is that a narrowing in the artery will cause a velocity change commensurate with the degree of stenosis as well as a change in the normal renal artery waveform downstream from the lesion. The normal renal artery waveform demonstrates a rapid systolic upstroke and an early systolic peak (Fig. 5-11, *A*). The waveform becomes dampened downstream from a stenosis. This consists of a slow systolic acceleration (tardus) and a decreased and rounded systolic peak (parvus) (Fig. 5-11, *B*). It also results in a decrease in the *resistive index,* defined as the end-diastolic velocity (EDV) subtracted from the peak systolic velocity (PSV) divided by PSV: (PSV – EDV)/PSV. The normal resistive index is 0.70 to 0.72.

The entire length of the renal artery should be examined for the highest velocity signal. The origins of the renal arteries are important to identify because this area is often affected by atherosclerosis, but the arteries are often difficult to visualize because of overlying bowel gas. Within the kidney, medullary branches and cortical branches in the upper, middle, and lower thirds should be included to attempt detection of stenosis in accessory or branch renal arteries.

Proximal and distal criteria exist for diagnosis of significant renal artery stenosis, usually defined as stenosis greater than 60%. The *proximal* criteria detect changes in the Doppler signal at the site of stenosis and provide sensitivities and specificities ranging from, respectively, 0% to 98% and 37% to 98%.[9,10] Technical failure rates are typically 10% to 20%.[11] Renal artery stenosis may also be missed if PSV is low because of poor cardiac output or aortic stenosis. False-positive results can occur when renal artery velocity is increased because of high-flow states, such as hyperthyroidism or vessel tortuosity.[12] The *distal* criteria are related to detection of a tardus-parvus waveform distal to a stenosis; sensitivities and specificities of 66% to 100% and 67% to 94%, respectively, have been reported.[13,14] Technical failure with distal criteria is much lower than with proximal evaluation (<5%). False-negative results can occur from stiff poststenotic vessels, which will decrease the tardus-parvus effect.[15] The tardus-parvus effect may also be a result of aortic stenosis, low cardiac output, or collaterals in complete occlusion, giving a false-positive result.

Combining the proximal and distal criteria improves the detection of stenoses. Sensitivity of 97% and specificity of 98% can be achieved when both the extrarenal and the intrarenal arteries are examined.[16] When it is technically successful, Doppler ultrasound

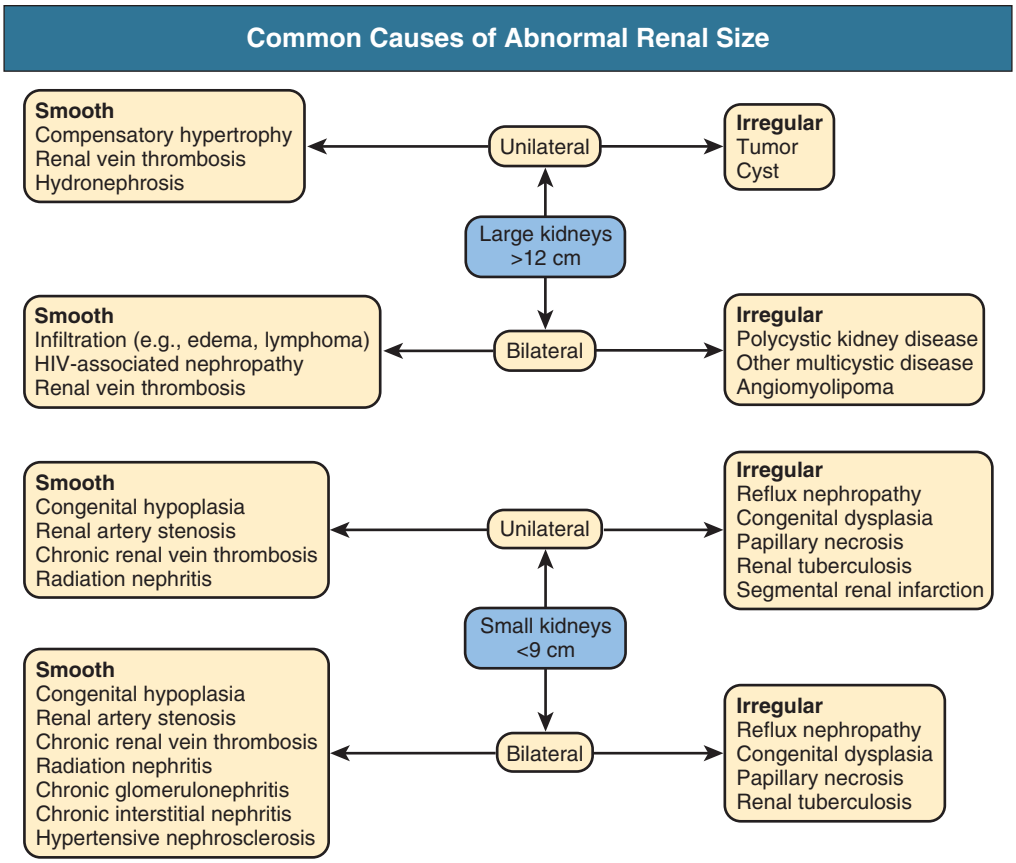


Figure 5-1 Common causes of abnormal kidney size.

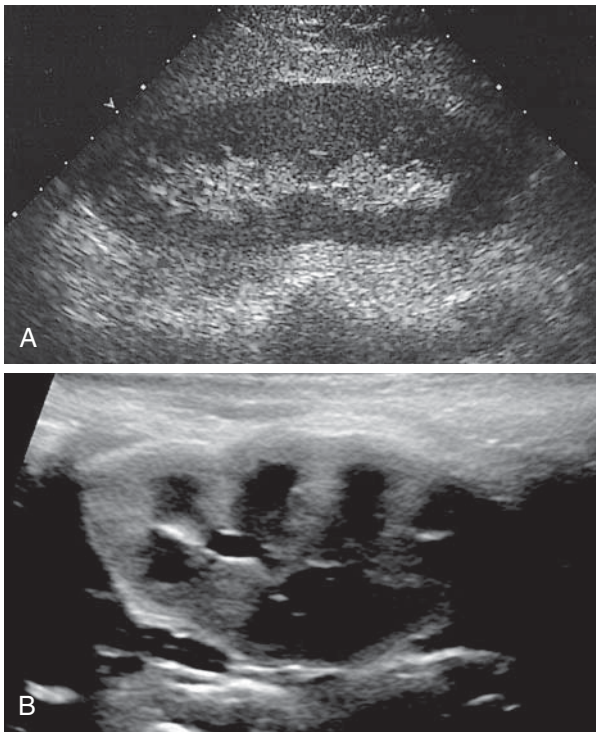


Figure 5-2 Ultrasound images of kidney. A, Normal sagittal renal ultrasound image. The cortex is hypoechoic compared with the echogenic fat containing the renal sinus. **B,** Normal renal ultrasound image in an infant. Note the hypoechoic pyramids.

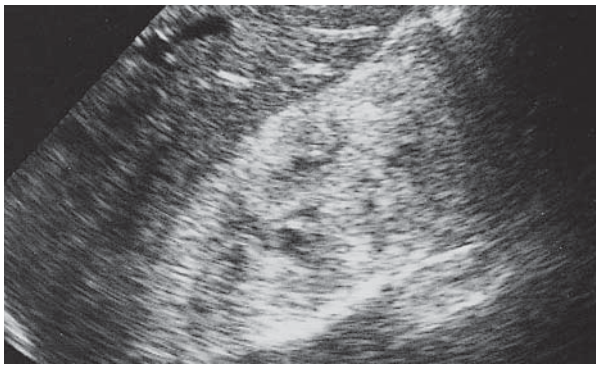


Figure 5-3 Nephropathy associated with human immunodeficiency virus (HIV). Enlarged echogenic kidney with lack of corticomedullary distinction. Bipolar length of kidney is 14.2 cm.

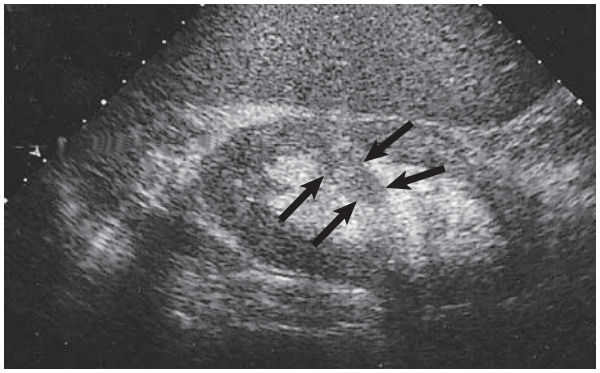


Figure 5-4 Sagittal renal ultrasound image. Column of Bertin is present *(arrows)* and is easily identified because of echotexture similar to that of renal cortex.

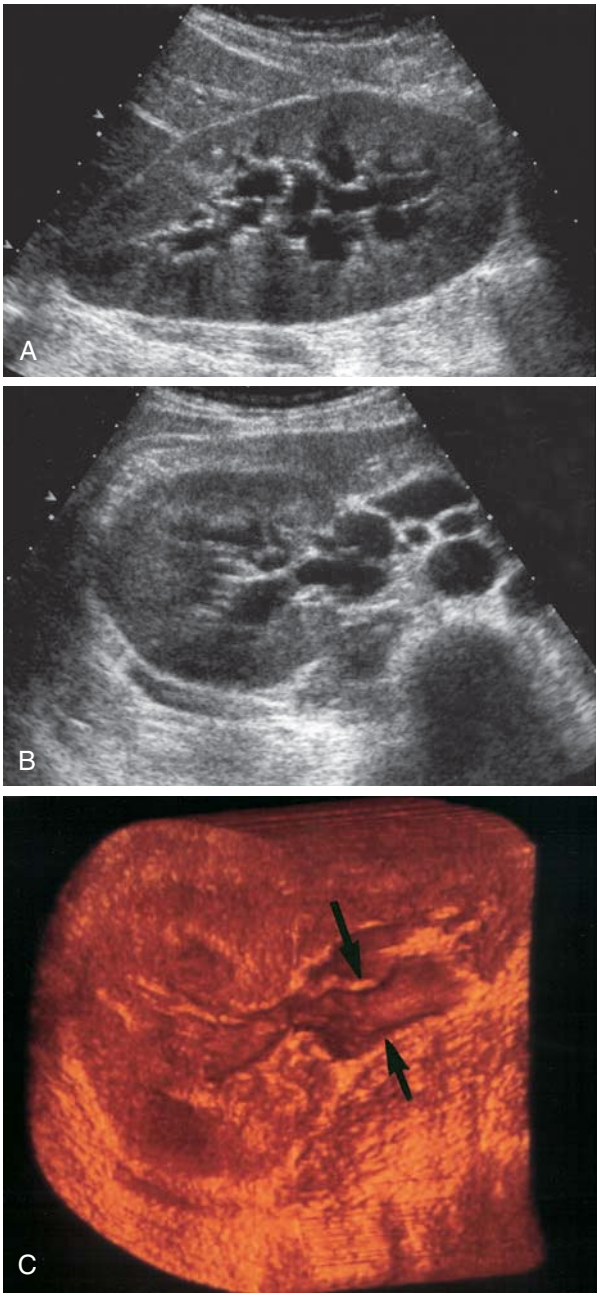


Figure 5-5 Renal ultrasound study demonstrating hydronephrosis. **A,** Sagittal ultrasound image. **B,** Transverse image. **C,** Transverse three-dimensional surface-rendered image; *arrows* indicate the dilated proximal ureter.

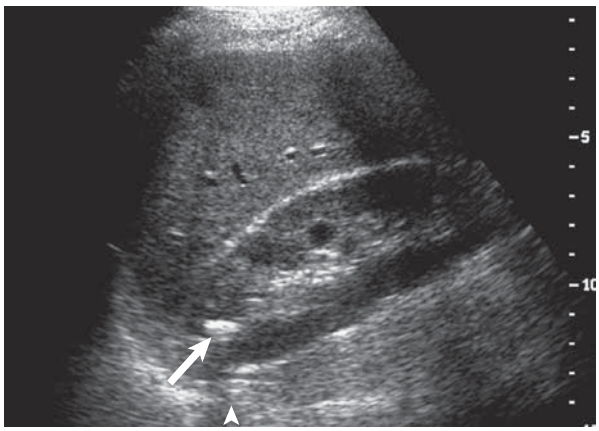


Figure 5-6 Renal calculus *(arrow)* of upper pole. Note the acoustic shadowing *(arrowhead)* on sagittal ultrasound image.

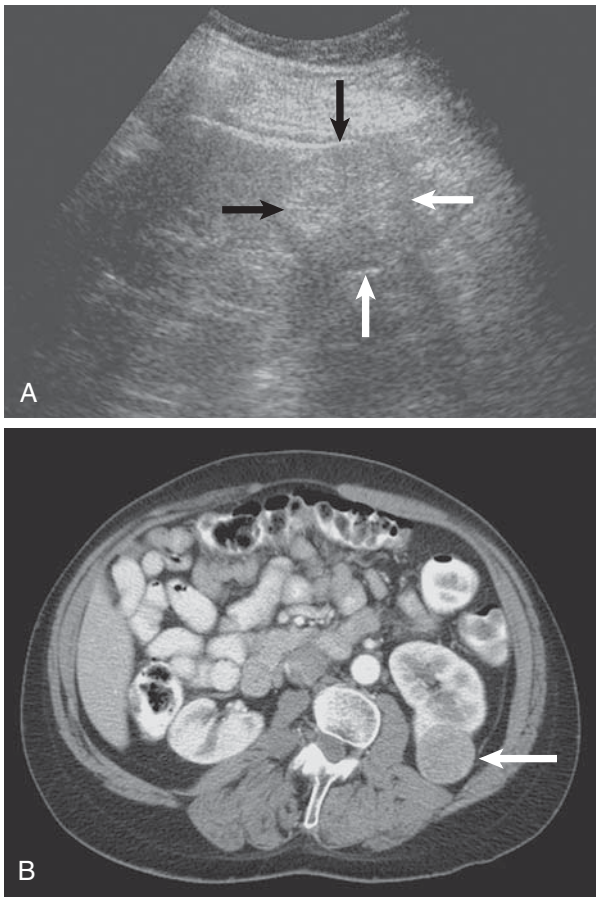


Figure 5-7 Evaluation of renal mass. A, Sagittal ultrasound image shows large hyperechoic mass arising from lower pole *(arrows)*. **B,** Corresponding contrast-enhanced CT scan shows renal cell carcinoma *(arrow)*.

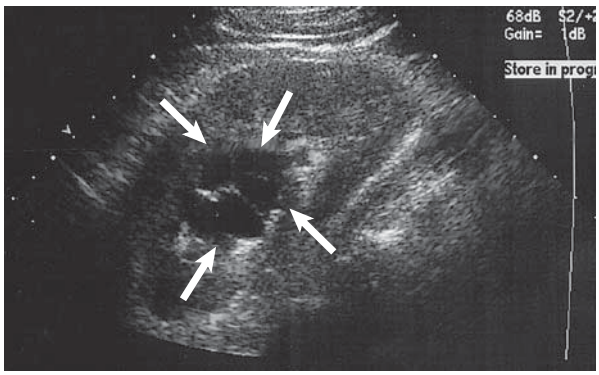


Figure 5-8 Complex renal cyst *(arrows).* Sagittal ultrasound image.

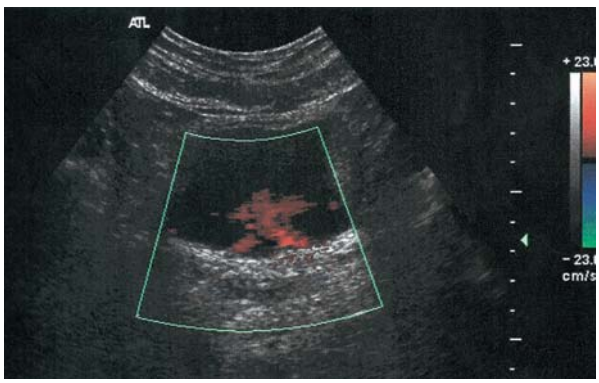


Figure 5-9 Bilateral ureteral jets in bladder. Color Doppler ultrasound study detects this normal appearance.

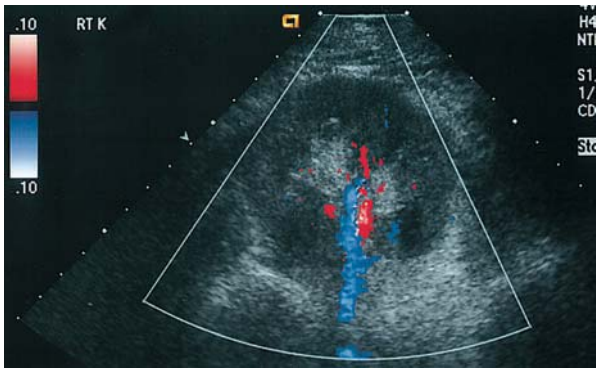


Figure 5-10 Ultrasound evaluation of kidney. Transverse color Doppler image shows the artery as *red* and the vein as *blue*.

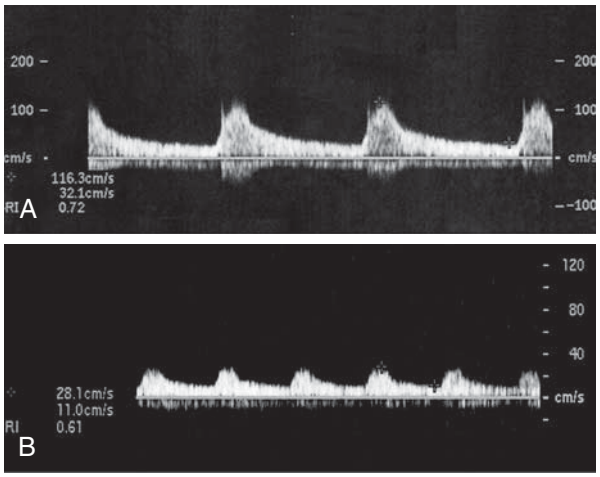
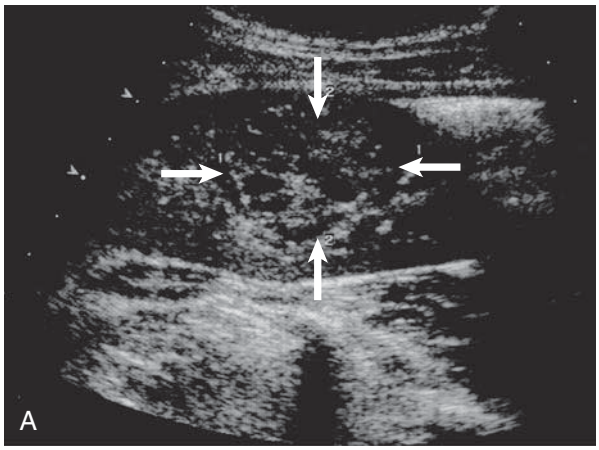


Figure 5-11 Renal artery color Doppler image and spectral tracing. A, Normal renal artery tracing shows rapid systolic upstroke and early systolic peak velocity (~100 cm/s). **B,** Tardus-parvus waveform demonstrates slow systolic upstroke (acceleration) and decreased peak systolic velocity (~20 cm/s) associated with renal artery stenosis. Note different scales on vertical axis.



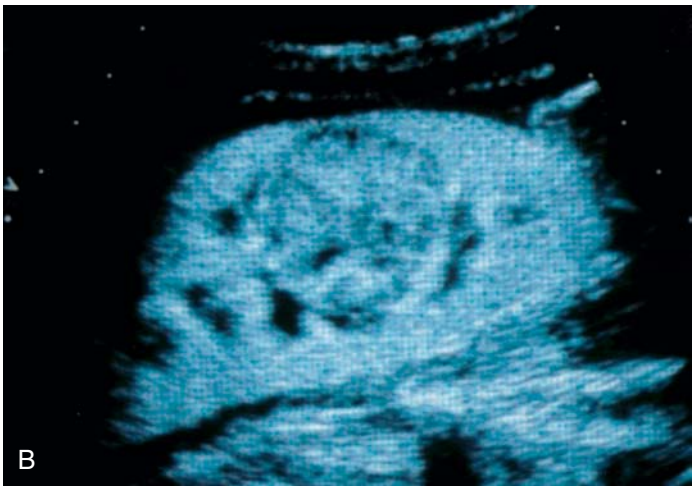


Figure 5-12 Contrast ultrasonography. A, Sagittal renal ultrasound image with a large, central renal cell cancer *(arrows)*. **B,** Central cancer better seen after injection of contrast material. *(Courtesy Dr. Christoph F. Dietrich.)*

has a negative predictive value of more than 90%.[16] However, reliable results require a skilled and experienced sonographer and a long examination time. Despite these limitations, Doppler studies also have several advantages. Noninvasive, inexpensive, and widely available, Doppler studies also allow structural and functional assessment of the renal arteries and imaging without exposure to radiation or nephrotoxic agents.

Some physicians prefer CT angiography (CTA) or magnetic resonance angiography (MRA) as a faster and more reliable screening tool than ultrasound, but at present the choice should depend on local expertise and preference. For further discussion of the diagnosis and management of renovascular disease, see Chapters 39 and 66.

Contrast-Enhanced and Three-Dimensional Ultrasound

Ultrasound contrast agents, initially introduced to assess cardiac perfusion, are now being used to evaluate perfusion to other organs, such as the kidney. These intravenous agents are microbubbles 1 to 4 μm in diameter (smaller than erythrocytes) that consist of a shell surrounding the echo-producing gas core. The microbubbles oscillate in response to the ultrasound beam frequency and give a characteristic increased echo signal on the image. Preliminary studies evaluating renal perfusion in dysfunctional kidneys show reduced flow compared with normal kidneys as well as improved lesion detection (Fig. 5-12). However, the clinical adoption of microbubble imaging in the kidney remains uncertain, particularly with the general availability and robustness of CT and MRI, and its use is off-label in the United States and not presently reimbursed.

Two-dimensional ultrasound images can be reconstructed into three-dimensional (3D) volume images by a process similar to 3D reconstructions for MRI and CT. Although the current techniques are time-consuming, technical improvements should decrease 3D reconstruction time. Potential applications include vascular imaging and fusion with MRI or positron emission tomography (PET).

PLAIN RADIOGRAPHY AND INTRAVENOUS UROGRAPHY

The use of intravenous urography (IVU) has receded as cross-sectional imaging by CT or MRI has become more widely applied to the urinary tract. Although now with few primary indications in many centers, contrast urography may still be a key investigation in parts of the world where economic limitations mean that cross-sectional imaging is not available. However, plain radiography, often called a KUB (kidneys, ureter, bladder), still has an important role

in the identification of soft tissue masses, bowel gas pattern, calcifications, and renal location.

Renal Calcification

Most renal calculi are radiodense, although only about 60% of urinary stones detected on CT are visible on plain films.[17] CT demonstrates nonopaque stones, which include uric acid, xanthine, and struvite stones. However, neither CT nor plain radiography may detect calculi associated with protease inhibitor therapy.[18] Oblique films are sometimes obtained to confirm whether a suspicious upper quadrant calcification is renal in origin. Calculi that are radiolucent on plain films are usually detected as filling defects on IVU. IVU has higher sensitivity than radiography but lower sensitivity than CT. If available, CT is the imaging modality of choice for detection of urinary calculi.[19]

Nephrocalcinosis may be medullary (Fig. 5-13, *A* and *B*) or cortical *(C)* and is localized or diffuse. The common causes of nephrocalcinosis are discussed in Chapter 59 (see Box 59-7).

Intravenous Contrast Urography

Before contrast material is administered, an abdominal compression device may be placed, to compress the midureters against the bony pelvis. This retains the excreted contrast material in the upper tract and distends the renal pelvis and calyces. The first film is usually performed at 30 seconds after contrast injection, when the renal parenchyma is at peak enhancement. Subtle renal masses are often detected only on these early films. The compression device is then removed, and films of the entire abdomen are obtained at 5 minutes, when there is renal excretion of the contrast agent and the ureters are best evaluated. Films with the patient prone may be required to visualize the entirety of the ureter. A filled-bladder film is obtained. A postvoid film of the bladder assesses emptying and assists in evaluation of the distal ureters, which may be obscured by a distended contrast-filled bladder. The usual contrast volume injected for IVU is similar to that for routine abdominal CT. The primary difference is timing of imaging. IVU is contraindicated in patients with a history of allergic reactions to radiographic contrast agents. When the glomerular filtration rate (GFR) is less than 60 ml/min, IVU

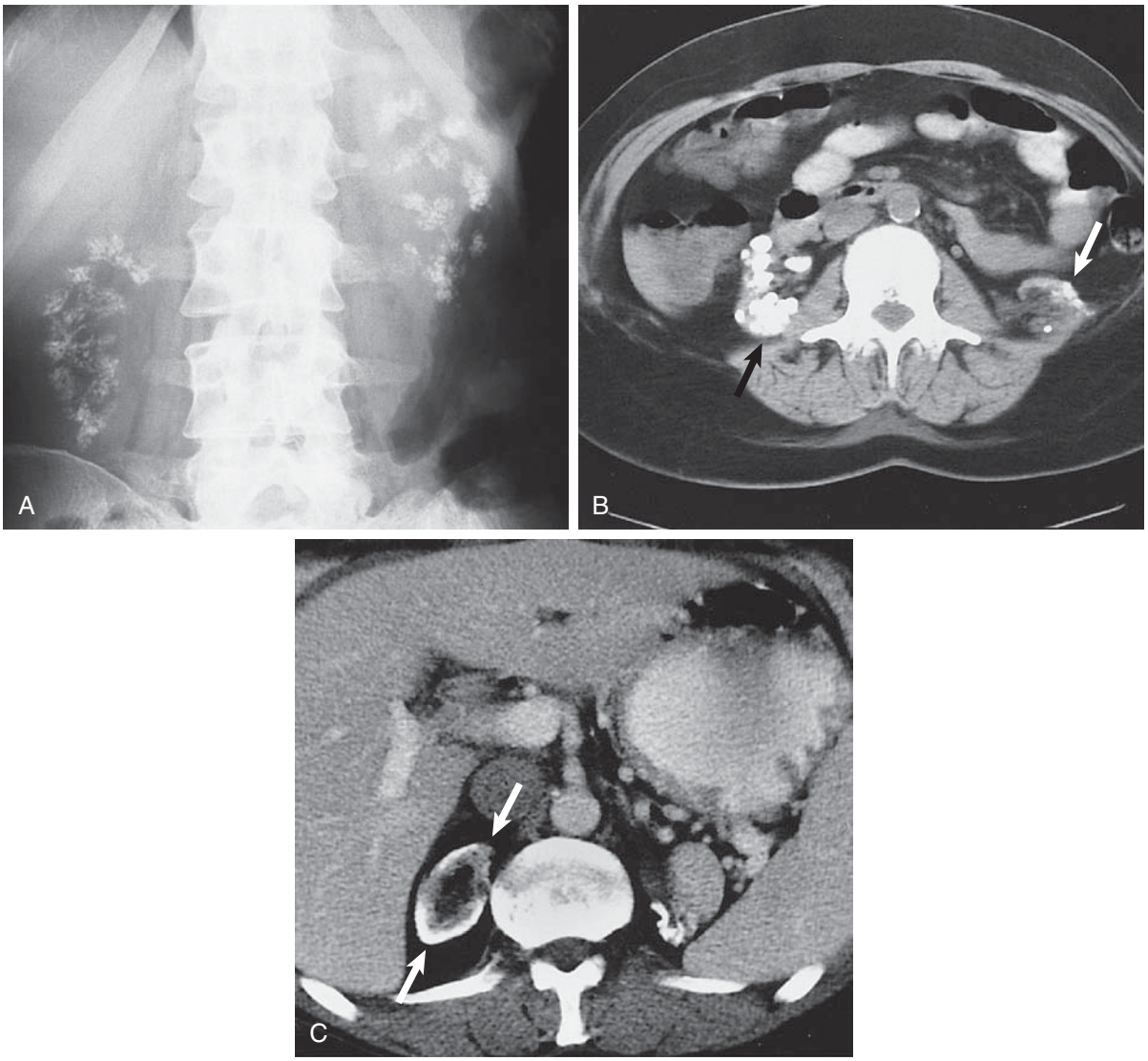


Figure 5-13 Nephrocalcinosis. A, Plain x-ray film shows bilateral medullary nephrocalcinosis in a patient with distal renal tubular acidosis. **B,** Noncontrast CT scan in a patient with hereditary oxalosis and dense bilateral renal calcification *(arrows)*. The left kidney is atrophic. **C,** Noncontrast CT scan shows cortical nephrocalcinosis in the right kidney *(arrows)* after cortical necrosis.

yields increasingly poor images, and the risk of nephrotoxicity also increases.

Kidneys

Evaluation of the kidneys on IVU (as well as CT and MRI) should include their number, location, axis, size, contour, and degree of enhancement. Renal size is variable, but a normal kidney should be about three to four lumbar vertebral bodies in length. The renal outline should be smooth and sharply demarcated from the retroperitoneal fat. Renal enhancement after contrast administration should be symmetric and progress centrally from the cortex, with excretion evident in the ureters by 5 minutes. Asymmetry of renal enhancement may indicate renal artery disease.

Pelvicalyceal System

The pelvicalyceal system is best evaluated on the early postcontrast films. Normally, there are about 10 to 12 calyces per kidney. The calyces drain into the infundibula, which in turn empty into the renal pelvis (Fig. 5-14). The infundibulum and renal pelvis should have smooth contours without filling defects. In a common variant, vessels can cross the pelvicalyceal system or ureters, causing extrinsic compression defects that should not be mistaken for tumors or other urothelial lesions. When more than one calyx drains into an infundibulum, it is known as a *compound calyx,* most frequently seen in the poles. The normal calyx is gently cupped. Calyceal distortion occurs with papillary necrosis and reflux nephropathy.

Ureters

The ureters are often seen segmentally because of active peristalsis. The ureters should be free of filling defects and smooth. In the abdomen, the ureters lie in the retroperitoneum, passing anterior to the transverse processes of the vertebral bodies. In the pelvis, the ureters course laterally and posteriorly, eventually draining into the posteriorly located vesicoureteral junction. At the vesicoureteral junction, the ureters gently taper. Medial bowing or displacement of the ureter is often abnormal and can be seen secondary to ureter displacement from retroperitoneal masses, lymphadenopathy, and retroperitoneal fibrosis.

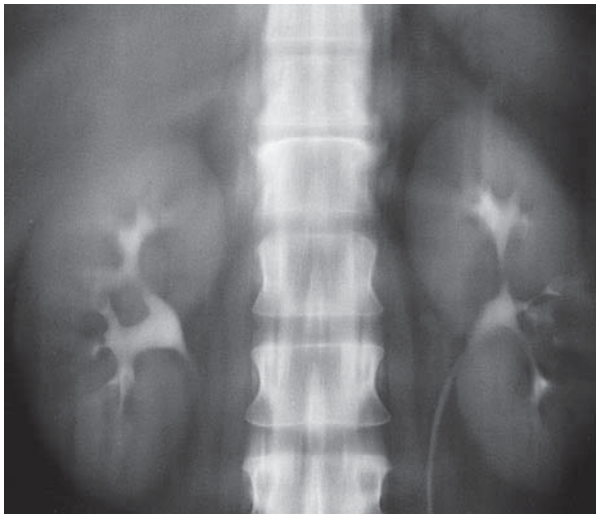


Figure 5-14 Normal parenchymal enhancement and normal renal excretion. Early postcontrast tomogram in intravenous urography.

Bladder

The bladder should be rounded and smooth walled. Benign indentations on the bladder include the uterus, prostate gland, and bowel. In chronic bladder outlet obstruction and neurogenic bladder, numerous trabeculations and diverticula may be seen around the bladder outline.

RETROGRADE PYELOGRAPHY

Retrograde pyelography is performed when the ureters are poorly visualized on other imaging studies or when samples of urine need to be obtained from the kidney for cytology or culture. Patients who have severe allergies to contrast agents or impaired renal function can be evaluated with retrograde pyelography. The examination is performed by placing a catheter through the ureteral orifice under cystoscopic guidance and advancing it into the renal pelvis. With use of fluoroscopy, the catheter is slowly withdrawn while radiocontrast is injected (see Figs. 60-2 and 60-11). This technique provides excellent visualization of the renal pelvis and ureter and can also be used for cytologic sampling from suspect areas.

ANTEGRADE PYELOGRAPHY

Antegrade pyelography is performed through a percutaneous renal puncture and is used when retrograde pyelography is not possible. Ureteral pressures can be measured, hydronephrosis evaluated, and ureteral lesions identified (see Fig. 60-14). The examination is often performed as a prelude to nephrostomy placement. Both antegrade pyelography and retrograde pyelography are invasive and should be performed only when other studies are inadequate.

ILEAL CONDUITS

After cystectomy or bladder failure, numerous types of continent or incontinent urinary diversions can be surgically created. One of the most common diversions is the ileal conduit; an ileal loop is isolated from the small bowel, and the ureters are implanted into the loop. This end of the loop is closed, and the other end exits through the anterior abdominal wall. This type of conduit can be evaluated by an excretory or a retrograde study. The excretory or *antegrade* study is performed and monitored in the same way as an IVU. A *retrograde* examination, also referred to as a loop-o-gram, is obtained when the ureters and conduit are suboptimally evaluated on the excretory study. A Foley catheter is placed into the stoma and contrast slowly instilled. The ureters should fill by reflux because the ureteral anastomoses are not of the antireflux variety (Fig. 5-15).

CYSTOGRAPHY

A cystogram is obtained when more detailed radiographic evaluation of the bladder is required. *Voiding* cystography is performed to identify ureteral reflux and to assess bladder function and urethral anatomy. A urethral catheter is placed into the bladder, the urine drained, contrast infused, and bladder filled under fluoroscopic guidance. Early frontal and oblique films with the patient supine are obtained while the bladder is filling. Ureteroceles are best identified on early films. When the bladder is full, multiple films are obtained with varying degrees of obliquity. Reflux may be seen on these films. To obtain a voiding cystogram, the catheter is removed, the patient

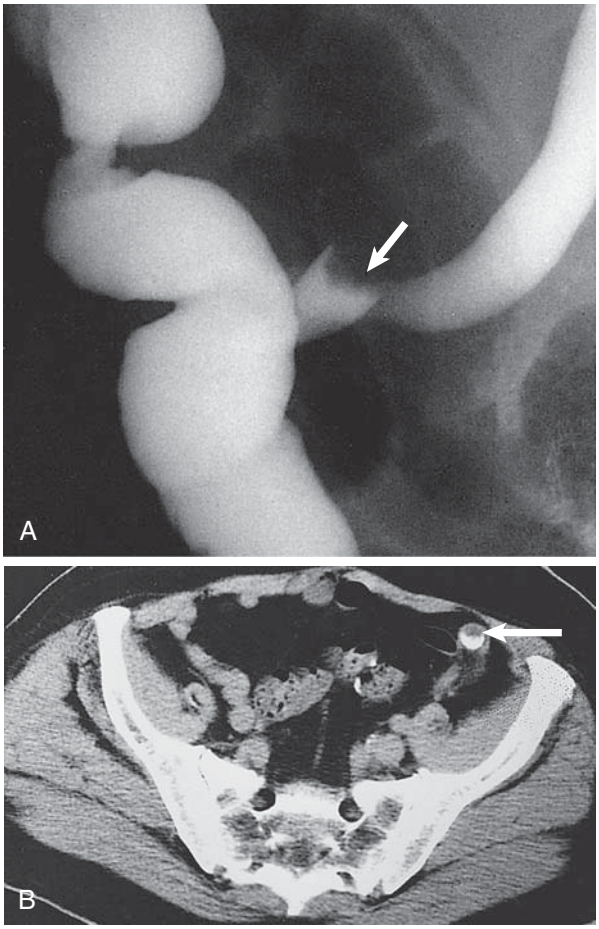


Figure 5-15 Imaging of an ileal conduit. A, Loop-o-gram. A recurrent transitional carcinoma is present in the reimplanted left ureter *(arrow)*. **B,** CT scan clearly shows the tumor as a filling defect in anterior aspect of the opacified ureter *(arrow)*.

voids, and contrast is followed into the urethra. Occasionally, bladder diverticula are seen only on the voiding films. When the patient has completely voided, a final film is used to assess the amount of residual urine as well as the mucosal pattern.

Radionuclide cystography is an alternative often used in children. It is useful in the diagnosis of reflux, but it does not provide the detailed anatomy that is seen with contrast cystography.

COMPUTED TOMOGRAPHY

Computed tomography examination of the kidneys is performed to evaluate suspect renal masses, to locate ectopic kidneys (Figs. 5-16 and 5-17), to investigate calculi, to assess retroperitoneal masses, and to evaluate the extent of parenchymal involvement in patients with acute pyelonephritis (Figs. 5-18 and 5-19). Helical CT scanners allow the abdomen and pelvis to be scanned at 3-mm to 5-mm intervals with one or two breath-held acquisitions, which eliminates motion artifact. Newer multidetector row CT results in multiple slices of information (64-slice and even 320-slice machines are now common) being acquired simultaneously, allowing the entire abdomen and pelvis to be covered in one breath-hold, using even submillimeter intervals. However, the improved CT imaging comes at a price of significant radiation exposure to the patient. The CT data can be reconstructed in multiple planes and even 3D for improved anatomic visualization and localization.

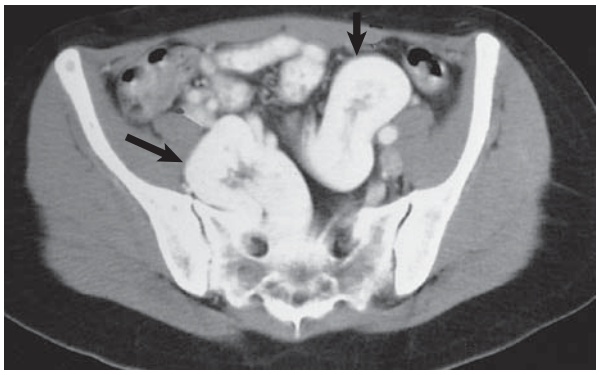


Figure 5-16 Bilateral pelvic kidneys *(arrows)* on CT.

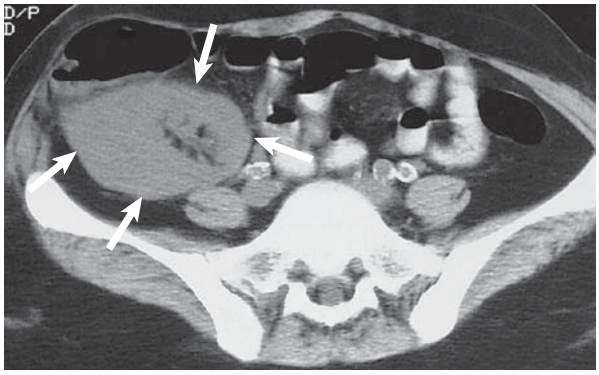


Figure 5-17 Normal renal transplant *(arrows)* on CT.

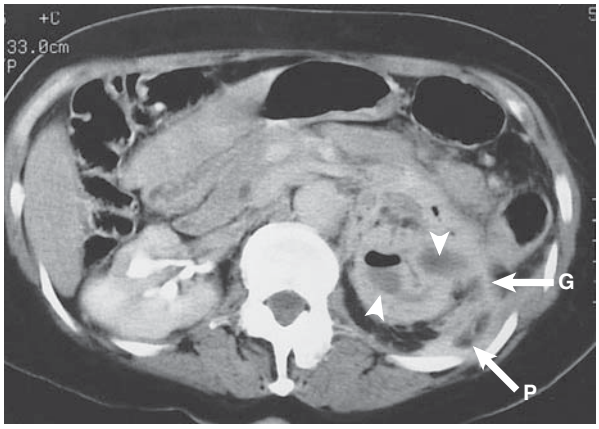


Figure 5-18 Emphysematous pyelonephritis. Contrast-enhanced CT scan shows gas *(arrowheads)* within an enlarged left kidney and marked enhancement of Gerota fascia *(G)* and posterior perirenal space *(P)*, indicative of inflammatory involvement.

Tissue Density

The Hounsfield unit (HU) scale is a measurement of relative densities determined by CT. Distilled water at standard pressure and temperature is defined as 0 HU; the radiodensity of air is defined as −1000 HU. All other tissue densities are derived from this (Table 5-4). Tissues can vary in their exact HU measurements and will also change with contrast enhancement. Water, fat, and soft tissue can often look identical on the scan, depending on the window and level settings of the image, so actual HU measurement is essential to characterize the tissues accurately.

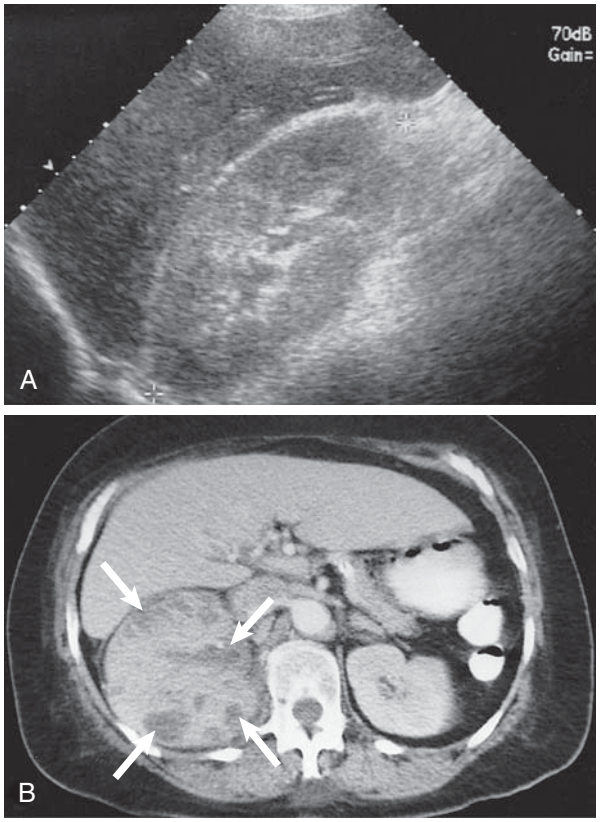


Figure 5-19 Acute pyelonephritis. A, Ultrasound image demonstrates an enlarged echogenic kidney. Bipolar length of kidney is 12.9 cm. **B,** CT scan with contrast enhancement obtained 24 hours later demonstrates multiple nonenhancing abscesses *(arrows)*.

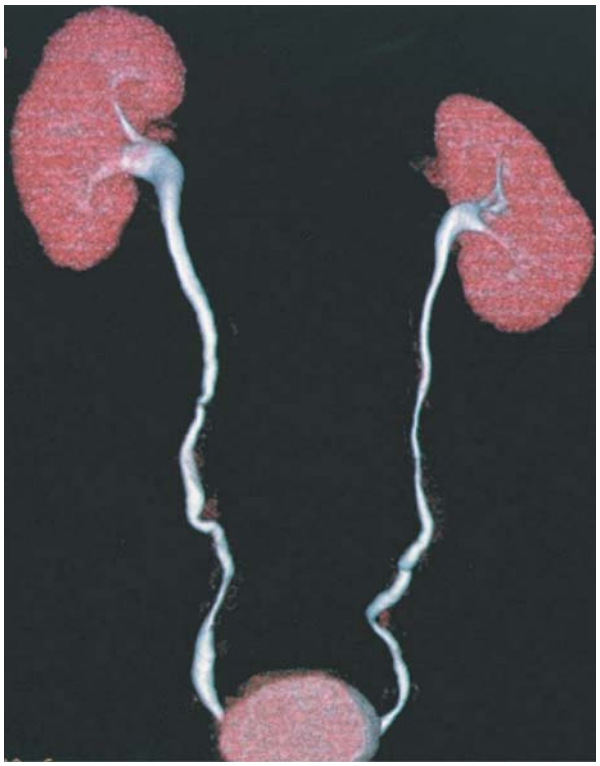


Figure 5-20 Noncontrast CT of bladder and kidney. Computer-reformatted, volume-rendered CT urogram obtained from axial CT acquisition.

Density of Common Substances Determined by Computed Tomography

Substance	HU
Air	–1000
Fat	–120
Water	0
Muscle	+40
Bone	+400 or more

Table 5-4 CT determination of density of common substances. Hounsfield unit (HU) scale is a measurement of relative densities compared with distilled water.

Contrast-Enhanced and Noncontrast Computed Tomography

The CT examination of the kidneys can be performed with or without intravenous administration of contrast material. Noncontrast imaging allows the kidneys to be evaluated for the presence of calcium deposition and hemorrhage, which are obscured after contrast administration.

Noncontrast CT (CT urography, CTU) is the examination of choice in patients with suspected nephrolithiasis and has replaced the KUB and IVU in most situations.[20,21] The study consists of unenhanced images from the kidneys through the bladder for detection of calculi (Fig. 5-20). CTU has the advantage of being both highly sensitive (97% to 100%) and specific (94% to 96%) for diagnosis of urinary calculi.[19,22] Noncontrast CT can identify a possible obstructing calculus as well as the extent of parenchymal and perinephric involvement.

In cases other than stone evaluation, the kidneys are imaged after contrast administration. The kidneys are imaged in the corticomedullary phase for evaluation of the renal vasculature as well as in the nephrographic phase for evaluation of the renal parenchyma. The degree of enhancement can be assessed in both solid masses and complex cysts (see Fig. 60-10).

A compression device can be used as in IVU. Delayed images through the kidneys and bladder are performed for evaluation of the opacified and distended collecting system, ureters, and bladder.[23,24] After acquisition, the axial images can be reformatted into coronal or sagittal planes to optimize visualization of the entire collecting system. The CT study can be tailored to the individual clinical scenario. For example, the corticomedullary phase can be eliminated to decrease the radiation dose if there is no concern about a vascular abnormality or no need for presurgical planning. A diuretic or saline bolus can be administered after contrast to better distend the collecting system and ureters during the excretory phase.

The kidneys should be similar in size and show equivalent enhancement and excretion. During the corticomedullary phase, there is brisk enhancement of the cortex. The cortical mantle should be intact. Any disruption of the cortical enhancement requires further evaluation; it may be caused by acute pyelonephritis (see Fig. 5-19), scarring, mass lesions, or infarction (Fig. 5-21). During the excretory phase, the entire kidney and renal pelvis enhance. Delayed excretion and delay in pelvicalyceal appearance of contrast material may be found in obstruction (Fig. 5-22), but also in renal parenchymal disease such as acute tubular necrosis.

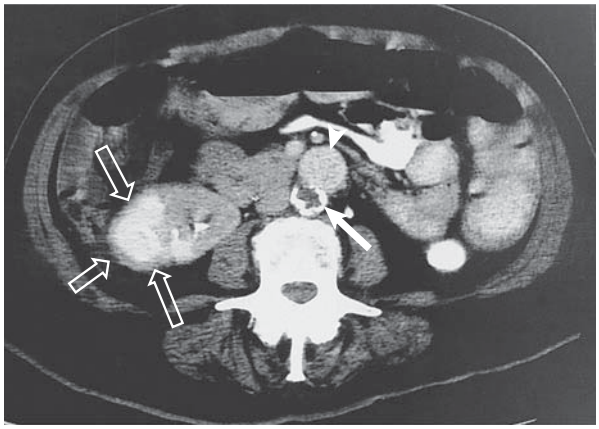


Figure 5-21 Renal infarction. CT scan showing an infarct *(open arrows)* involving half of the right kidney after aortic bypass surgery. The native aorta has a densely calcified wall *(arrow)*. The aortic graft is anterior to the native aorta *(arrowhead)*.

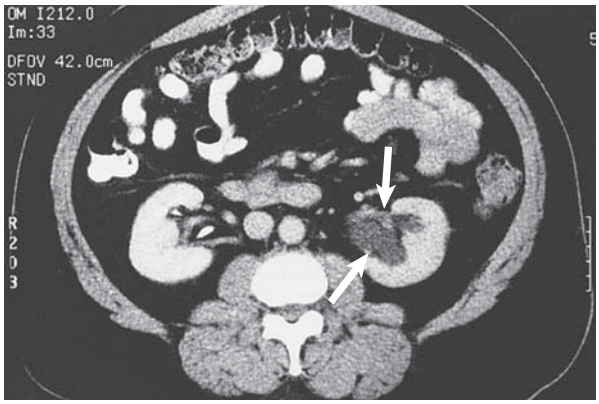


Figure 5-22 Delayed excretion in left kidney secondary to distal calculus. Contrast-enhanced CT scan shows dilated left renal pelvis *(arrows)*.

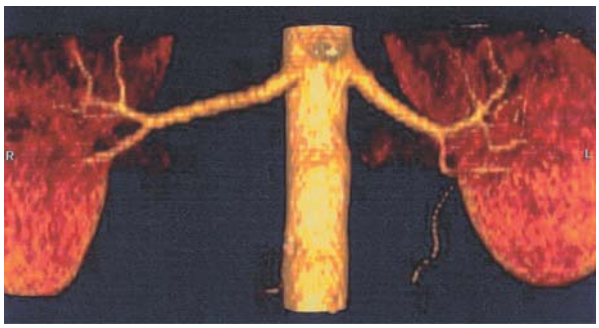


Figure 5-23 Normal renal arteries. Three-dimensional reformatted CT angiogram.

Computed Tomographic Angiography

Helical scanning facilitates CTA, which can produce images similar to conventional angiograms, but it is less invasive. A bolus of contrast material is administered, and the images are obtained at 0.5-mm to 3-mm consecutive intervals. The contrast bolus is timed for optimal enhancement of the aorta. The tightly focused and narrow CT beam allows higher resolution and better subsequent multiplanar reconstructions. The aorta and branch vessels are well demonstrated (Fig. 5-23). This technique is now widely used in living transplant donor evaluation (see Fig. 103-2), providing information not only on arterial and venous anatomy but also on size, number, and location of the kidneys as well as any ureteral anomalies of number or position.

In addition, CTA can be used to screen for atheromatous renal artery stenosis, with sensitivity of 96% and specificity of 99% for the detection of hemodynamically significant stenosis compared with digital subtraction angiography (DSA).[25] Furthermore, CTA allows visualization of both the arterial wall and lumen, which helps in planning renal artery revascularization procedures. Another advantage of CTA is the depiction of accessory renal arteries as well as nonrenal causes of hypertension, such as adrenal masses. CTA can be used to diagnose fibromuscular dysplasia but has a much lower sensitivity (87%) than DSA.[26]

Limitations of Computed Tomography

There are some limitations of CT. The cradle that the patient lies on usually has an upper weight limit of 100 to 200 kg (300 to 400 lb), but newer scanners can now accommodate up to 270 kg (600 lb). Obese patients often have suboptimal scans because of weight artifact and need higher radiation exposures to adjust for x-ray attenuation. Contrast-enhanced CT studies are contraindicated in patients with an allergy to radiographic contrast dye and in patients with impaired renal function. To minimize contrast-induced nephropathy, contrast should not be given to patients with GFR less than 30 ml/min without carefully assessing risks and benefits. Contrast should be used with caution in patients with GFR of 30 to 60 ml/min per 1.73 m^2. If contrast is administered, subjects should be hydrated with intravenous saline and/or bicarbonate solution; the additional value of prophylaxis with oral *N*-acetylcysteine continues to be debated (see Contrast-Induced Nephropathy).

Computed tomography is very sensitive to metal artifact and patient motion. Retroperitoneal clips and intramedullary rods will cause extensive streak artifact, which severely degrades the images. Patients who are unable to remain motionless will also have suboptimal or even nondiagnostic studies, and sometimes sedation or general anesthesia may be needed to obtain diagnostic scans, particularly in children. Intensive care unit and critically ill patients can be scanned by CT as long as they are stable enough to be transported to the CT suite. Ultrasound should be considered as an alternative to CT in the seriously ill patient who cannot be safely transported.

MAGNETIC RESONANCE IMAGING

Although it should only rarely be the first examination used to evaluate the kidneys, MRI is typically an adjunct to other imaging. The major advantage of MRI over other modalities is direct multiplanar imaging. CT is limited to slice acquisition in the axial plane of the abdomen, and coronal and sagittal planes are acquired only by reconstruction, which can lead to loss of information.

Tissues contain an abundance of hydrogen, the nuclei of which are positively charged protons. These protons spin on their axis, producing a magnetic field (magnetic moment). When a patient is placed in a strong magnetic field in an MRI scanner, some of the protons align themselves with the field. When a radiofrequency pulse is applied, some of the protons aligned with the field will absorb energy and reverse their direction. This absorbed energy is given off as a radiofrequency pulse as the protons relax (return to their original alignment), producing a voltage in the receiver coil. The coil is the hardware that covers the region of interest. For renal imaging, a body coil or torso coil is used. Relaxation is a 3D event giving rise to two parameters: T1 relaxation results in the recovery of magnetization in the longitudinal (spin-lattice) plane, whereas T2

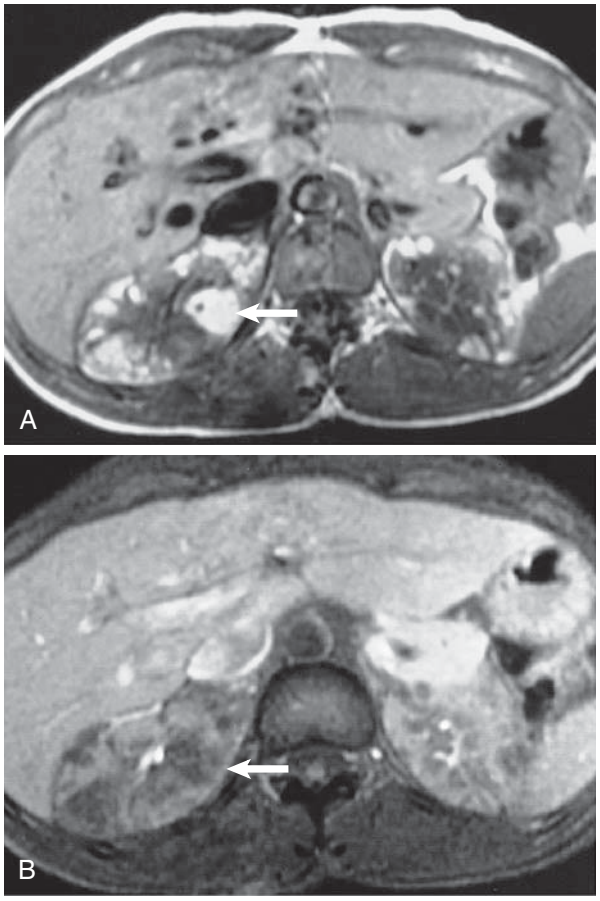


Figure 5-24 Tuberous sclerosis on MRI. Multiple renal angiomyolipomas are seen. **A,** T1-weighted MR image. The tumors are high in signal on T1 because of their fat; *arrow* shows the largest tumor. **B,** T1-weighted MR image with fat suppression. The fat within the tumors is now low in signal *(arrow)*.

results from the loss of transverse (spin-spin) magnetization. A rapid-sequence variant of T2 in common use is fast spin echo (FSE). Hydrogen ions move at slightly different rates in the different tissues. This difference is used to select imaging parameters that can suppress or aid in the detection of fat and water. Fluid, such as urine, is dark or low in signal on T1-weighted sequences and bright or high in signal on FSE sequences. Fat is bright on T1 and not as bright on FSE sequences (Fig. 5-24). The sequences and imaging planes selected must be tailored to the individual MR study. Diffusion-weighted imaging evaluates the freedom of water molecules to diffuse in tissues; restriction of diffusion is imaged as bright areas on the scan and is seen in infection, neoplasia, inflammation, and ischemia.

Standard MR images usually include T1, T2, or FSE sequences and often additional contrast-enhanced T1 images. The imaging plane varies according to the clinical concerns. Usually, at least one sequence is performed in the axial plane. Sagittal and coronal images cover the entire length of the kidney and can make some subtle renal parenchymal abnormalities more conspicuous (Fig. 5-25).

On T1-weighted sequences, the normal renal cortex is higher in signal than the medulla, producing a distinct corticomedullary differentiation, which becomes indistinct in parenchymal renal disease. It is analogous to the echogenic kidney seen on ultrasound. On FSE sequences, the corticomedullary distinction is not as sharp but should still be present.

Contrast-Enhanced Magnetic Resonance Imaging

As with CT, intravenous contrast material can be administered to allow further characterization of renal lesions. Gadolinium is a *paramagnetic* contrast agent frequently used in MRI and is much less nephrotoxic than iodinated contrast material.[27] Adverse reactions to gadolinium are discussed later (see Magnetic Resonance Contrast Agents). Paramagnetic contrast agents are currently being evaluated for measurement of glomerular function.

After injection of gadolinium, the vessels appear high in signal, or white, on T1-weighted sequences. Multiple images can be obtained in a single breath-held acquisition. This technique is useful for lesion characterization in patients who cannot receive iodinated contrast material. As with contrast-enhanced CT, the kidneys initially show symmetric cortical enhancement, which progresses to excretion. A delay in enhancement can be seen with renal artery stenosis.

Magnetic Resonance Urography

There are two techniques for performing magnetic resonance urography (MRU).[28,29] The first technique is sometimes called *static* MRU. Because urine contains abundant water, it will demonstrate high signal on a T2-weighted image. Therefore, a heavily T2-weighted sequence accentuates the static fluid in the collecting system and ureters, which stands out against the darker background soft tissues. Static MRU can be performed rapidly, which is a benefit in imaging of children. A disadvantage is that any fluid in the abdomen or pelvis, such as fluid collections or fluid in small bowel, will demonstrate similar bright signal that can obscure superimposed structures. Also, the collecting system and ureters need to be distended for acquisition of good MR images.

The second technique, often referred to as *excretory* MRU, is similar to CTU. Intravenous administration of gadolinium is followed by T1-weighted imaging. This technique allows some assessment of renal function because the contrast is filtered by the kidney and excreted into the urine (see Fig. 60-10). The opacified collecting system and ureters are well seen, and a diuretic can be administered to further dilate the renal pelvis and ureters if necessary. A limitation of MRU is in the detection of calculi because calcification is poorly visualized by MRI.

Because CTU and MRU are comparable examinations in identifying the cause and anatomic location of urinary obstruction, the choice of modality is a matter of local preference. CTU is the better choice in the evaluation of urinary tract calculi. In patients with renal impairment caused by obstruction, MRU is superior to CTU in identifying noncalculous causes of obstruction, whereas CTU is superior in identifying calculous causes of obstruction.[30,31] CTU is also more widely available, faster, and less expensive than MRU. MRU is better suited in patients with allergy to iodinated contrast agents and sometimes in children when radiation is an issue. MRU is also useful in depicting the anatomy in patients with urinary diversion to bowel conduits.

Magnetic Resonance Angiography

Although MRA can be performed with or without intravenous contrast, contrast provides better images. The aorta and branch vessels are beautifully demonstrated (Fig. 5-26). By adjustment of timing and type of sequences, the abdominal venous structures can be visualized (Fig. 5-27). MRA is performed to evaluate the renal arteries for stenosis and is less invasive than catheter angiography (Fig. 5-28).

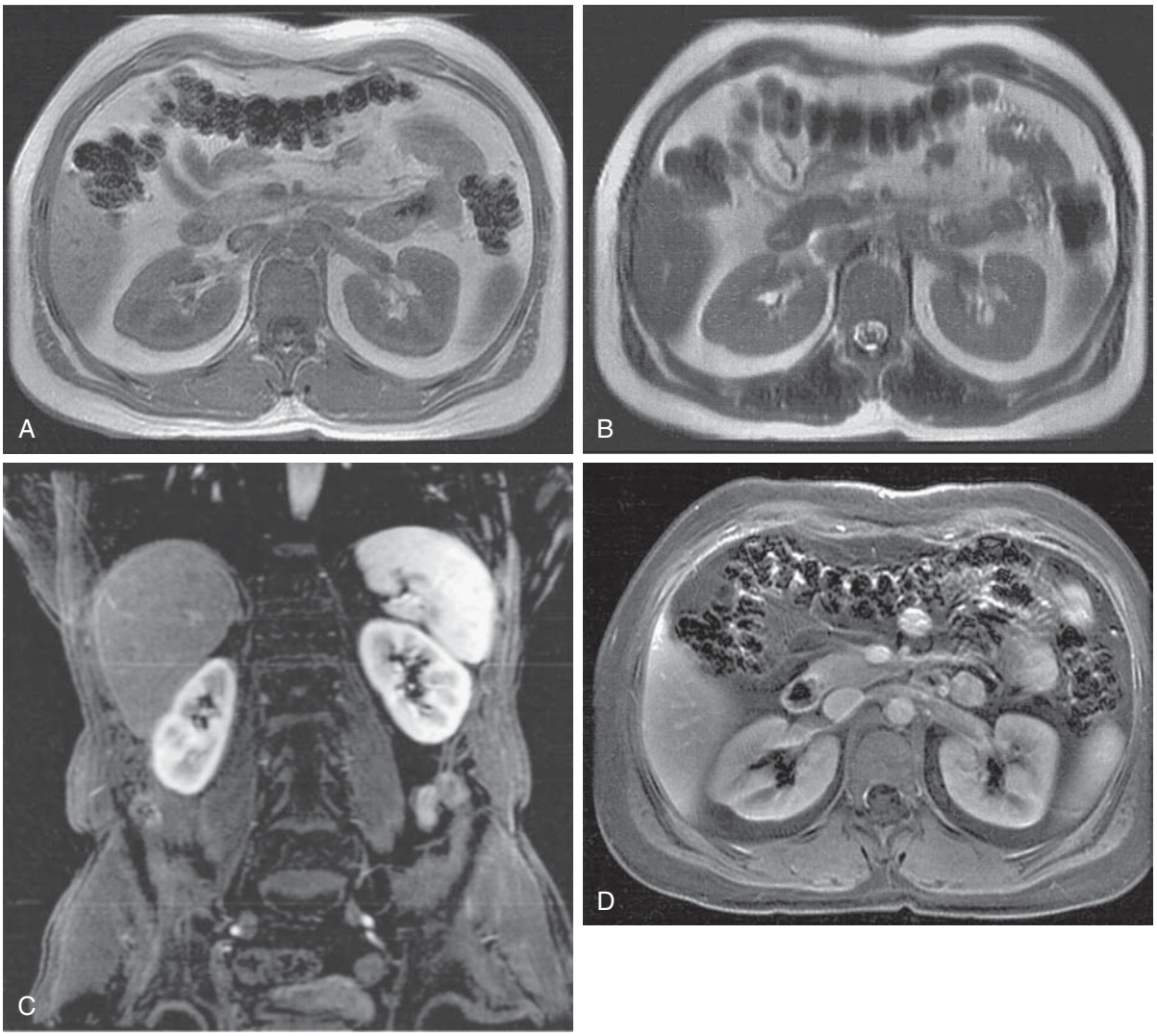


Figure 5-25 Normal MR images through kidneys. A, T1-weighted MR image. Note the distinct corticomedullary differentiation. **B,** Fast spin-echo MR image. Urine in the collecting tubules causes the high signal within the renal pelvis on this sequence. **C,** Coronal T1-weighted, fat-suppressed MR image after contrast administration. **D,** Axial T1-weighted, fat-suppressed image after contrast administration.

Technical advances, including faster sequences, now give sensitivity of 97% and specificity of 93% compared with DSA for contrast-enhanced MRA in the detection of renal artery stenosis.[32] MRA without gadolinium has a lower sensitivity (53% to 100%) and specificity (65% to 97%) for detection of renal artery stenosis.[33] MRA has limited power to assess accessory renal arteries and therefore is not an ideal study to evaluate fibromuscular dysplasia. It has become the primary screening modality in patients with hypertension, declining renal function, or allergy to iodinated contrast agents.[34] Where MRA is unavailable, Doppler ultrasound can be used.

Disadvantages of Magnetic Resonance Imaging

As with CT, MRI has some disadvantages. The table and gantry are confining, so claustrophobic patients may be unable to cooperate. Patients with some types of internal metallic hardware, such as pacemakers or cerebral aneurysm clips, cannot undergo MRI. Determination of in-stent stenosis is impossible as metallic artifact from renal artery stents completely obscures the lumen. Even with the new, fast imaging techniques, patients need to be able to cooperate with breath-holding instructions to minimize motion-related artifacts. MRI with gadolinium has until recently been contraindicated in patients with GFR below 30 ml/min/1.73 m^2 because of the risk of nephrogenic systemic fibrosis[35] (see later, Magnetic Resonance Contrast Agents).

MRI can be used in intensive care unit and critically ill patients only if they are stable enough to be transported to the MRI suite and have no implanted metallic devices. Ventilated patients can undergo MRI; however, specific MRI-compatible, nonferromagnetic ventilators and other life support devices must be used. Because of the confined nature of the MRI gantry, visualization and monitoring of the patient during the scan are compromised.

Incidental Findings

With the growth of cross-sectional imaging, incidental renal lesions are being found with increasing frequency. Almost 70% of renal cell carcinomas are discovered incidentally on imaging studies performed for other reasons. There is an age-dependent incidence of

Figure 5-26 Magnetic resonance angiography. Coronal 3D MR angiogram after contrast administration shows normal renal arteries.

Figure 5-27 Magnetic resonance venography.

renal cysts, from about 5% in patients younger than 30 to almost one third of those older than 60.[36] The differentiation of solid and cystic lesions is the first mandate because as many as two thirds of solid lesions are found to be malignant.[37] MRI is ideally suited for lesion evaluation and is often better than ultrasound, particularly for

Figure 5-28 Dysplasia on MR angiography. Coronal 3D MR angiogram shows fibromuscular dysplasia of the proximal right renal artery.

complex cystic lesions. Parameters being characterized include solid versus cystic, overall lesion complexity, lesion enhancement, involvement of renal vasculature and collecting system, and extension into perirenal tissues and organs. Diffusion-weighted MRI sequences are also being studied as a means of further differentiating benign and malignant solid lesions.

MEASUREMENT OF GLOMERULAR FILTRATION RATE

Renal blood flow and split renal function can be evaluated by CT and MRI.[38-40] The attenuation of the accumulated contrast material within the kidney is directly proportional to the GFR. Taking into account the renal volume, the function of each kidney can be determined. Although both modalities yield similar information, MRI is used more in children and in patients with allergy to contrast agents. This technique has not yet gained full acceptance, and renal scintigraphy remains a widely used method for determination of renal function, as discussed later.

ANGIOGRAPHY

Angiography is now most often performed for therapeutic intervention, such as embolotherapy or angioplasty and stenting, preceded by diagnostic angiography to evaluate the renal arteries for possible stenosis (Fig. 5-29). With improved resolution and scanning techniques, CTA and MRA have replaced conventional angiography, even for detection of accessory renal arteries, which are often small and bilateral but a possible cause of hypertension. However, angiography remains the gold standard (reference) test for the diagnosis of renal artery stenosis and fibromuscular dysplasia. There also remains a role for diagnostic angiography in the evaluation of medium- and large-vessel vasculitis and detection of renal infarction.

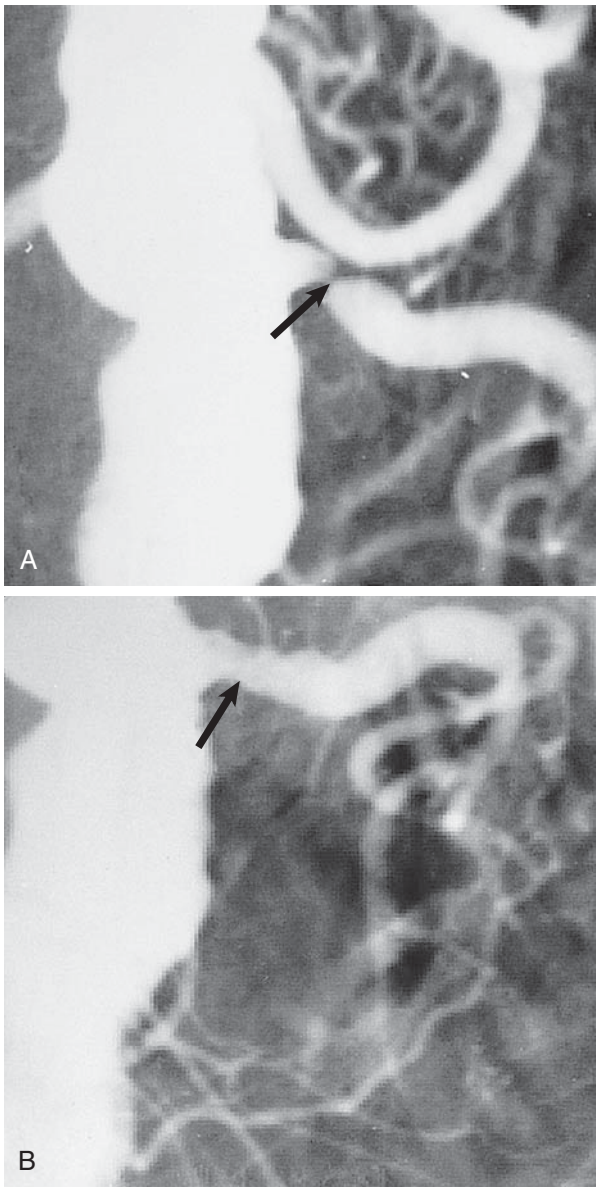


Figure 5-29 Left renal artery stenosis and angioplasty. A, Aortogram demonstrating a tight left renal artery stenosis *(arrow)*. **B,** Postangioplasty image with marked improvement of the stenosis *(arrow)*. *(Courtesy Dr. Harold Mitty.)*

The conventional angiogram is performed through arterial puncture, followed by catheter placement in the aorta. An abdominal aortogram is obtained to identify the renal arteries. Selective renal artery catheterization can be performed as necessary. Contrast is administered intra-arterially, and the images are obtained with conventional film or more often with DSA. Conventional angiography images are superior but require higher doses of contrast material and more radiation exposure. DSA uses computer reconstruction and manipulation to generate the images, with the advantage that previously administered and excreted contrast material and bones can be digitally removed to better visualize the renal vasculature. As well as with the risk of contrast-induced nephropathy, angiography is associated with a risk of cholesterol embolization (see Chapter 66). Pathologic evidence of cholesterol embolization is common, but clinically significant symptoms occur infrequently (1% to 2%).[41]

Choice of Radionuclide in Renal Imaging

Imaging Target	Radiotracer
Glomerular filtration rate	^{99m}Tc-DTPA
Glomerular filtration rate with renal impairment	^{99m}Tc-MAG3, ^{131}I-OIH
Effective renal plasma flow	^{99m}Tc-MAG3, ^{131}I-OIH
Renal scarring	^{99m}Tc-DMSA, ^{99}Tc-GH
Renal pseudotumor	^{99m}Tc-DMSA
Upper renal tract obstruction	^{99m}Tc-DTPA
Upper renal tract obstruction with renal impairment	^{99m}Tc-MAG3

Table 5-5 Choice of radionuclide in renal imaging.

RENAL VENOGRAPHY

Catheter venography was once used for evaluation of renal vein and gonadal vein thrombosis and for renal vein sampling to measure renin, but has largely been replaced with Doppler ultrasound, followed by contrast-enhanced CT or MRI (see Fig. 5-27).

NUCLEAR MEDICINE

Nuclear scintigraphy evaluates function as well as the anatomy seen with other diagnostic imaging modalities. Radiotracers are designed to accumulate in tissues or organs on the basis of underlying functions unique to that organ. The gamma camera captures the photons from a radiotracer within the patient and generates an image. Single-photon emission computed tomography (SPECT) is a specialized type of imaging whereby the emitted photons are measured at multiple angles, similar to CT, and multiplanar or even 3D images can be created. Three categories of radiotracers that differ in mode of renal clearance are used in renal imaging: glomerular filtration, tubular secretion, and tubular retention agents (Table 5-5).

Scintigraphy remains superior to the other imaging modalities in the evaluation of renal flow. It is the study of choice in the evaluation of renal transplants and for the evaluation of functional obstruction, especially when ultrasound evidence is equivocal. Scintigraphy is also widely used to measure GFR, although CT or MRI are preferred in some centers.

Nuclear scintigraphy also provides an accurate assessment of renal function, as in estimating the reduction in renal function after nephron-sparing surgery. Although CT, MRI, and contrast-enhanced ultrasound are being assessed for the evaluation of renal function, scintigraphy remains the preferred modality. Both CTA and MRA have replaced nuclear scintigraphy in the evaluation of renal artery stenosis and in evaluation of benign renal masses, such as a column of Bertin. Nuclear medicine is still used to assess the functional significance of renal artery stenosis independent of anatomy.

Glomerular Filtration Agents

Glomerular filtration agents are cleared by the glomerulus and can be used to measure GFR. Technetium Tc 99m–labeled diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) is the most common glomerular agent used for imaging and can also be used for GFR

calculation. In patients with poor renal function, renal imaging with tubular secretion agents such as mercaptoacetyltriglycine (^{99m}Tc-labeled MAG3) is superior to DTPA.[42,43]

Tubular Secretion Agents

Technetium-99m MAG3 is handled primarily by tubular secretion and can be used to estimate effective renal plasma flow. The clearance rate for ^{99m}Tc-MAG3 is 340 ml/min.[44]

Tubular Retention Agents

Tubular retention agents include ^{99m}Tc-labeled dimercaptosuccinate (DMSA) and less often ^{99m}Tc-labeled glucoheptonate (GH). These agents provide excellent cortical imaging and can be used in suspected renal scarring or infarction, in pyelonephritis, and for clarification of renal pseudotumors. These agents bind with high affinity to the sulfhydryl groups of the proximal tubules.

Renogram

A renogram (or renal scintigram) is generated by scintigraphy and provides information about blood flow, renal uptake, and excretion. Time-activity graphs are produced that plot blood flow of the radiotracer into each kidney relative to the aorta. Peak cortical enhancement and pelvicalyceal clearance of the tracer are also plotted. DTPA or MAG3 can be used to generate the renogram. The relative radiotracer uptake can be measured and can provide split or differential information about renal function (Fig. 5-30).

The blood pool or flow images are obtained after bolus injection of the radiotracers. Images are obtained with the gamma camera every few seconds for the first minute. The second component of the renogram evaluates renal function by measuring radiotracer uptake and excretion by the kidney. In normal patients, the peak renal cortical concentration occurs between 3 and 5 minutes after injection of tracer. Delayed transit of the isotope secondary to renal dysfunction (e.g., acute tubular necrosis or rejection) or obstructive uropathy will alter the curve of the renogram.

In cases of suspected obstructive uropathy, a diuresis renogram can be obtained. A loop diuretic is injected intravenously when radiotracer activity is present in the renal pelvis; a computer-generated washout curve is obtained. In patients with true obstruction, activity will remain in the renal pelvis, whereas it will quickly wash out in patients without an obstruction (Fig. 5-31; see also Fig. 60-12).

Cortical Imaging

Renal cortex imaging is performed with tubular retention agents, usually ^{99m}Tc-DMSA. Information about renal size, location, and contour can be obtained (Fig. 5-32). The cortical study is used most frequently for evaluation of renal scarring, particularly in children with reflux or chronic infections (see Chapter 63). It was formerly used for clarification of renal pseudotumors, such as a suspected column of Bertin, but this is now done with CT and MRI. Split renal function can also be determined from cortical imaging. Pinhole imaging (pinhole collimator magnifies the kidney to provide more anatomic detail than with planar imaging) and more recently SPECT have been found useful for detection of cortical defects caused by inflammation or scarring. Cortical imaging may be better than ultrasound in the evaluation of the young patient with urinary tract infection.[45] An infection, scar, or space-occupying lesion (tumor or cyst) will create a cortical defect, and correlation of the cortical defect

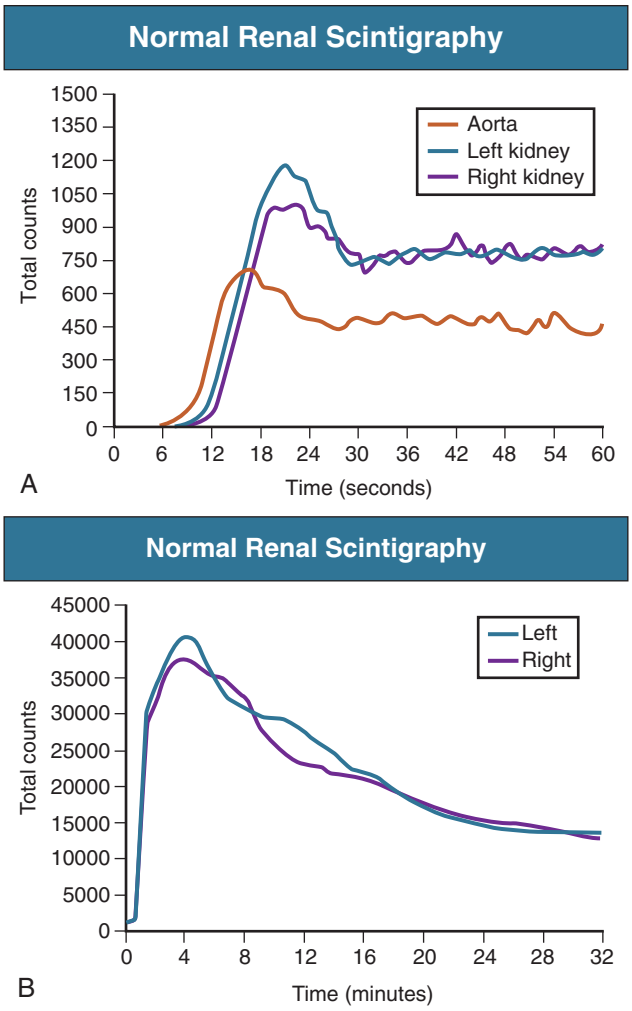


Figure 5-30 Normal ^{99m}Tc-labeled DTPA study: time-activity curves. **A,** Early (0-1 minute), showing renal blood flow. **B,** Later (0-30 minutes), showing renal uptake and excretion of tracer. *(Courtesy Dr. Chun Kim.)*

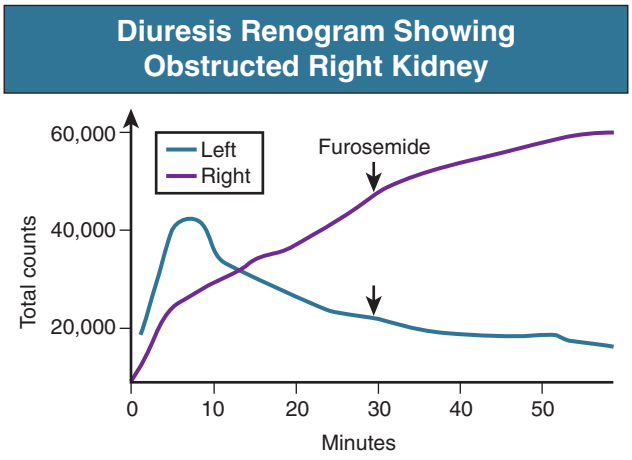


Figure 5-31 Diuresis renogram showing obstructed right kidney. Isotope continues to accumulate in the right kidney despite intravenous furosemide (given at ↓). Isotope excretion in the left kidney is normal.

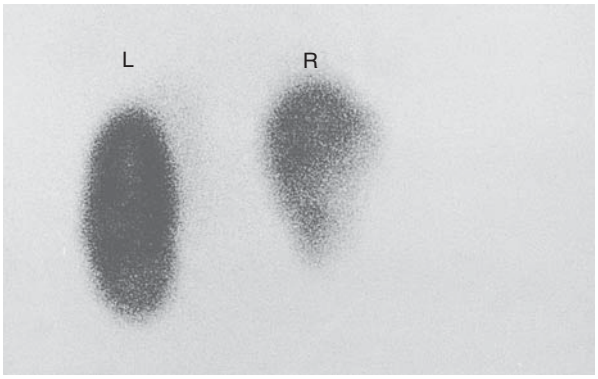


Figure 5-32 Renal infarct. ^{99m}Tc-DMSA scan in a newborn with an infarct of the right lower pole *(R)* secondary to embolus from umbilical catheter. *(Courtesy Dr. Chun Kim.)*

site with other cross-sectional imaging should be performed to differentiate these entities.

Vesicoureteral Reflux

In children with suspected vesicoureteral reflux, a standard cystogram is obtained. If reflux is shown, follow-up is subsequently performed with radioisotope cystography, which exposes the child to a lower radiation dose and can be used to quantitate the bladder capacity when reflux occurs. The study is performed after instillation of technetium pertechnetate through a catheter into the bladder. Images are obtained during voiding.

Renal Transplant

Renal transplants are easily evaluated with scintigraphy. ^{99m}Tc-MAG3 is cleared through tubular secretion, which is maintained in most kidneys to a better degree than glomerular filtration in renal failure. Because many transplant recipients have declining renal function, ^{99m}Tc-MAG3 is the first-choice nuclide.

As with the normal kidneys, information about blood flow and function can be determined. Postoperative complications involving the artery, vein, or ureter are also well delineated. Nuclear imaging can help define acute tubular necrosis versus rejection in transplant patients with declining renal function. Ultrasound with Doppler evaluation of resistive index is often a complementary investigation, and choice of imaging modality in part depends on local expertise and preference.

POSITRON EMISSION TOMOGRAPHY

Positron emission tomography scanning uses radioactive positron emitters, most often ^{18}F-labeled fluorodeoxyglucose (FDG). The FDG is intravenously injected and distributes in the body according to metabolic activity. Any process, such as a tumor or infection, that causes increased metabolic activity will result in an area of increased uptake on the scan. These areas of abnormality need to be differentiated from normally hypermetabolic tissues, such as brain, liver, bone marrow, and to some extent heart and bowel (Fig. 5-33). Because FDG is cleared through the kidneys and excreted in the urine, PET scanning has a limited role in renal imaging but is useful in the staging and follow-up of metastatic renal cancer.[46,47]

Figure 5-33 Normal PET scan. Note normal radiotracer uptake in brain, heart, intestines, and liver with normal excretion in kidneys.

MOLECULAR IMAGING

With molecular imaging, radiology is moving from the identification of generic anatomy and nonspecific enhancement patterns to assessment of specific molecular differences in tissues and disease processes. Nuclear imaging presently is molecular based but still nonspecific (e.g., FDG-PET, renal DTPA). The newer focus of molecular imaging studies dynamic processes such as metabolic activity, cell proliferation, apoptosis, receptor status, and antigen modulation. Typically, this involves imaging of biochemical and physiologic processes. Techniques are being developed with optical scanning, MRI, and ultrasound as well as with radionuclides.

Applications are established in clinical practice, particularly in oncology (e.g., CD20 imaging in lymphoma), and work is under way for renal-specific molecular imaging. For example, MR renal cell imaging may soon be available to help differentiate acute tubular necrosis from renal rejection and renal cell cancer from benign tumors.

RADIOLOGIC CONTRAST AGENTS

X-ray Contrast Agents

Contrast agents continue to have a role in many imaging techniques. A triiodinated benzene ring forms the chemical basis for CT intravascular contrast agents. Conventional contrast agents have high osmolality, about five times greater than plasma osmolality. They give excellent renal opacification, but this contributes to their toxicity. Modifications to the benzene ring have led to newer contrast agents, including low-osmolar and more recently iso-osmolar nonionic agents, which are less nephrotoxic.

Intravascular iodinated contrast material rapidly passes through the capillary pores into the interstitial, extracellular space and into the renal tubules through glomerular filtration.[48] In patients with normal renal function, the kidneys eliminate almost all the contrast agent. Extrarenal routes of excretion include the liver and bowel wall and account for less than 1% of elimination, but this can increase when renal function is compromised. The half-time in patients with normal renal function is 1 to 2 hours, compared with 2 to 4 hours in dialysis patients.[49]

The overall incidence of contrast reactions for iodinated agents is 3.1% to 4.7%.[50-52] Twenty percent of patients who have a contrast reaction will experience a reaction on reexposure that may be similar or worse. Contrast reactions can be anaphylactoid or chemotoxic reactions. The anaphylactoid reactions mimic an allergic response, whereas the chemotoxic reactions are believed to be mediated by direct toxic effects of the contrast material. The exact mechanism of contrast reaction is not known but is likely to be multifactorial. Formation of antigen-antibody complexes, complement activation, protein binding, and histamine release have all been cited as possible mechanisms.

Reactions may be minor, intermediate, or severe. Minor reactions include heat sensation, nausea, and mild urticaria. Intermediate reactions include vasovagal reaction, bronchospasm, and generalized urticaria. Severe reactions include profound hypotension, pulmonary edema, and cardiac arrest. The use of low-osmolar or iso-osmolar contrast agents reduces the incidence of minor and intermediate contrast reactions. The reported incidence of death related to high-osmolar contrast agents is 1 in 40,000. Immediate treatment of reactions should be directed toward the symptoms. In patients with a history of contrast allergy, pretreatment on reexposure is usually recommended. Various protocols are used but typically include antihistamines and corticosteroids.

Contrast-Induced Nephropathy

Acute kidney injury (AKI) associated with the administration of contrast material has been reported as the third most common cause of in-hospital AKI.[52] Patients with normal renal function rarely develop contrast-induced renal failure. In patients with GFR less than 45 ml/min, iodinated contrast agents should be used with caution because the risk for contrast-induced nephropathy is increased.[53] Nephrotoxicity ranges in severity from a nonoliguric transient fall in GFR to severe renal failure requiring dialysis. The combination of preexisting renal impairment and diabetes is the major risk factor. Other risk factors are diabetes, cardiovascular disease, use of diuretics, advanced age (>75 years), multiple myeloma in dehydrated patients, hypertension, uricosuria, and high-dose contrast. Both ionic and nonionic contrast media can induce nephrotoxicity, although nonionic contrast is significantly less nephrotoxic. In end-stage renal disease, contrast administration may result in fluid overload because of thirst induced by the osmotic load.

The two major theories for the pathogenesis of contrast-induced nephropathy are renal vasoconstriction, perhaps mediated by alterations in nitric oxide, and direct nephrotoxicity of the contrast agent. Most underlying cellular events occur within the first 60 minutes after administration of the contrast agent, with the greatest risk in the first 10 minutes.

There is some evidence that suggests that patients with diabetes and heart failure have altered nitric oxide metabolism, which may account for their increased risk for contrast-induced nephrotoxicity. Tubular injury produces oxygen free radicals, possibly from the vasoconstriction. In animal studies, reduction in antioxidant enzymes associated with hypovolemia contributes to the injury.[54] Hydration with normal saline or sodium bicarbonate is the mainstay of prevention; no substantial evidence shows that sodium bicarbonate offers any advantage over saline.[55] Oral *N*-acetylcysteine, a thiol-containing antioxidant, is often given in conjunction with hydration but has not proved to be consistently protective.[56] In most patients the renal failure is transient, and the patients recover without incident.

An important differential diagnosis for contrast-induced nephropathy in patients with vascular disease undergoing catheter angiography is cholesterol embolization (see Chapters 66 and 69).

In patients with GFR less than 60 ml/min, low-osmolar or iso-osmolar contrast agents should be used and the doses reduced. Repetitive, closely performed contrast studies should be avoided. In high-risk patients, alternative imaging studies, ultrasound, MRI, or noncontrast CT should always be considered. The prevention and management of contrast-induced nephropathy is further discussed in Chapter 73.

Magnetic Resonance Contrast Agents

The two classes of MRI contrast agents are diffusion and nondiffusion agents. Diffusion agents, with appropriate timing of imaging sequences, can delineate vessels as well as parenchymal tissues. Nondiffusion agents remain in the bloodstream and are primarily useful for MRA. All the contrast agents are based on the paramagnetic properties of gadolinium. Gadolinium itself is highly toxic and is given only when it is tightly chelated (e.g., Gd-DOTA, Gd-DTPA).

Minor reactions such as headache and nausea occur in 3% to 5% of patients; but life-threatening reactions and nephrotoxic reactions are rare. In patients with renal impairment, a rare severe reaction, nephrogenic systemic fibrosis, has been described (see Chapter 88), and therefore the use of gadolinium agents is contraindicated in patients with severe renal impairment. The most recent guidelines confirm that MRI using high-risk gadolinium-containing contrast agents is contraindicated in patients with AKI and in those with CKD stages 4 and 5 (i.e., GFR <30 ml/min/1.73 m^2).[35] However, lower-risk cyclic gadolinium–containing contrast agents allow contrast MRI to be undertaken with caution in patients with CKD stages 4 and 5, with a minimum interval of 7 days between repeat studies.

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CHAPTER 6

Renal Biopsy

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DEFINITION

Percutaneous renal biopsy was first described in the early 1950s by Iversen and Brun[1] and Alwall.[2] These early biopsies were performed with the patient in the sitting position by use of a suction needle and intravenous urography for guidance. An adequate tissue diagnosis was achieved in less than 40% of these early cases. In 1954, Kark and Muehrcke[3] described a modified technique using the Franklin-modified Vim-Silverman needle, with the patient in a prone position and an exploring needle used to localize the kidney before insertion of the biopsy needle. These modifications yielded a tissue diagnosis in 96% of cases, and no major complications were reported. Since then, the basic renal biopsy procedure has remained largely unchanged, although the use of real-time ultrasound and refinement of biopsy needle design have offered significant improvements. Renal biopsy is now able to provide a tissue diagnosis in more than 95% of patients, with a life-threatening complication rate of less than 0.1%.

INDICATIONS FOR RENAL BIOPSY

Ideally, analysis of a renal biopsy sample should identify a specific diagnosis, reflect the level of disease activity, and provide information to allow informed decisions about planned treatment. Although not always able to fulfill these criteria, the renal biopsy remains a valuable clinical tool and is of particular benefit in the clinical situations discussed next (Box 6-1).

Nephrotic Syndrome

Routine clinical and serologic examination of patients with nephrotic syndrome usually allows the clinician to determine whether a systemic disorder is present. In adults and in adolescents beyond puberty without systemic disease, there is no reliable way to predict the glomerular pathologic process with confidence by noninvasive criteria alone; therefore a renal biopsy should be performed. In children age 1 year up to puberty, a presumptive diagnosis of minimal change disease (MCD) can be made. Renal biopsy is reserved for nephrotic children with atypical features, including microscopic hematuria, reduced serum complement levels, renal impairment, and failure to respond to corticosteroids.

Acute Kidney Injury

In most patients with acute kidney injury or AKI on a background of chronic kidney disease (CKD), the cause can be determined without a renal biopsy. Obstruction, reduced renal perfusion, and acute tubular necrosis (ATN) can usually be identified from other lines of investigation. In a minority of patients, however, a confident diagnosis cannot be made, and a renal biopsy should be performed on an urgent basis so that appropriate treatment can be started before irreversible renal injury develops. This is particularly true in patients with AKI accompanied by active urine sediment or with suspected drug-induced or infection-induced acute interstitial nephritis.

Systemic Disease Associated with Renal Dysfunction

Patients with diabetes mellitus and renal dysfunction do not usually require biopsy if the clinical setting is associated with diabetic nephropathy, as in isolated proteinuria, diabetes of long duration, or evidence of other microvascular complications. Renal biopsy should be performed, however, if the presentation is atypical, such as proteinuria associated with glomerular hematuria (acanthocytes), absence of retinopathy or neuropathy (in patients with type 1 diabetes), onset of proteinuria less than 5 years from documented onset of diabetes, uncharacteristic change in renal function or renal disease of acute onset, and presence of immunologic abnormalities.

Serologic testing for antineutrophil cytoplasmic antibody (ANCA) and for anti–glomerular basement membrane antibodies has allowed a confident diagnosis of renal small-vessel vasculitis or Goodpasture disease without invasive measures in most patients. Nonetheless, a renal biopsy should still be performed to confirm the diagnosis and to clarify the extent of active inflammation versus chronic fibrosis and thus the potential for recovery. This information may be important in helping to decide whether to initiate or continue immunosuppressive therapy, particularly in patients who may tolerate immunosuppression poorly.

Lupus nephritis can usually be diagnosed by noninvasive criteria such as autoantibodies, urine protein excretion, renal function, and urine sediment abnormalities. Some experts argue that this information can be used to gauge the severity of renal involvement and to inform decisions about initial immunosuppressive treatment. However, a renal biopsy will clarify the underlying pathologic lesion, level of acute activity, and extent of chronic fibrosis, thereby providing robust guidance for evidence-based therapy.

The diagnosis of viral infection–related nephropathy (e.g., hepatitis B virus–associated membranous nephropathy) is suggested by the presence of the expected glomerular lesion in association with evidence of active viral infection. However, the identification of virus-specific protein or DNA or RNA in the renal biopsy tissue by immunopathologic and molecular pathologic techniques (e.g., *in situ* hybridization) can ensure the diagnosis.

Other systemic diseases, such as amyloidosis, sarcoidosis, and myeloma, can be diagnosed with renal biopsy. However, because these diagnoses can often be made by other investigative approaches,

Indications for Renal Biopsy

Nephrotic Syndrome

Routinely indicated in adults

In prepubertal children, indicated only if clinical features atypical of minimal change disease

Acute Kidney Injury

Indicated if obstruction, reduced renal perfusion, and acute tubular necrosis have been ruled out

Systemic Disease with Renal Dysfunction

Indicated in patients with small-vessel vasculitis, anti–glomerular basement membrane disease, and systemic lupus

Indicated in patients with diabetes only if atypical features present

Non-nephrotic Proteinuria

May be indicated if proteinuria >1 g/24 h

Isolated Microscopic Hematuria

Indicated only in unusual circumstances

Unexplained Chronic Kidney Disease

May be diagnostic (e.g., identify IgA nephropathy even in "end-stage kidney")

Familial Renal Disease

Biopsy of one affected member may give diagnosis and minimize further investigation of family members

Renal Transplant Dysfunction

Indicated if ureteral obstruction, urinary sepsis, renal artery stenosis, and toxic calcineurin inhibitor levels are not present

Box 6-1 Indications for renal biopsy

a renal biopsy is indicated only if the diagnosis remains uncertain or if knowledge of renal involvement would change management.

Renal Transplant Dysfunction

Renal allograft dysfunction in the absence of ureteral obstruction, urinary sepsis, renal artery stenosis, or toxic levels of calcineurin inhibitors requires a renal biopsy to determine the cause. In the early post-transplantation period, this is most useful in differentiating acute rejection from ATN and the increasingly prevalent BK virus nephropathy. Later, renal biopsy can differentiate late acute rejection from chronic allograft nephropathy, recurrent or *de novo* glomerulonephritis (GN), and calcineurin inhibitor toxicity. The accessible location of the renal transplant in the iliac fossa facilitates biopsy of the allograft and allows repeated biopsies when indicated. This has encouraged many units to adopt a policy of *protocol* (surveillance) biopsies to detect subclinical acute rejection and renal scarring and to guide the choice of immunosuppressive therapy (see Chapter 104).

Non-nephrotic Proteinuria

The value of renal biopsy in patients with non-nephrotic proteinuria is debatable. All conditions that result in nephrotic syndrome can cause non-nephrotic proteinuria, except for MCD. However, the benefit of specific treatment with corticosteroids and other immunosuppressive agents in these patients probably does not justify the risk of significant drug-related side effects. In patients with proteinuria of more than 1 g/day, generic treatment with strict blood pressure control and angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) alone or in combination reduces proteinuria and reduces the risk for development of progressive renal dysfunction (see Chapter 80). Nonetheless, although the renal biopsy may not lead to an immediate change in management, it can be justified in these circumstances because it will provide prognostic information, may identify a disease for which a different therapeutic approach is indicated, and may provide clinically important information about the future risk of disease recurrence after renal transplantation.

Isolated Microhematuria

Patients with microhematuria should initially be evaluated to identify structural lesions such as renal stones or renal and urothelial malignant neoplasms if they are older than 40 years. The absence of a structural lesion suggests that the hematuria may have a glomerular source. Biopsy studies have identified glomerular lesions in up to 75% of biopsies.[4] In all series, IgA nephropathy has been the most common lesion, followed by thin basement membrane nephropathy. In the absence of nephrotic proteinuria, renal impairment, or hypertension, the prognosis for patients with these conditions is excellent, and because specific therapies are not available, renal biopsy is not necessary and patients require only follow-up. Biopsy should be performed only if the result would provide reassurance to the patient, avoid repeated urologic investigations, or provide specific information, as in the evaluation of potential living kidney donors, in familial hematuria, or for life insurance and employment purposes.

Unexplained Chronic Kidney Disease

Renal biopsy can be informative in the patient with unexplained chronic renal impairment and normal-sized kidneys, because in contrast to AKI, it is often difficult to determine the underlying cause with clinical criteria alone. Studies have shown that in these patients with CKD, the biopsy will demonstrate disease that was not predicted in almost half.[5] However, if both kidneys are small (<9 cm on ultrasound), the risks of biopsy are increased, and the diagnostic information may be limited by extensive glomerulosclerosis and tubulointerstitial fibrosis. In this setting, however, immunofluorescence studies may still be informative. For example, glomerular IgA deposition may be identified despite advanced structural damage.

Familial Renal Disease

A renal biopsy can be helpful in the investigation of patients with a family history of renal disease. A biopsy performed in one affected family member may secure the diagnosis for the whole family and avoid the need for repeat investigation. Conversely, a renal biopsy may unexpectedly identify disease that has an inherited basis, thereby stimulating evaluation of other family members.

Role of Repeat Renal Biopsy

In some patients, a repeat biopsy may be indicated. For example, the pathologic changes in lupus nephritis may evolve, necessitating treatment adjustment. Also, corticosteroid-resistant/dependent MCD or frequently relapsing MCD may actually represent a missed diagnosis of focal segmental glomerulosclerosis (FSGS), which may be detected on repeat biopsy. Some nephrologists believe that repeat biopsy in patients who have had aggressive immunosuppressive therapy of crescentic GN can help determine the most appropriate next line of therapy.

VALUE OF RENAL BIOPSY

Biopsy Adequacy

In the assessment of a renal biopsy, the number of glomeruli in the sample is the major determinant of whether the biopsy will be diagnostically informative.

For a focal disease such as FSGS, the diagnosis could be made on a biopsy specimen containing a single glomerulus that contains a typical sclerosing lesion. However, the probability that FSGS is not present in a patient with nephrotic syndrome and minimal changes on the biopsy specimen depends on the actual proportion of abnormal glomeruli in the kidney and the number of glomeruli obtained in the biopsy specimen. For example, if 20% of glomeruli in the kidney have sclerosing lesions and five glomeruli are sampled, there is a 35% chance that all the glomeruli in the biopsy specimen will be normal and that the biopsy will miss the diagnosis. By contrast, in the same kidney, if 10 or 20 glomeruli are sampled, the chance of obtaining all normal glomeruli is reduced to 10% and less than 1%, respectively, and the biopsy is more discriminating. This argument assumes that any segmental lesions present in the biopsy specimen are actually identified; this requires the biopsy specimen to be sectioned at multiple levels.

Unless all glomeruli are affected equally, the probability that the observed involvement in the biopsy specimen accurately reflects true involvement in the kidney depends not only on the number of glomeruli sampled but also on the proportion of affected glomeruli. For example, in a biopsy specimen containing 10 glomeruli, of which three are abnormal (30%), there is a 95% probability that the actual glomerular involvement is between 7% and 65%. In the same kidney, if the biopsy specimen contained 30 glomeruli with 30% being abnormal, the 95% confidence intervals are narrowed to 15% and 50%.

Therefore the interpretation of the biopsy needs to take into account the number of glomeruli obtained. A typical biopsy sample will contain 10 to 15 glomeruli and will be diagnostically useful. Nonetheless, it must be appreciated that because of the sampling issue, a biopsy sample of this size will occasionally be unable to diagnose focal diseases and at best will provide imprecise guidance on the extent of glomerular involvement.

An adequate biopsy should also provide samples for immunohistology and electron microscopy (EM). Immunohistology is provided by either immunofluorescence on frozen material or immunoperoxidase on fixed tissue, according to local protocols and expertise. It is helpful for the biopsy cores to be viewed under an operating microscope immediately after being taken to ensure that they contain cortex and that when the cores are divided, the immunohistology and EM samples both contain glomeruli.

If the material obtained for a complete pathologic evaluation is insufficient, a discussion with the pathologist should address how best to proceed before the tissue is placed in fixative, so that the material can be processed in a way that will provide maximum information for the specific clinical scenario. For example, if the patient has heavy proteinuria, most information will be gained from EM because it is able to demonstrate podocyte foot process effacement, focal sclerosis, electron-dense deposits of immune complexes, and the organized deposits of amyloid.

If a sample is supplied for immunofluorescence microscopy but contains no glomeruli, it may be possible to reprocess the paraffin-embedded sample to identify immune deposits by immunoperoxidase or immunofluorescence techniques.

Is Renal Biopsy a Necessary Investigation?

The role of the renal biopsy has been much debated. Early studies suggested that renal biopsy provided diagnostic clarity in the majority of patients, but that this information did not alter management, with the exception of those with heavy proteinuria or systemic disease. More recent prospective studies have suggested that the renal biopsy identifies a diagnosis different from that predicted on clinical grounds in 50% to 60% of patients and leads to a treatment change in 20% to 50%.[6] This is particularly apparent in patients with heavy proteinuria or AKI, more than 80% of whom have biopsy findings that alter their management.[7]

PREBIOPSY EVALUATION

The prebiopsy evaluation identifies issues that may compromise the safety and success of the procedure (Fig. 6-1). It will determine

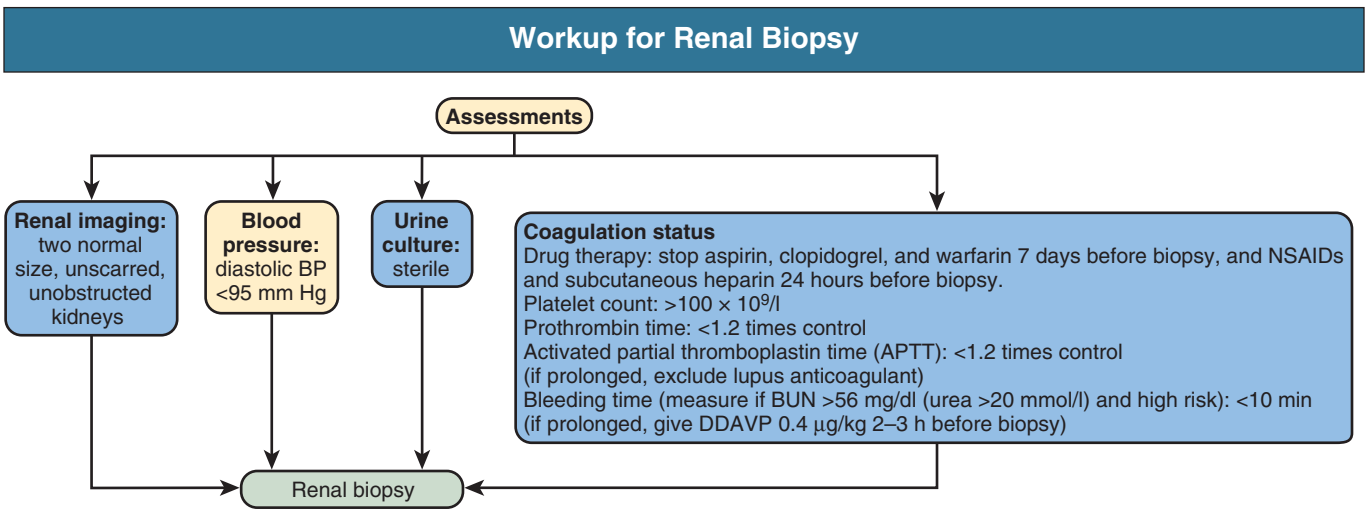

Figure 6-1 Workup for renal biopsy. *NSAID,* Nonsteroidal anti-inflammatory drug; *BUN,* blood urea nitrogen; *DDAVP,* desmopressin.

whether the patient has two normal-sized unobstructed kidneys, sterile urine, controlled blood pressure, and no bleeding diathesis. A thorough history should be taken to identify evidence of a bleeding diathesis, such as previous prolonged surgical bleeding, spontaneous bleeding, family history of bleeding, and ingestion of medication that increases bleeding risk, including antiplatelet agents and warfarin.

An ultrasound scan should be performed to assess kidney size and to identify significant anatomic abnormalities, such as solitary kidney, polycystic or simple cystic kidneys, malpositioned kidneys, horseshoe kidneys, small kidneys, and hydronephrosis.

The value of the *bleeding time* in patients undergoing renal biopsy is controversial. The predictive value of the bleeding time for postrenal biopsy bleeding has never been prospectively tested. Retrospective studies, however, demonstrated a threefold to fivefold increase in bleeding complications after renal biopsy in patients with prolonged bleeding time. Prospective studies of percutaneous liver biopsy patients showed a fivefold increase in bleeding complications in those with uncorrected bleeding times.[8] A consensus document concluded that the bleeding time is a poor predictor of postsurgical bleeding, but it does correlate with clinical bleeding episodes in uremic patients.[9]

Several approaches to the management of bleeding risk have been adopted. First, all subjects undergoing biopsy should discontinue any agent that can prolong bleeding, including aspirin (7 days before biopsy), clopidogrel (7 days), warfarin (7 days), nonsteroidal anti-inflammatory drugs (NSAIDs; 24 hours), and subcutaneous heparin (24 hours). Many centers measure the prebiopsy bleeding time and administer 1-desamino-8-D-arginine vasopressin (desmopressin, DDAVP; 0.4 µg/kg intravenously 2 to 3 hours before biopsy) if the bleeding time is prolonged beyond 10 minutes. Another method no longer measures the bleeding time but routinely administers DDAVP to patients with significant renal impairment (blood urea nitrogen level >56 mg/dl [urea >20 mmol/l] or serum creatinine concentration >3 mg/dl [250 µmol/l]). Platelet transfusion can also be used to reverse clopidogrel-induced platelet dysfunction when the renal biopsy is urgent.

The routine use of desmopressin in low-risk patients (estimated GFR > 60 ml/min; blood pressure <140/90 mm Hg; normal coagulation parameters) has been shown to reduce the risk of hematoma formation after biopsy compared with placebo (13.7% vs. 30.5%, respectively).[10] The hematomas were clinically silent, however, and no patient in either group had macrohematuria or required a transfusion. The study was also unable to determine the risks related to DDAVP (thrombosis or hyponatremia). Therefore use of DDAVP prophylaxis in all patients undergoing renal biopsy cannot be recommended.

The use of thromboelastography (TEG) has been described in the patient undergoing renal transplant biopsy.[11] TEG provides an overall measure of the coagulation, platelet, and fibrinolytic systems in one assay and thus may be more predictive of clinical bleeding. In this study, most bleeding episodes were associated with normal clotting test results, but TEG was the only assay associated with an increased risk of postbiopsy bleeding. The role of TEG in the patient undergoing native kidney biopsy requires further evaluation.

Contraindications to Renal Biopsy

The contraindications to percutaneous renal biopsy are listed in Table 6-1. The major contraindication is a bleeding diathesis. If the disorder cannot be corrected and the biopsy is deemed indispensable, alternative approaches can be used, such as open biopsy, laparoscopic biopsy, or transvenous (usually transjugular) biopsy.

Contraindications to Renal Biopsy

Kidney Status	Patient Status
Multiple cysts	Uncontrolled bleeding diathesis
Solitary kidney	Uncontrolled blood pressure
Acute pyelonephritis	Uremia
Perinephric abscess	Obesity
Renal neoplasm	Uncooperative patient

Table 6-1 Contraindications to renal biopsy. Most contraindications are relative rather than absolute. Clinical circumstances that necessitate urgent renal biopsy may be overridden, except for uncontrolled bleeding diathesis.

Inability of the patient to comply with instructions during renal biopsy is another major contraindication. Sedation or, in extreme cases, general anesthesia may be necessary.

Hypertension (>160/95 mm Hg), hypotension, perinephric abscess, pyelonephritis, hydronephrosis, severe anemia, large renal tumors, and cysts are relative contraindications to renal biopsy. When possible, these should be corrected before the biopsy is undertaken.

The presence of a solitary functioning kidney has been considered a contraindication to percutaneous biopsy, and some argue that the risk of biopsy is reduced by direct visualization at open biopsy. However, the postbiopsy nephrectomy rate of 1/2000 to 1/5000 is comparable to the mortality rate associated with the general anesthetic required for an open procedure. Therefore, in the absence of risk factors for bleeding, percutaneous biopsy of a solitary functioning kidney can be justified.

RENAL BIOPSY TECHNIQUE

Percutaneous Renal Biopsy

Native Renal Biopsy

At our centers, the kidney biopsy is performed by nephrologists with continuous (real-time) ultrasound guidance and disposable automated biopsy needles. We use 16-gauge needles as a compromise between the greater tissue yield of larger needles and the trend toward fewer bleeding complications of smaller needles. For most patients, premedication or sedation is not required. The patient is prone, and a pillow is placed under the abdomen at the level of the umbilicus to straighten the lumbar spine and to splint the kidneys. Figure 6-2 shows the anatomic relationships of the left kidney. Ultrasound is used to localize the lower pole of the kidney where the biopsy will be performed (usually the left kidney). An indelible pen mark is used to indicate the point of entry of the biopsy needle. The skin is sterilized with povidone-iodine (Betadine) or chlorhexidine solution. A sterile fenestrated sheet is placed over the area to maintain a sterile field. Local anesthetic (2% lidocaine [lignocaine]) is infiltrated into the skin at the point previously marked.

While the anesthetic takes effect, the ultrasound probe is covered in a sterile sheath. Sterile ultrasound jelly is applied to the skin, and under ultrasound guidance, a 10-cm, 21-gauge needle is guided to the renal capsule and further local anesthetic infiltrated into the perirenal tissues, then along the track of the needle on withdrawal. A stab incision is made through the dermis to ease passage of the biopsy needle. This is passed under ultrasound guidance to the kidney capsule (Fig. 6-3). As the needle approaches the capsule, the patient is instructed to take a breath until the kidney is moved to a position such that the lower pole rests just under the biopsy needle, and then to stop breathing. The biopsy needle tip is advanced to the renal capsule, and the trigger mechanism is released, firing the

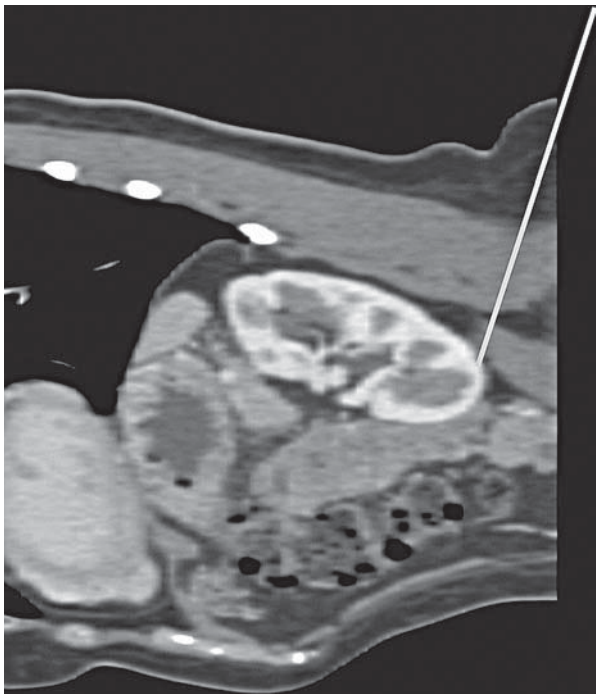

Figure 6-2 Computed tomography through the left kidney. The angle of approach of the needle is demonstrated. Note the relative adjacency of the lower pole of the kidney to other structures, particularly the large bowel.

Figure 6-3 Renal biopsy procedure. The biopsy needle is introduced at an angle of approximately 70 degrees to the skin and is guided by continuous ultrasound. The operator is shown wearing a surgical gown. This is not strictly necessary; sterile gloves and maintenance of a sterile field are sufficient.

needle into the kidney (Fig. 6-4). The needle is immediately withdrawn, the patient is asked to resume breathing, and the contents of the needle are examined (Fig. 6-5). We examined the tissue core under an operating microscope to ensure that renal cortex has been obtained (Fig. 6-6). A second pass of the needle is usually necessary to obtain additional tissue for immunohistology and EM. If insufficient tissue is obtained, further passes of the needle are made. In our experience, however, passing the needle more than four times is associated with a modest increase in the postbiopsy complication rate.

Once sufficient renal tissue has been obtained, the skin incision is dressed and the patient rolled directly into bed for observation.

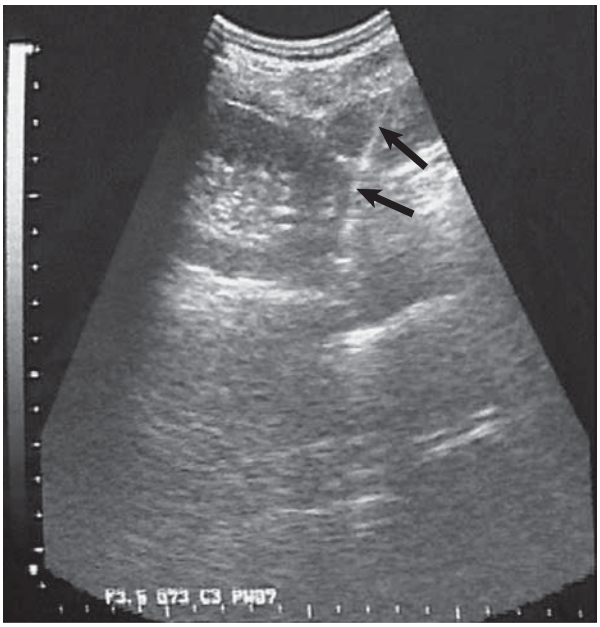

Figure 6-4 Renal biopsy imaging. Ultrasound scan shows the needle entering the lower pole of the left kidney. *Arrows* indicate the needle track, which appears as a fuzzy white line.

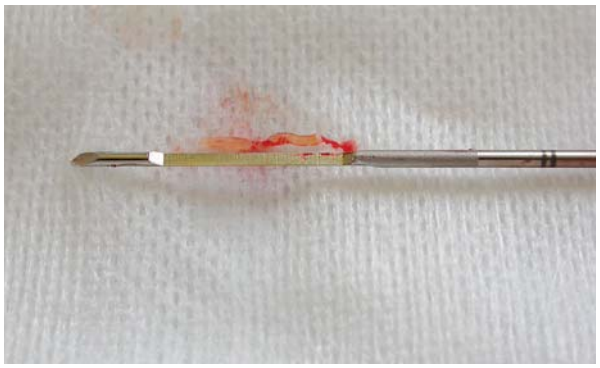

Figure 6-5 Renal biopsy sample. A core of renal tissue is demonstrated in the sampling notch of the biopsy needle.

No single fixative has been developed that allows good-quality light microscopy, immunofluorescence, and EM to be performed on the same sample. Therefore, the renal tissue is often divided into three samples and placed in formalin for light microscopy, normal saline for subsequent snap-freezing in liquid nitrogen for immunofluorescence, and glutaraldehyde for EM. Some centers are able to produce satisfactory light microscopy, immunohistochemistry, and EM on formalin-fixed biopsy material, although this depends on the expertise of individual laboratories.

The percutaneous renal biopsy technique has several variations. Whereas the majority of biopsies are guided by ultrasound, some operators choose to use it only to localize the kidney and to determine the depth and angle of approach of the needle, then performing the biopsy without further ultrasound guidance. The success and complication rates appear to be no different from those seen with continuous ultrasound guidance. For technically challenging biopsies, computed tomography can be used to guide the biopsy needle.

For obese patients and patients with respiratory conditions who find the prone position difficult, the supine anterolateral approach has recently been described.[12] Patients lie supine with the flank on the side to be sampled elevated by 30 degrees with towels under the

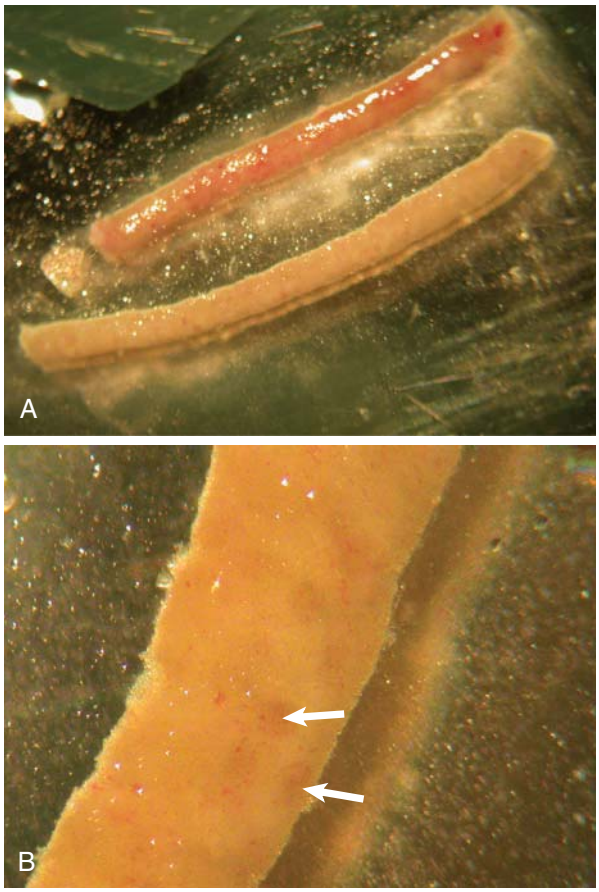

Figure 6-6 Renal biopsy micrographs. Appearance of renal biopsy material under the operating microscope. **A,** Low-power view shows two good-sized cores. **B,** Higher-magnification view shows the typical appearance of glomeruli *(arrows)*.

shoulder and buttocks. The biopsy needle is inserted through the Petit (inferior lumbar) triangle, bounded by the latissimus dorsi muscle, 12th rib, and iliac crest. This technique provides good access to the lower pole of the kidney, is better tolerated than the prone position by these patients, and has a diagnostic yield and safety profile comparable to the standard technique for native renal biopsy.

Renal Transplant Biopsy

Biopsy of the transplant kidney is facilitated by the proximity of the kidney to the anterior abdominal wall and the lack of movement on respiration. It is performed under real-time ultrasound guidance with use of an automated biopsy needle. In most patients, the renal transplant biopsy is performed to identify the cause of acute allograft dysfunction. In these circumstances, the goal is to identify acute rejection, and therefore the diagnosis can be made on a formalin-fixed sample alone for light microscopy. If vascular rejection is suspected, a snap-frozen sample for C4d immunostaining should also be obtained (although some laboratories are able to detect C4d on formalin-fixed material). If recurrent or *de novo* GN is suspected in patients with chronic allograft dysfunction, additional samples for EM and immunohistology should be collected.

Postbiopsy Monitoring

After the biopsy, the patient is placed supine and subjected to strict bed rest for 6 to 8 hours. The blood pressure is monitored frequently, the urine examined for visible hematuria, and the skin puncture site examined for excessive bleeding. If there is no evidence of bleeding after 6 hours, the patient is sat up in bed and subsequently allowed to move. If visible hematuria develops, bed rest is continued until the bleeding settles.

Conventionally, patients have been observed for complications in the hospital for 24 hours after biopsy. However, outpatient (day-case) renal biopsy with same-day discharge after 6 to 8 hours of observation has become increasingly popular for both native and renal transplant biopsies. Largely driven by financial and resource implications of overnight hospital admission, this has been justified by the perception that the significant complications of renal biopsy will become apparent during this shortened period of observation. This view has been challenged by a study of 750 native renal biopsies, which showed that only 67% of major complications, defined as those that either required a blood transfusion or an invasive procedure or resulted in urinary tract obstruction, septicemia, or death, were apparent by 8 hours after biopsy.[13] These authors concluded that the widespread application of an early discharge policy after renal biopsy is not in the patient's best interest, and that a 24-hour observation period is preferable.

In Leicester, approximately half of renal biopsies are outpatient procedures. The patient population is selected to avoid those with the highest risk of complications, including impaired renal function (estimated GFR <30 ml/min), small kidneys, and uncontrolled hypertension. In addition, we require that the patient not be alone at home for at least one night after the biopsy. This selection policy has proved to be safe. Of 429 outpatient biopsies performed in our unit, 6% developed a self-limited postbiopsy complication within 6 hours that required a short hospital admission. Five patients returned after same-day discharge with biopsy-related complications, one with visible hematuria at 24 hours and four with loin pain between 3 and 5 days after biopsy. All patients recovered with conservative management. We believe that outpatient renal biopsy is acceptably safe when a low-risk patient group is selected.

A study investigated whether ultrasound 1 hour after biopsy is able to predict bleeding complications.[14] The absence of hematoma was predictive of an uncomplicated course, but the identification of hematoma was not reliably predictive of a significant biopsy complication; identification of hematoma at 1 hour had a 95% negative predictive value and 43% positive predictive value. The role of this imaging in the wider clinical setting remains to be determined given the additional expense of routine postbiopsy ultrasound.

Alternatives to the Percutaneous Approach

When the percutaneous approach is contraindicated, other approaches to renal biopsy have been described. The choice of technique depends on the safety, morbidity, recovery period, and adequacy of the technique, but mainly on the local expertise available.

Transvenous (Transjugular or Transfemoral) Renal Biopsy

Transvenous sampling of the kidney is theoretically safer than the percutaneous approach because the needle passes from the venous system into the renal parenchyma and is directed away from large blood vessels. In addition, any bleeding that occurs should be directed back into the venous system, and if capsular perforation develops, significant bleeding points can be immediately identified and controlled by coil embolization. Others argue that coil embolization of the punctured vein is unhelpful because significant bleeding into a perirenal hematoma or the urine indicates an arterial breach that requires selective angiography and arterial embolization.

Transvenous renal biopsy cannot be regarded as routine because it involves specialist skills and additional time and expense compared with the percutaneous approach. The main indication for this approach is an uncontrollable bleeding diathesis. It has also been advocated for patients receiving artificial ventilation in the intensive care unit; the need to obtain tissue from more than one organ, including the kidney, liver, or heart; large-volume ascites that precludes the prone position; uncontrolled hypertension; morbid obesity; severe respiratory insufficiency; solitary kidney; failed percutaneous approach; and coma.

The patient lies supine, and the right internal jugular vein is cannulated. A guidewire is passed into the inferior vena cava (IVC), and a catheter is passed over the guidewire and selectively into the right renal vein, which is shorter and enters the IVC at a more favorable angle than the left renal vein. A sheath is passed over the catheter to a suitable peripheral location in the kidney with the aid of contrast enhancement. Finally, the biopsy device (usually a side-cut biopsy needle system) is passed through the sheath and samples are taken. Contrast is then injected into the biopsy track to identify capsular perforation, and embolization coils are inserted if brisk bleeding is identified.

The quality of renal tissue obtained by transjugular biopsy is variable, although studies report diagnostic yields of more than 90%.[15] The complication rate appears comparable to that seen with percutaneous renal biopsy, which is reassuring given that these are high-risk patients.

Open Renal Biopsy

Open renal biopsy has been established as a safe alternative to percutaneous biopsy when uncorrectable contraindications exist. In a series of 934 patients, tissue adequacy was 100% with no major complications.[16] This is an effective approach with minimal postprocedure complications, but the risk of general anesthesia and the delayed recovery time have prevented its widespread adoption. Open biopsy may still be performed, however, when a renal biopsy is required in patients who are otherwise undergoing abdominal surgery.

Laparoscopic Renal Biopsy

Laparoscopic renal biopsy requires general anesthesia and two laparoscopic ports in the posterior and anterior axillary lines to gain access to the retroperitoneal space. Laparoscopic biopsy forceps are used to obtain cortical biopsy samples, and the biopsy sites are coagulated with laser and packed to prevent hemorrhage. In the largest study of laparoscopic renal biopsy, adequate tissue was obtained in 96% of 74 patients.[17] Significant bleeding occurred in three patients, the colon was injured in one, and a biopsy was performed inadvertently on the spleen and liver, respectively, in two others. Inadvertent biopsy was subsequently averted by the use of intraoperative ultrasound to define the anatomy in difficult cases.

COMPLICATIONS OF RENAL BIOPSY

The complication rates compiled from large series of renal biopsies are shown in Table 6-2.

Complications of Renal Biopsy

Complication	Percentage
Visible hematuria	3.5%
Need for blood transfusion	0.9%
Need for intervention to control bleeding	0.7% (0.6% angiographic; 0.1% surgical)
Death	0.02%

Table 6-2 Complications in 9474 native kidney biopsies. *(Data from reference 19.)*

Pain

Patients should be informed about the inevitable dull ache around the needle entry site when the local anesthetic wears off after renal biopsy. Simple analgesia with acetaminophen (paracetamol) or acetaminophen-codeine combinations usually suffices. More severe pain in the loin or abdomen on the side of the biopsy suggests significant perirenal hemorrhage. Opiates may be necessary for pain relief, with appropriate investigation to clarify the severity of the bleed. Patients with visible hematuria may develop clot colic and describe the typical severe pain associated with ureteral obstruction.

Hemorrhage

A degree of perirenal bleeding accompanies every renal biopsy. The mean decrease in hemoglobin after a biopsy is approximately 1 g/dl.[18] Significant perirenal hematomas are almost invariably associated with severe loin pain. Both visible hematuria and painful hematoma are seen in 3% to 4% of patients after biopsy. The initial management is strict bed rest and maintenance of normal coagulation indices. If bleeding is brisk and associated with hypotension or prolonged and fails to settle with bed rest, renal angiography should be performed to identify the source of bleeding. Coil embolization can be performed during the same procedure, and this has largely eliminated the need for open surgical intervention and nephrectomy.

Arteriovenous Fistula

Most postbiopsy arteriovenous fistulas are detected by Doppler ultrasound or contrast-enhanced computed tomography and, when looked for specifically, can be found in as many as 18% of patients. Because most are clinically silent and more than 95% resolve spontaneously within 2 years, fistulas should not be routinely sought. In a small minority of patients, arteriovenous fistulas can lead to visible hematuria (typically recurrent, dark red, and often with blood clots), hypertension, and renal impairment, which requires embolization.

Other Complications

A variety of rare complications of renal biopsy have been reported, including biopsy performed on other organs (liver, spleen, pancreas, bowel, gallbladder), pneumothorax, hemothorax, calyceal-peritoneal fistula, dispersion of carcinoma, and *Page kidney* (compression of kidney by perirenal hematoma leading to renin-mediated hypertension).

Death

Death resulting directly from renal biopsy has become much less common according to recent biopsy series compared with earlier reports. Most deaths are the result of uncontrolled hemorrhage in high-risk patients, particularly those with severe renal impairment.

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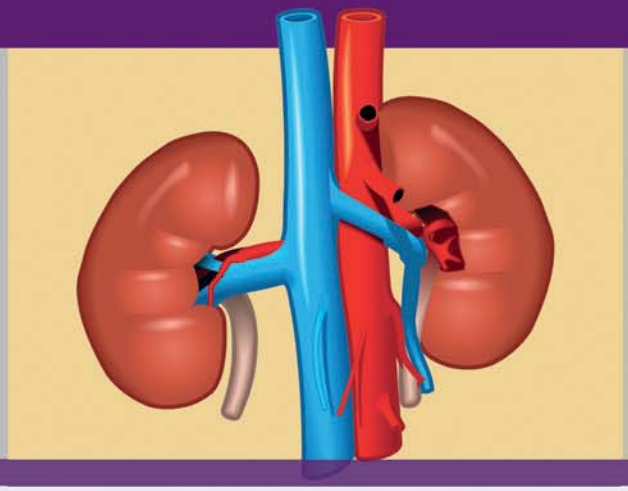

SECTION III

Fluid and Electrolyte Disorders

CHAPTER 7

Disorders of Extracellular Volume

Elwaleed A. Elhassan and Robert W. Schrier

EXTRACELLULAR FLUID COMPARTMENT

Water is the predominant constituent of the human body. In healthy individuals, it makes up 60% of a man's body weight and 50% of a woman's body weight. Body water is distributed in two compartments: the intracellular fluid (ICF) compartment, containing 55% to 65% of body water, and the extracellular fluid (ECF) compartment, containing the remaining 35% to 45%. The ECF is further subdivided into two spaces: the *interstitial* space accounts for about three fourths of ECF, and the *intravascular* space represents the remaining fourth (Table 7-1).

Total body water diffuses freely between the intracellular space and the extracellular spaces in response to solute concentration gradients. Therefore the amount of water in different compartments depends entirely on the quantity of solute in that compartment. The major solute in the ECF is sodium ion (Na^+), and the major intracellular solute is potassium ion (K^+). The maintenance of this distribution is fulfilled by active transport through the Na^+,K^+–adenosine triphosphate (ATP)–dependent pumps on the cell membrane, and this determines the relative volume of different compartments. Because sodium is the predominant extracellular solute, the ECF is determined primarily by the sodium content of the body and the mechanisms responsible for its maintenance. The amount of sodium is therefore tightly regulated by modulation of renal retention and renal excretion in situations of deficient and excess ECF, respectively.

Fluid movement between the intravascular and interstitial spaces of the ECF occurs across the capillary wall and is governed by Starling forces, namely, the capillary hydrostatic pressure and colloid osmotic pressure. The transcapillary hydrostatic pressure gradient exceeds the corresponding oncotic pressure gradient, thereby favoring movement of plasma ultrafiltrate into the extravascular compartment. The return of fluid into the intravascular compartment occurs through lymphatic flow.

Maintaining the ECF volume determines the adequacy of the circulation and in turn the adequacy of delivery of oxygen, nutrients, and other substances needed for organ functions as well as removal of waste products. This is achieved despite day-to-day variations in the intake of sodium and water, with the ECF volume varying by only 1% to 2%.

The term *effective arterial blood volume* is used to describe the blood volume detected by the sensitive arterial baroreceptors in the arterial circulation. The effective arterial blood volume (EABV) can change independently of the total ECF volume. EABV can explain the sodium and water retention in different clinical situations (see later discussion).

REGULATION OF EXTRACELLULAR FLUID HOMEOSTASIS

Circulatory stability depends on a meticulous degree of ECF homeostasis. The operative homeostatic mechanisms include an *afferent* sensing limb, comprising several volume and stretch detectors distributed throughout the vascular bed, and an *efferent* effector limb. Adjustments in the effector mechanisms occur in response to afferent stimuli by sensing-limb detectors, to modify circulatory parameters. Disorders of either sensing mechanisms or effector mechanisms can lead to failure of adjustment of sodium handling by the kidney, with resultant hypertension or edema formation in the patient with positive sodium balance, or hypotension and hypovolemia in the patient with negative sodium balance.

Afferent (Sensor) Limb

Afferent limb (sensing) sites include low-pressure cardiopulmonary receptors (atrial, ventricular, and pulmonary stretch receptors), high-pressure arterial baroreceptors (carotid, aortic arch, and renal sensors), central nervous system (CNS) receptors, and hepatic receptors (Table 7-2). The cardiac atria possess the distensibility and the compliance needed to monitor changes in intrathoracic venous volume. An increase in left atrial pressure suppresses the release of antidiuretic hormone (ADH), also called arginine vasopressin (AVP). Atrial distention and a sodium load cause release into the circulation of atrial natriuretic peptide (ANP), a polypeptide normally stored in secretory granules within atrial myocytes. The closely related brain natriuretic peptide (BNP) is stored primarily in ventricular myocardium and is released when ventricular diastolic pressure rises. The atrial-renal reflexes enhance renal sodium and water excretion on sensing of a distended left atrium.

The sensitive arterial stretch receptors in the carotid artery, aortic arch, and glomerular afferent arteriole respond to a decrease in arterial pressure. Information from these nerve endings is carried by the vagal and glossopharyngeal nerves to vasomotor centers in the medulla and brainstem. In the normal situation, the prevailing discharge from these receptors exerts a tonic restraining effect on the heart and circulation by inhibiting the sympathetic outflow and augmenting parasympathetic activity. In addition, changes in transmural pressure across the arterial vessels and the atria also influence the secretion of AVP and renin and the release of ANP. Activation of the arterial receptors signals the kidney to retain sodium and water by increases in the sympathetic activity and by increases in vasopressin release. Stimulation of the sympathetic nervous system also enhances the renin-angiotensin-aldosterone system (RAAS). A rise in arterial

Total Body Water for 70 kg Man (60% or 42 Liters)			
		Extracellular Water (1/3 or 14 l)	
Electrolyte (mmol/l)	Intracellular Water (2/3 or 28 l)	*Interstitial (3/4 or 10.5 l)*	*Blood (1/4 or 3.5 l)*
Na	25	140	
K	150	4.5	
Mg	0.5	1.0	
Ca	0.01	2.4	
Cl	2	100	
HCO_3	6	25	
Phos	1.4	1.2	

Table 7-1 Composition of body fluid compartments. The table indicates the relative size of the compartments and their approximate absolute volume (in liters) in a 70-kg adult. Electrolyte concentrations are shown in milimoles per liter.

Major Mechanisms in Extracellular Fluid Homeostasis	
Afferent (Sensing)	**Efferent (Effector)**
Cardiopulmonary receptors	Renal-angiotensin-aldosterone system (RAAS)
Atrial	Prostaglandins
Ventricular	Arginine vasopressin (AVP)
Pulmonary	Natriuretic peptides
High-pressure baroreceptors	Atrial (ANP)
Carotid	Brain (BNP)
Aortic	C-type (CNP)
Renal	Other hormones
Glomerular afferent	Nitric oxide (NO)
Juxtaglomerular apparatus	Endothelin
Central nervous system receptors	Kallikrein-kinin system
Hepatic receptors	

Table 7-2 Homeostatic mechanisms in extracellular fluid (ECF) volume. Adjustments in the effector mechanisms occur in response to afferent stimuli by sensing limb detectors.

pressure elicits the opposite response, resulting in decreased catecholamine release and natriuresis.

Renal sensing mechanisms include the juxtaglomerular apparatus, which is involved in the generation and release of renin from the kidney. Renin secretion is inversely related to perfusion pressure and directly related to intrarenal tissue pressure. Solute delivery to the macula densa is also an important determinant of renin release because of the tubuloglomerular feedback (TGF) mechanism; an increase in chloride passage through the macula densa results in inhibition of renin release, whereas a decrease in concentration results in enhanced secretion of renin. Renal nerve stimulation through activation of β-adrenergic receptors of the juxtaglomerular apparatus cells directly stimulates renin release. Other receptors reside in the CNS and hepatic circulation but have been less well defined.

Efferent (Effector) Limb

The stimulation of the effector limb of the ECF volume homeostasis leads to activation of effector mechanisms (Table 7-2). These effector mechanisms aim predominantly at modulation of renal sodium and water excretion to preserve circulatory stability.

Sympathetic Nervous System

Sympathetic nerves that originate in the prevertebral celiac and paravertebral ganglia innervate cells of the afferent and efferent arterioles, juxtaglomerular apparatus, and renal tubule. Sympathetic nerves alter renal sodium and water handling by direct and indirect mechanisms.[2] Increased nerve stimulation indirectly stimulates proximal tubular sodium reabsorption by altering preglomerular and postglomerular arteriolar tone, thereby influencing filtration fraction. Renal nerves directly stimulate proximal tubular fluid reabsorption through receptors on the basolateral membrane of the proximal convoluted tubule cells. These effects on sodium handling are further amplified by the ability of the sympathetic nerves to stimulate renin release, which leads to the formation of angiotensin II (Ang II) and aldosterone.

Renin-Angiotensin-Aldosterone System

Renin formation by the juxtaglomerular apparatus increases in response to the aforementioned ECF homeostatic afferent limb stimuli. Renin converts angiotensinogen to angiotensin I, which is then converted to Ang II by the action of angiotensin-converting enzyme (ACE); Ang II can subsequently affect circulatory stability and volume homeostasis. It is an effective vasoconstrictor and modulator of renal sodium handling mechanisms at multiple nephron sites. Ang II preferentially increases the efferent arteriolar tone and thus affects the glomerular filtration rate (GFR) and filtration fraction by altering Starling forces across the glomerulus, which leads to enhanced proximal sodium and water retention. Ang II also augments sympathetic neurotransmission and enhances the TGF mechanism. In addition to these indirect mechanisms, Ang II directly enhances proximal tubular volume reabsorption by activating apical membrane sodium-hydrogen (Na^+-H^+) exchangers. In addition to a nephron effect, Ang II enhances sodium absorption by stimulating the adrenal gland to secrete aldosterone, which in turn increases sodium reabsorption in the cortical collecting tubule.

Prostaglandins

Prostaglandins are proteins derived from arachidonic acid that modulate renal blood flow and sodium handling. Important renal prostaglandins include PGI_2, which mediates baroreceptor (but not beta-adrenergic) stimulation of renin release. PGE_2 is stimulated by Ang II and has vasodilatory properties. Increased level of Ang II, AVP, and catecholamines stimulates synthesis of prostaglandins, which in turn act to dilate the renal vasculature, to inhibit sodium and water reabsorption, and further to stimulate renin release. By doing so, renal prostaglandins serve to dampen and counterbalance the physiologic effects of the hormones that elicit their production and so maintain renal function. Inhibition of prostaglandins by nonsteroidal anti-inflammatory drugs (NSAIDs) leads to magnification of the effect of vasoconstricting hormones and unchecked sodium and water retention.

Arginine Vasopressin

The polypeptide AVP is synthesized in supraoptic and paraventricular nuclei of the hypothalamus and is secreted by the posterior pituitary gland. Besides osmotic control of AVP release, there is also a nonosmotic regulatory pathway sensitive to EABV.[3] AVP release is suppressed in response to ECF volume overload sensed by increased afferent impulses from arterial baroreceptors and atrial receptors, whereas decreased ECF volume has the opposite effect. AVP release leads to antidiuresis and, in high doses, to systemic vasoconstriction through the V_1 receptors.[4] The antidiuretic action of AVP results from the effect on the principal cell of the collecting duct through activation of the V_2 receptor. AVP increases the synthesis and

provokes the insertion of aquaporin 2 water channels into the luminal membrane, thereby allowing water to be reabsorbed down the favorable osmotic gradient. AVP may also lead to enhanced Na^+ reabsorption and K^+ secretion. AVP appears to have synergistic effects with aldosterone on sodium transport in the cortical collecting duct.[5] AVP stimulates potassium secretion by the distal nephron, and this serves to preserve potassium balance during ECF depletion, when circulating levels of vasopressin are high and tubular delivery of sodium and fluid is reduced.

Natriuretic Peptides

Atrial natriuretic peptide is a polypeptide hormone that stimulates diuresis, natriuresis, and vasorelaxation. ANP is primarily synthesized in the cardiac atria and released in response to a rise in atrial distention. ANP augments sodium and water excretion by increasing the GFR, possibly by dilating the afferent arteriole and constricting the efferent arteriole. Furthermore, it inhibits sodium reabsorption in the cortical collecting tubule and inner medullary collecting duct, reduces renin and aldosterone secretion, and opposes the vasoconstrictive effects of Ang II. BNP is another natriuretic hormone that is produced in the cardiac ventricles. It induces natriuretic, endocrine, and hemodynamic responses similar to those induced by ANP.[6] Circulating levels of ANP and BNP are elevated in congestive heart failure (CHF) and in cirrhosis with ascites, but not to levels sufficient to prevent edema formation. In addition, in those edematous states, there is resistance to the actions of natriuretic peptides.

C-type natriuretic peptide (CNP) is produced by endothelial cells, where it is believed to play a role in the local regulation of vascular tone and blood flow. However, its physiologic significance in the regulation of sodium and water balance in humans is not well defined.

Other Hormones

Other hormones that contribute to renal sodium handling and ECF volume homeostasis include nitric oxide (NO), endothelin, and the kallikrein-kinin system. NO is an endothelium-derived mediator that has been shown to participate in the natriuretic responses to increases in blood pressure or ECF volume expansion, so-called pressure natriuresis. Endothelins are natriuretic factors, and kinins are potent vasodilator peptides; their physiologic roles are not yet fully defined.

EXTRACELLULAR FLUID VOLUME CONTRACTION

Contraction of ECF volume refers to a decrease in ECF volume caused by sodium or water loss exceeding intake. Losses may be renal or extrarenal through the gastrointestinal tract, skin, and lungs or by sequestration in potential spaces in the body (e.g., abdomen, muscle) that are not in hemodynamic equilibrium with the ECF (Table 7-3). The reduction in ECF volume occurs simultaneously from both the interstitial and the intravascular compartment and is determined by whether the volume loss is primarily solute-free water or a combination of sodium and water. The loss of solute-free water has a lesser effect on intravascular volume because of the smaller amount of water present in the ECF compared with the ICF and the free movement of water between fluid compartments.

Major Causes of Extracellular Fluid Volume Depletion

Renal	Extrarenal
Diuretic use	Gastrointestinal losses
Tubular disorders	Vomiting
Genetic	Gastrointestinal suctioning
Bartter and Gitelman syndromes	Diarrhea
Pseudohypoaldosteronism type 1	Ileostomy/colostomy secretions
Acquired tubular disorders	Dermal losses
Acute kidney injury	Sweat
Recovery phase of oliguric kidney injury	Exudative skin disease
Release of urinary tract obstruction	Third-space sequestration
Hormonal and metabolic disturbances	Ascites
Mineralocorticoid deficiency or resistance	Pleural effusion, hydrothorax
Primary adrenal insufficiency (Addison disease)	Intestinal obstruction
Hyporeninemic hypoaldosteronism	Retroperitoneal collection
Diabetes mellitus	Hemorrhage
Chronic interstitial renal diseases	Internal
Solute diuresis	External
Renal water loss	
Diabetes insipidus	

Table 7-3 Major causes of extracellular fluid volume depletion

Extrarenal Causes

Gastrointestinal Losses

Approximately 3 to 6 liters of fluids and digestive juices are secreted daily throughout the gastrointestinal tract, and most of this fluid is reabsorbed. Vomiting or nasogastric suction may cause volume loss that is usually accompanied by metabolic alkalosis, whereas diarrhea may result in volume depletion that is accompanied by metabolic acidosis.

Dermal Losses

Sweat is typically hypotonic, leading to more water loss than salt loss. Sweat production can be excessive in high ambient temperature or with prolonged exercise in hot, humid climates and may lead to volume depletion. Loss of the skin barrier with superficial burns and exudative skin lesions may lead to significant ECF volume depletion.

Third-Space Sequestration

Body fluid accumulation in potential spaces that are not in hemodynamic equilibrium with the ECF compartment can cause volume depletion. This pathologic accumulation, often called third-space sequestration, includes ascites, hydrothorax, and intestinal obstruction, with fluid collecting in the peritoneal cavity, pleural space, and intestines, respectively, and leading to significant ECF volume loss. Severe pancreatitis may result in retroperitoneal fluid collections.

Hemorrhage

Hemorrhage occurring internally (e.g., from bleeding esophageal varices) or externally (e.g., trauma) may lead to significant volume loss.

Renal Losses

In the normal individual, about 25,000 mmol of sodium is filtered every day, and a small amount of that quantity is excreted in the urine. The small quantities of sodium excreted in urine relative to the filtered load depend on intact tubular reabsorptive mechanisms to adjust urinary sodium excretion according to the degree needed to maintain ECF homeostasis. Impairment in the integrity of these sodium reabsorptive mechanisms can result in significant sodium deficit and volume depletion.

Diuretic Use

Most of the widely used diuretic medications inhibit specific sites for sodium reabsorption at different segments of the nephron. Diuretics may cause renal sodium wasting, volume contraction, and metabolic acid-base disturbances if abused or inappropriately prescribed. Ingestion of osmotic diuretics results in obligatory renal sodium and water loss, as discussed in detail later.

Genetic and Acquired Tubular Disorders

Tubular sodium reabsorption may be disrupted in several genetic disorders that include Bartter syndrome and Gitelman syndrome (see Chapter 49). These autosomal recessive disorders are caused by mutations of sodium transporters that are targets of diuretics or other transporters that are their essential cellular partners. Both syndromes result in sodium wasting, volume contraction, and hypokalemic metabolic alkalosis.[7] The tubular defect in Bartter syndrome resembles that of chronic ingestion of loop diuretics. Five variants result from a defect in any of several genes that direct the functioning of transporters in the thick ascending limb of Henle loop. Gitelman syndrome, which is more common in adults, is caused by a defect of sodium chloride (NaCl, salt) reabsorption in the distal tubule. It resembles chronic thiazide diuretic ingestion. Pseudohypoaldosteronism type 1 (PHA1) is a rare inherited disorder characterized by renal sodium wasting and hyperkalemic metabolic acidosis. Acquired tubular disorders that may be accompanied by salt wasting include acute kidney injury (AKI), during the recovery phase of oliguric AKI or urinary obstruction (see Chapters 60 and 71).

Hormonal and Metabolic Disturbances

Mineralocorticoid deficiency and resistance states often lead to sodium wasting. This may occur in the setting of primary adrenal insufficiency (Addison disease) and PHA1. Salt wasting can also be seen in chronic tubular and interstitial renal diseases. Severe hyperglycemia or high levels of blood urea during release of urinary tract obstruction can lead to obligatory renal sodium and water loss secondary to glucosuria or urea diuresis, respectively.

Renal Water Loss

Diabetes insipidus (DI) represents a spectrum of diseases resulting from AVP deficiency, causing *central* DI, or tubular resistance, causing *nephrogenic* DI, to the actions of AVP. The most common causes of polyuria from nephrogenic DI in adults are chronic lithium ingestion, hypercalcemia, and less frequently, hypokalemia (see Chapter 8). In these disorders the tubular reabsorption of solute-free water is impaired. This generally results in a lesser effect on ECF volume because, in contrast to sodium, there is a relatively smaller amount of the total body water in the ECF compartment compared with the ICF compartment.

Clinical Manifestations

The spectrum of the clinical manifestations of volume contraction depends on the amount and rate of ECF volume loss as well as on the vascular and renal responses to that loss. An adequate history and physical examination are crucial to elucidate the cause of hypovolemia. Symptoms are usually nonspecific and can range from mild postural symptoms, thirst, muscle cramps, and weakness to drowsiness and disturbed mentation with profound volume loss. Physical examination may reveal tachycardia, cold clammy skin, postural or recumbent hypotension, and reduced urine output, depending on the degree of volume loss (Box 7-1). Reduced jugular venous pressure (JVP) noted at the base of the neck is a useful parameter of volume depletion and may roughly estimate the central venous pressure (CVP). However, an elevated CVP does not exclude hypovolemia in patients with underlying cardiac failure or pulmonary hypertension. The lack of symptoms or discernible physical findings does not preclude volume depletion in an appropriate clinical setting, and hemodynamic monitoring and administration of a fluid challenge may be necessary.

Clinical Evaluation of Extracellular Fluid Volume Depletion

Mild to Moderate Volume Loss

- Thirst
- Delay in capillary refill
- Postural dizziness, weakness
- Dry mucous membranes and axillae
- Cool clammy extremities and collapsed peripheral veins
- Tachypnea
- Tachycardia with pulse rate >100 beats/min, or postural pulse increment of 30 beats/min or more
- Postural hypotension (systolic blood pressure decrease >20 mm Hg on standing)
- Low jugular venous pulse
- Oliguria

Severe Volume Loss and Hypovolemic Shock

- Depressed mental status (or loss of consciousness)
- Peripheral cyanosis
- Reduced skin turgor (in young patients)
- Marked tachycardia, low pulse volume
- Supine hypotension (systolic blood pressure <100 mm Hg)

Box 7-1 Clinical evaluation of extracellular fluid volume depletion

Laboratory Tests

Laboratory parameters may assist in defining the underlying causes of volume depletion. Hemoconcentration and increased serum albumin concentration may be seen early with hypovolemia, but anemia or hypoalbuminemia caused by a concomitant disease may confound interpretation of these laboratory values. In healthy individuals, the blood urea nitrogen (BUN)–serum creatinine ratio is approximately 10 mg/dl (40 mmol/l). In volume-contracted states, this ratio may significantly increase because of an associated differential increase in urea reabsorption in the collecting duct. Several clinical conditions affect this ratio. Upper gastrointestinal hemorrhage and administration of corticosteroids increase urea production, and hence the BUN/creatinine ratio increases. Malnutrition and underlying liver disease diminish urea production, and thus the ratio is less helpful to support volume depletion in such clinical settings.

Urine osmolality and specific gravity may be elevated in hypovolemic states but may be altered by an underlying renal disease that leads to renal sodium wasting, concomitant intake of diuretics, or a solute diuresis. Hypovolemia normally promotes avid renal sodium reabsorption, resulting in low urine sodium concentration and low fractional excretion of sodium. Urine chloride follows a similar pattern because sodium and chloride are generally reabsorbed together. Volume depletion with metabolic alkalosis (e.g., with vomiting) is an exception because of the need to excrete the excess bicarbonate in conjunction with sodium to maintain electroneutrality; in this case, urine chloride concentration is a better index of sodium

avidity. The fractional excretion of sodium (FE_{Na}) is calculated by the following formula:

$$FE_{Na} = [U_{Na} \times P_{creat} / U_{creat} \times P_{Na}] \times 100$$

where U_{Na} and U_{creat} are urinary sodium and creatinine concentrations, respectively, and P_{Na} and P_{creat} are serum sodium and creatinine concentrations, respectively. Elevated FE_{Na} is most helpful in the diagnosis of AKI; FE_{Na} less than 1% is consistent with volume depletion.

Therapy for Extracellular Volume Contraction

The goal of treatment for ECF volume depletion is to replace the fluid deficit and ongoing losses, in general with a fluid that resembles the lost fluid. The first step is estimating the magnitude of volume loss using such tools as clinical parameters for mild to moderate versus severe volume loss (Box 7-1), which can also be assessed by invasive monitoring when necessary. The initial replacement volume is then determined and delivered with an administration rate that is tailored to the patient, as subsequently judged by frequent monitoring of clinical parameters. Mild volume contraction can usually be corrected through the oral route. In patients with hypovolemic shock and evidence of life-threatening circulatory collapse or organ dysfunction, intravenous (IV) fluid must be administered as rapidly as possible until clinical parameters improve. In most patients, however, a slow, more careful approach is warranted, particularly in elderly patients and those with an underlying cardiac condition, to avoid overcorrection with subsequent pulmonary or peripheral edema.

Crystalloid solutions with sodium as the principal cation are effective because they distribute primarily in the ECF. One third of an infusate of isotonic saline remains inside and expands the intravascular compartment, whereas two thirds distributes into the interstitial compartment. Colloid-containing solutions include human albumin (5% and 25%) and hetastarch (6% hydroxyethyl starch, HES). Because of large molecular size, these solutions remain within the vascular compartment, provided the transcapillary barrier is intact and not disrupted by capillary leak states, such as often occurs with multiorgan failure or systemic inflammatory response syndrome. The solutions augment the plasma oncotic pressure and thus expand the plasma volume by counteracting the capillary hydraulic pressure.

Colloid-containing solutions have not shown an advantage in the treatment of hypovolemic states. A meta-analysis of 55 studies showed no outcome difference between critically ill patients who received albumin and those who received crystalloids.[8] A large, multicenter trial that randomized medical and surgical critical patients to receive fluid resuscitation with 4% albumin or normal saline showed similar mortality, measured morbidity parameters, and hospitalization rates in the two groups.[9] Conversely, a recent study randomly assigned intensive care unit patients with severe sepsis to fluid resuscitation with either 6% hetastarch or Ringer acetate.[10] Patients who received hetastarch had increased mortality risk and were more likely to require renal replacement therapy, raising concerns about its safety in such patients. Consequently, artificial colloids should be avoided in patients with severe sepsis or at risk of developing AKI.[11]

Isotonic saline is usually the preferred initial choice in volume-depleted patients with normal serum [Na^+] and most of those with low serum [Na^+]. Furthermore, isotonic saline is the preferred fluid to restore ECF volume in hypovolemic patients with hypernatremia. Once euvolemia is established, further fluid therapy should be delivered to gradually correct tonicity in the form of hypotonic (0.45%) saline. Administration of large volumes of isotonic saline may result in the development of hyperchloremic metabolic acidosis; lactated-Ringer solution can be substituted if that takes place. Hypokalemia may be present initially or may subsequently ensue. It should be corrected by adding appropriate amounts of potassium chloride to replacement solutions.

Hypovolemic shock may be accompanied by lactic acidosis resulting from tissue hypoperfusion. Fluid resuscitation restores tissue oxygenation and will decrease the production of lactate. Correction of acidosis with sodium bicarbonate ($NaHCO_3$) has the potential for increasing tonicity, expanding volume, worsening intracellular acidosis from increased carbon dioxide production, and not improving hemodynamics compared with isotonic saline. Use of $NaHCO_3$ for correction of cardiac contractility coexisting with lactic acidosis has not been well documented by clinical studies. Therefore, $NaHCO_3$ to manage lactic acidosis in the setting of volume depletion is not recommended (unless arterial pH <7.1).

EXTRACELLULAR FLUID VOLUME EXPANSION

Expansion of ECF volume refers to excess fluid accumulation in the ECF compartment, usually resulting from sodium and water retention by the kidneys. Generalized edema results from an apparent increase in the interstitial fluid volume, most often in response to cardiac failure, cirrhosis with ascites, and nephrotic syndrome. Weight gain of several liters usually precedes clinically apparent edema. Localized excess fluid may accumulate in the peritoneal and pleural cavities, leading to ascites and pleural effusion, respectively.

Pathogenesis

Renal sodium and water retention secondary to arterial underfilling leads to an alteration in capillary hemodynamics that favors fluid movement from the intravascular compartment into the interstitium. In general, these two processes account for edema formation.

Capillary Hemodynamic Disturbances

According to the Starling equation, the exchange of fluid between the plasma and the interstitium is determined by the hydrostatic and oncotic pressures in each compartment. Interstitial fluid excess results from a decrease in plasma oncotic pressure or an increase in capillary hydrostatic pressure. In other words, edema is a result of an increase in fluid movement from the intravascular compartment to the interstitial space or a decrease in fluid movement from the interstitial space to the intravascular compartment, or both. Thus, the degree of interstitial fluid accumulation as determined by rate of fluid removal by the lymphatic vessels is a determinant of edema.

The capillary hydrostatic pressure is relatively insensitive to alterations in arterial pressure. The stability of the capillary pressure is a result of variations in the precapillary sphincter, which governs how much arterial pressure is transmitted to the capillary, a locally controlled response called *autoregulation*. In contrast, the venous end is not similarly well regulated. Therefore, when the blood volume expands, as in CHF and renal disease, capillary hydrostatic pressure increases, and edema ensues. Venous obstruction works by the same mechanism to cause edema, as exemplified at least partially by ascites formation in liver cirrhosis and by acute pulmonary edema after sudden impairment in cardiac function (e.g., myocardial infarction). In hepatic cirrhosis and nephrotic syndrome, another factor in edema formation is reduction in plasma oncotic pressure, with a tendency for fluid transudation into the interstitial space. The balance of the Starling forces acting on the capillary favors the net filtration

into the interstitium because capillary hydrostatic pressure exceeds the plasma colloid pressure in several tissues throughout the length of the capillary. In these tissues, a substantial amount of filtered fluid is returned to the circulation through lymphatic channels, which serve as a protective mechanism for minimizing edema formation.

Renal Sodium Retention

The mechanism for maintenance of ECF volume expansion and edema formation is renal sodium retention, which can be primary or secondary in response to reduction in EABV (Table 7-4).

Primary Renal Sodium Retention A primary defect in renal sodium excretion can occur with both acute and chronic renal failure and with glomerular disease. Patients with AKI have a limited ability to excrete sodium and water. Advanced chronic kidney disease may lead to sodium and water retention by GFR reduction secondary to a decrease in functioning nephrons. Primary renal sodium retention characterizes some forms of glomerulonephritis and occurs through incompletely understood mechanisms in the presence of a relatively suppressed renin-angiotensin system (RAS), but frequently with decreased GFR.

States of mineralocorticoid excess or enhanced mineralocorticoid activity are associated with a phase of sodium retention. However, because of the phenomenon of *mineralocorticoid escape,* the clinical manifestation is generally hypertension rather than hypervolemia. In normal individuals, administration of a high-dose mineralocorticoid initially increases renal sodium retention so that ECF volume is increased. However, renal sodium retention then ceases, spontaneous diuresis ensues, sodium balance is reestablished, and there is no detectable edema. This escape from mineralocorticoid-mediated sodium retention explains why edema is not a characteristic feature of primary hyperaldosteronism. The pathophysiologic mechanism of mineralocorticoid escape involves an increase in GFR and reduction of proximal tubular sodium and water reabsorption. This leads to an increase in sodium and water delivery to the distal nephron site of aldosterone action, which overrides the sodium reabsorption of aldosterone. Other mechanisms believed to account for this phenomenon involve decreased expression of distal tubular thiazide-sensitive NaCl cotransporters,[12] increased secretion of ANP induced by hypervolemia,[13] and pressure natriuresis. *Pressure natriuresis* refers to the phenomenon whereby increasing renal perfusion pressure (caused in part by systemic hypertension) enhances sodium excretion. These mechanisms act by decreasing tubular reabsorption at sites other than the aldosterone-sensitive cortical collecting duct.

Major Causes of Extracellular Volume Fluid Expansion

Primary Renal Sodium Retention	Secondary Renal Sodium Retention*
Acute kidney injury	Cardiac failure
Advanced chronic kidney disease	Cirrhosis
Glomerular diseases	Nephrotic syndrome
	Idiopathic edema
	Drug-induced edema
	Pregnancy

Table 7-4 Major causes of extracellular fluid volume expansion. *Secondary to reduced effective arterial blood volume depletion (arterial underfilling).

Renal Sodium Retention as Compensatory Response to Effective Arterial Volume Depletion

Pathophysiology of Arterial Underfilling Estimates of blood volume distribution indicate that 85% of blood circulates on the low-pressure venous side of the circulation, whereas an estimated 15% of blood is circulating in the high-pressure arterial circulation. Thus, an increase in total blood volume could occur, even when there is underfilling of the arterial circulation, if the increase in total blood volume is primarily caused by expansion of the venous compartment. Underfilling of the arterial circulation could result from a decrease in cardiac output, as occurs in low-output cardiac failure, or from systemic arterial vasodilation, which occurs early in cirrhosis as a result of decreased systemic vascular resistance (SVR) in the splanchnic circulation.[14] This hypothesis proposes that the events triggered by arterial underfilling as a result of either decreased cardiac output or systemic arterial vasodilation are compensatory responses necessary to restore arterial circulatory integrity (Fig. 7-1).

Renal Response to Arterial Underfilling If there is arterial underfilling, either due to a decrease in cardiac output or due to systemic

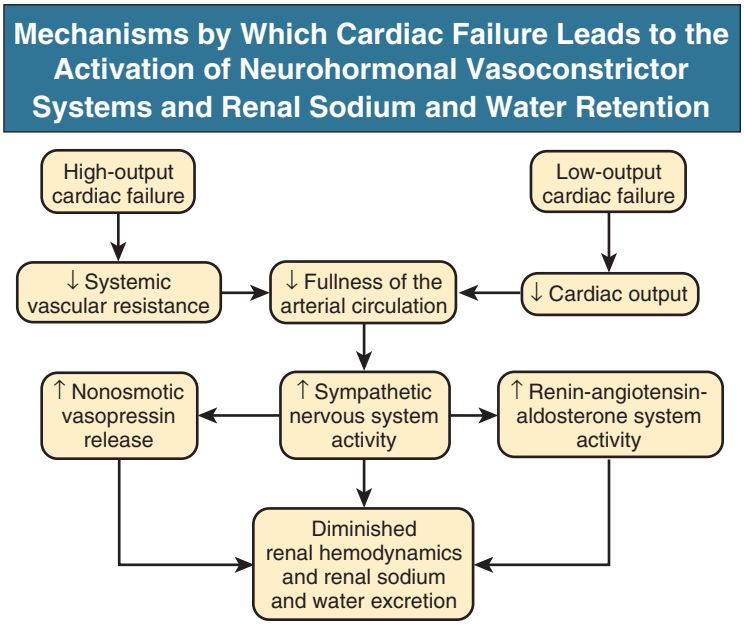

Figure 7-1 Mechanisms of cardiac failure. Cardiac failure results in activation of neurohormonal vasoconstrictor systems and retention of renal sodium and water. *(Modified from reference 48.)*

arterial vasodilation, the underfilling is sensed by the arterial stretch receptors. This leads to activation of the efferent limb of body fluid volume homeostasis. Specifically, a decrease in glossopharyngeal and vagal tone from the carotid and aortic receptors to the CNS leads to a rapid increase in sympathetic activity with associated activation of the RAAS axis and nonosmotic release of vasopressin. The resultant increase in SVR and renal sodium and water retention attenuates the arterial underfilling and associated diminished arterial perfusion. The purpose of these concerted actions is to maintain the arterial circulatory integrity and restore the perfusion to the vital organs, which is mandatory for survival.

Sodium and Water Retention in Cardiac Failure

The renal sodium and water retention that occurs in CHF involves several mediators.[15] Decreased cardiac output with arterial underfilling leads to reduced stretch of arterial baroreceptors. This results in increased sympathetic discharge from the CNS and resultant activation of the RAAS. Adrenergic stimulation and increased Ang II activate receptors on the proximal tubular epithelium that enhance sodium reabsorption. The renal vasoconstriction of the glomerular efferent arteriole by Ang II in CHF also alters net Starling forces in the peritubular capillary in a direction to enhance sodium reabsorption.[16] Thus, angiotensin and α-adrenergic stimulation increase sodium reabsorption in the proximal tubule by a direct effect on the proximal tubule epithelium and secondarily by renal vasoconstriction. This subsequently leads to decreased sodium delivery to the collecting duct, which is the major site of action of aldosterone and the natriuretic peptides. CHF patients experience renal resistance to natriuretic effects of atrial and ventricular peptides. The resultant decreased sodium delivery to the distal nephron impairs the normal escape mechanism from the sodium-retaining effect of aldosterone and impairs the effect of natriuretic peptides. These effects help explain why sodium retention and ECF expansion occur in CHF (Fig. 7-2). Accordingly, CHF patients have substantial natriuresis when spironolactone, a competitive mineralocorticoid receptor antagonist, is given in adequate doses to compete with increased endogenous aldosterone levels.[17]

Another outcome of the neurohumoral activation that occurs in cardiac failure is the baroreceptor-mediated nonosmotic release of AVP.[18] This nonosmotic AVP stimulation overrides the osmotic regulation of AVP and is the major factor leading to the hyponatremia associated with CHF.[19] AVP causes antidiuresis by activating V_2 receptors on the basolateral surface of the principal cells in the collecting duct.[20] Activation of these receptors initiates a cascade of intracellular signaling events by means of the adenylyl cyclase–cyclic adenosine monophosphate (cAMP) pathway, leading to an increase in aquaporin 2 (AQP2) water channel protein expression and its trafficking to the apical membrane of the collecting duct. This sequence of events leads to increased water reabsorption and can cause hyponatremia, which is an ominous prognostic indicator in patients with heart failure.[21] Concurrently, increased nonosmotic AVP release stimulates V_1 receptors on vascular smooth muscle cells and thereby may increase SVR. This adaptive vasoconstrictive response may become maladaptive and contribute to cardiac dysfunction in patients with severe heart failure.

The atrial-renal reflexes, which normally enhance renal sodium excretion, are impaired during CHF because renal sodium and water retention occurs despite elevated atrial pressure. Moreover, in contrast to normal subjects, plasma levels of ANP were found not to increase further during a saline load in patients with dilated cardiomyopathy and mild heart failure, and the natriuretic response was also blunted. The attenuation of these reflexes on the low-pressure side of the circulation not only is attributable to a blunting of the atrial-renal reflexes but also may be caused by counteracting arterial baroreceptor-renal reflexes. Autonomic dysfunction and blunted arterial baroreceptor sensitivity in CHF occur and are associated with increased circulating catecholamines and increased renal sympathetic activity. There is also evidence for parasympathetic withdrawal in CHF in addition to the increase in sympathetic drive.

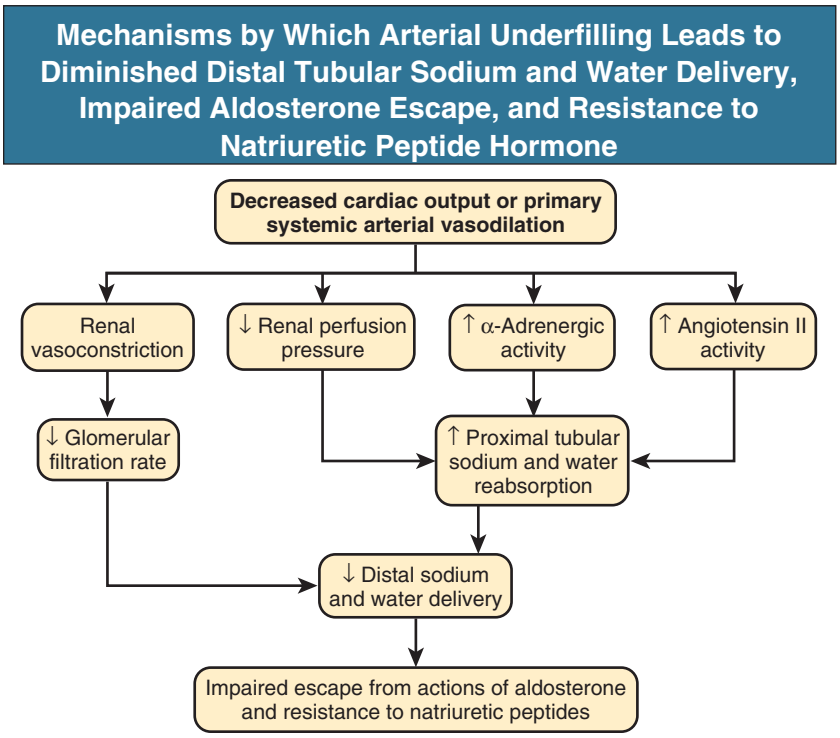

Figure 7-2 Mechanisms of arterial underfilling. Underfilling of arteries leads to reduced delivery of distal tubular sodium and water, impaired aldosterone escape, and resistance to natriuretic peptide hormone. *(Modified from reference 48.)*

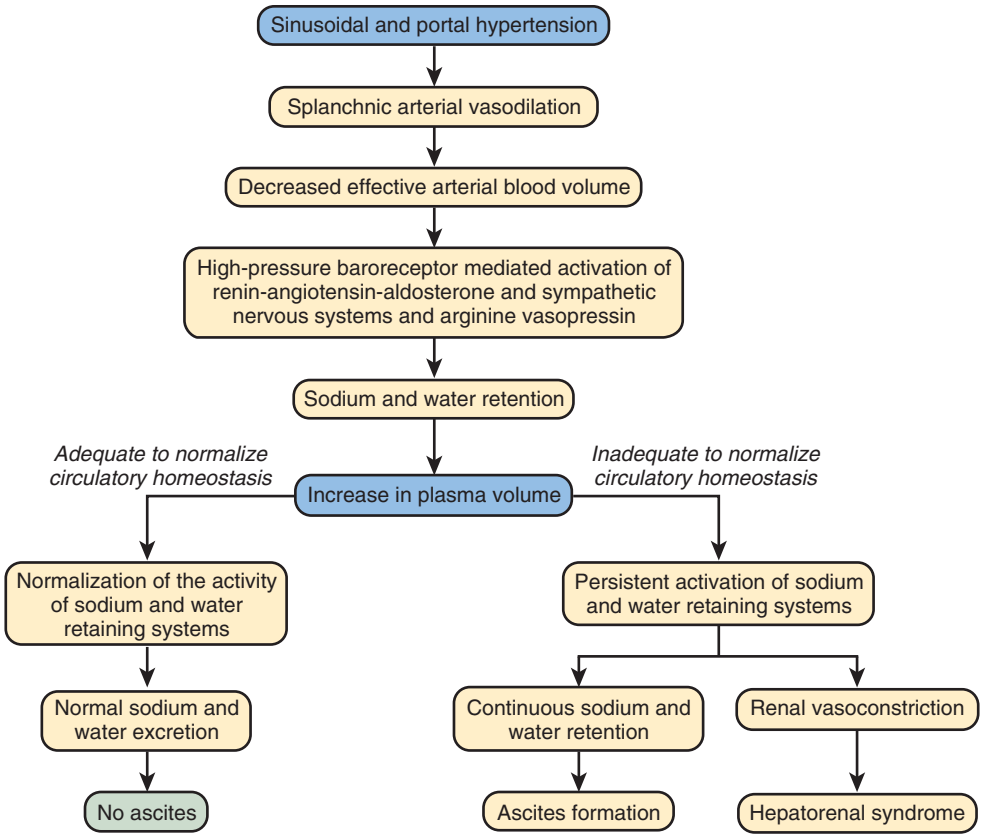

Figure 7-3 Liver cirrhosis. Pathogenesis of functional renal abnormalities and ascites formation. *(Modified from reference 27.)*

Sodium and Water Retention in Cirrhosis

Many pathogenetic aspects of sodium and water retention are similar in cirrhosis and CHF (Fig. 7-3). The arterial underfilling in cirrhosis, however, occurs secondary to splanchnic arterial vasodilation, with resultant water and sodium retention. The initial event in ascites formation in cirrhotic patients is likely sinusoidal and portal hypertension.[22] In cirrhotic patients, this is a consequence of distortion of hepatic architecture, increased hepatic vascular tone, or increased splenohepatic flow. Decreased intrahepatic bioavailability of NO and increased production of vasoconstrictors (angiotensin, endothelin) also are responsible for increased resistance in the hepatic vasculature.[23] Portal hypertension caused by increased sinusoidal pressure activates vasodilatory mechanisms in the splanchnic circulation.[24] These mechanisms, mediated at least partly by NO and carbon monoxide (CO) overproduction, lead to splanchnic and peripheral arteriolar vasodilation. In advanced stages of cirrhosis, arteriolar vasodilation causes underfilling of the systemic arterial vascular space. This event, through a decrease in EABV, leads to a fall in arterial pressure. Consequently, baroreceptor-mediated activation of the RAAS, sympathetic nervous system stimulation, and nonosmotic release of ADH occur to restore the blood volume homeostasis.[25] This involves compensatory vasoconstriction as well as renal sodium and water retention. However, splanchnic vasodilation also increases splanchnic lymph production, which exceeds the lymph transporting capacity, and thus lymph leakage into the peritoneal cavity occurs with ascites development.[26] Persistent renal sodium and water retention, along with increased splanchnic vascular permeability with lymph leakage into the peritoneal cavity, plays the major role in a sustained ascites formation.

Sodium and Water Retention in Nephrotic Syndrome

Unlike CHF and liver cirrhosis, in which the kidneys are structurally normal, the nephrotic syndrome is characterized by diseased kidneys that are often functionally impaired. Nephrotic patients typically have a higher arterial blood pressure, higher GFR, and less impairment of sodium and water excretion than patients with CHF and cirrhosis. Whereas edema is recognized as a major clinical manifestation of the nephrotic syndrome, its pathogenetic mechanism remains less clearly defined. Two possible explanations are the underfill and the overfill theories (Fig. 7-4). The underfill theory suggests that reduced plasma oncotic pressure from proteinuria increases fluid movement from the vascular to interstitial compartment. The resultant arterial underfilling culminates in activation of homeostatic mechanisms involving the sympathetic nervous system and the RAAS. The overfill theory, on the other hand, implicates primary renal sodium and water retention that translates into elevated total plasma volume, hypertension, and suppressed RAAS. Distinguishing between the two situations is important because it influences the approach to diuretic use in nephrotic patients.

The following observations support the underfill theory for edema formation. Plasma volume, systemic arterial blood pressure, and cardiac output are diminished in some nephrotic patients, especially in children with MCD (see Chapter 17), and can be corrected by plasma volume expansion with albumin infusion. The Starling forces governing the fluid movement across the capillary wall equal the difference of the hydrostatic pressure and the oncotic pressure gradients. The gradual decrease in the plasma albumin concentration and the plasma oncotic pressure is mitigated by the reduced entry of

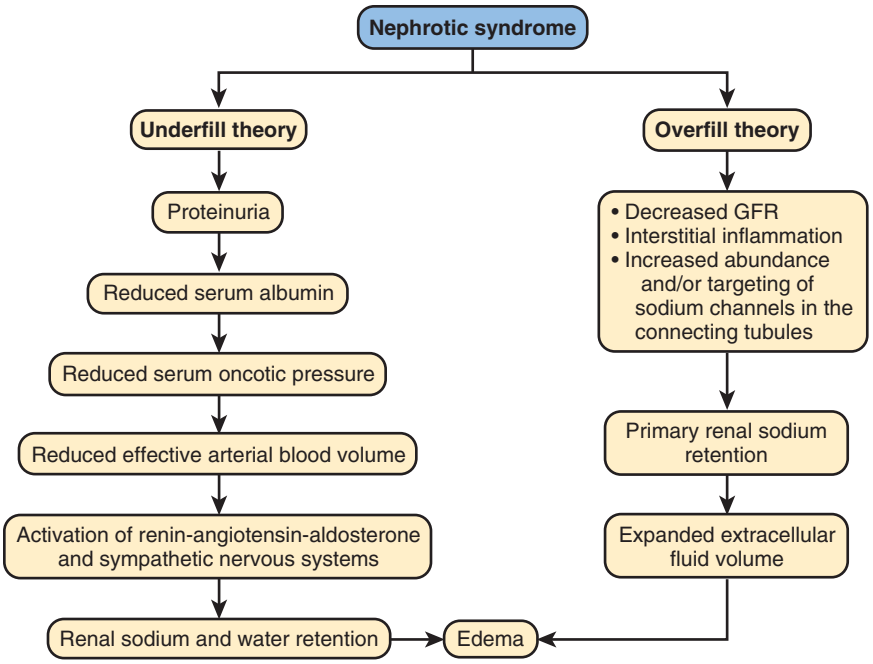

Figure 7-4 Nephrotic syndrome. Underfill and overfill theories in pathogenesis of edema in nephrotic syndrome.

albumin into the interstitial space and a concurrent decline in interstitial oncotic pressure. Consequently, less ECF volume expansion and edema formation is noted unless hypoalbuminemia is severe.[28] Thus, nephrotic patients who are underfilled and are predisposed to AKI despite generalized edema generally have serum albumin concentration of less than 2 g/dl (20 g/l).

Observations supporting the overfill theory include studies of adults with MCD who have increased blood volume and blood pressure. After remission induced by prednisone (or prednisolone), there are reductions in plasma volume and blood pressure decline, with an increase in plasma renin activity. However, evaluation of intravascular volume is somewhat unreliable because the afferent stimulus for edema formation appears to be a dynamic process, with different results at different phases of edema formation.[28] Also supporting primary renal sodium retention, experimental studies in animals with unilateral nephrotic syndrome demonstrate that sodium retention occurs secondary to increased reabsorption in the collecting tubules.[29] Increased abundance and apical targeting of epithelial sodium channel (ENaC) subunits in the connecting tubule and collecting duct play an important role in the pathogenesis of sodium retention in nephrotic syndrome in experimental animals.[30]

In summary, nephrotic patients with arterial underfilling are more likely to have MCD with severe hypoalbuminemia, preserved GFR, and low blood pressure or postural hypotension. Other glomerular diseases are more often associated with an overfill picture with volume expansion, raised blood pressure, and a decline in GFR. It has been postulated that interstitial inflammatory cells, a feature of some glomerular diseases other than MCD, may facilitate an increase in sodium retention and hypertension by releasing mediators that cause vasoconstriction.[31]

Drug-Induced Edema

Ingestion of several types of drugs may generate peripheral edema. Systemic vasodilators such as minoxidil and diazoxide induce arterial underfilling and subsequent sodium with water retention, through mechanisms similar to those in CHF or cirrhosis. Dihydropyridine calcium channel blockers may cause peripheral edema, which is related to redistribution of fluid from the vascular space into the interstitium, possibly induced by capillary afferent sphincter vasodilation in the absence of an appropriate microcirculatory myogenic reflex. This facilitates transmission of the systemic pressure to the capillary circulation.[32] Fluid retention and CHF exacerbation may be seen with thiazolidinedione therapy in patients with type 2 diabetes mellitus, involving activation of peroxisome proliferator–activated receptor γ (PPARγ) that leads to stimulation of sodium reabsorption by the sodium channels in collecting tubule cells.[33] NSAIDs can exacerbate volume expansion in CHF and cirrhotic patients by decreasing vasodilatory prostaglandins in the afferent arteriole of the glomerulus.

Idiopathic Edema

Idiopathic edema is a poorly defined syndrome characterized by intermittent edema secondary to sodium and water retention and most frequently noted on the upright position. Patients often complain of face and hand edema, leg swelling, and variable weight gain.[34] Idiopathic edema occurs most often in menstruating women. These patients also often misuse diuretics or laxatives, which may chronically stimulate the RAAS. The diagnosis of idiopathic edema is usually made by exclusion of other causes after history, physical examination, and investigation.

Sodium and Water Retention in Pregnancy

In the first trimester of normal pregnancy, systemic arterial vasodilation and a decrease in blood pressure occur in association with a compensatory increase in cardiac output.[35] After this state of arterial underfilling, RAAS activation with renal sodium and water retention occurs early in normal pregnancy. Decreased plasma osmolality, stimulated thirst, and persistent nonosmotic vasopressin release are other features of normal pregnancy. In contrast to disease states such as CHF and cirrhosis, pregnancy is associated with an increase in GFR and renal blood flow. The increased GFR, leading to higher filtered load and increased distal sodium delivery in pregnancy, no doubt contributes to the better escape from the sodium-retaining effect of aldosterone compared with CHF patients. This attenuates edema formation compared with other edematous disorders.

However, the cause of peripheral vasodilation in pregnancy is multifactorial. Estrogen upregulates endothelial NO synthase in pregnancy, and inhibitors of NO synthesis normalize the systemic and renal hemodynamics in rat pregnancy.[36] The placenta creates an arteriovenous fistula in the maternal circulation, which contributes to systemic vasodilation. High levels of vasodilating prostaglandins are another contributing factor.[37] Relaxin level increases early in gestation, which can also contribute to the circulatory changes in the kidney and other maternal organs during pregnancy.[38]

Clinical Manifestations

A thorough patient history and physical examination are important to identify the etiology of ECF volume expansion and edema. A known history of an underlying disease, such as coronary artery disease, hypertension, or liver cirrhosis, can pinpoint the underlying mechanism of edema formation. Patients with left-sided heart failure may present with exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Patients with right-sided heart failure or biventricular failure may exhibit weight gain and lower limb swelling. Physical examination reveals increased JVP, pulmonary crackles, a third heart sound, or dependent peripheral edema that may be elicited in the ankles or sacrum.

Nephrotic patients classically present with periorbital edema because of their ability to lie flat during sleep. However, those with severe disease may exhibit marked generalized edema with anasarca. Cirrhotic patients present with ascites and lower limb edema caused by portal hypertension and hypoalbuminemia. Physical examination may reveal stigmata of chronic liver disease and splenomegaly.

Diagnostic and Therapeutic Approach to Extracellular Volume Expansion

Management of ECF volume expansion consists of recognizing and treating the underlying cause and attempting to achieve negative sodium balance by dietary sodium restriction and administration of diuretics. Before embarking on diuretic therapy in a congested patient, it is imperative to appreciate that ECF volume expansion may have occurred as a compensatory mechanism for arterial underfilling, as in CHF and cirrhosis. A judicious approach is therefore necessary to avoid a precipitous fall in cardiac output and tissue perfusion. Rapid removal of excess fluid is generally necessary only in life-threatening situations, such as pulmonary edema and hypervolemia-induced hypertension, whereas a more gradual approach is warranted in less compromised patients.

Moderate dietary sodium restriction (2 to 3 g/day; 86 to 130 mmol/day) should be encouraged. If salt substitutes are used, it is important to consider that these contain potassium chloride and thus should not be used for patients with advanced renal impairment or those concurrently taking potassium-sparing diuretics. Restriction of total fluid intake is usually necessary only for hyponatremic patients. Any concomitant medications that promote sodium restriction (e.g., NSAIDs) should be discontinued. Diuretics are the cornerstone of therapy to remove excess volume. Other measures can be used in patients with inadequate response or lack of response to diuretics. In those with liver cirrhosis, large-volume paracentesis with albumin infusion can be used to remove large volumes of ascitic fluid. Interventional maneuvers to shunt ascitic fluid to a central vein can also be considered in refractory ascites and may improve the GFR and sodium excretion. Extracorporeal fluid removal by ultrafiltration can be used in patients with acute decompensated heart failure accompanied by renal insufficiency or diuretic resistance. ACE inhibitors and angiotensin receptor blockers (ARBs) are adjunctive disease-modifying agents in patients with CHF or nephrotic syndrome. Additional aggressive therapies for cardiac failure include antiarrhythmic agents, positive inotropes, and mechanical devices, such as left ventricular assist device.

The treatment of suspected diuretic-induced edema, which is associated with persistent secondary hyperaldosteronism, is to withdraw diuretics for 3 to 4 weeks after informing the patient that edema may worsen initially. If the edema does not improve after 4 weeks, spironolactone can be instituted at 50 to 100 mg/day and increased to a maximum of 200 mg/day.

Diuretics

Principles of Action

Diuretics are the mainstay of therapy for edematous states, with five classes based on the predominant sites of diuretic action along the nephron (Fig. 7-5). Most diuretics reach their luminal transport sites through tubular fluid secretion. All diuretics except osmotic agents have a high degree of protein binding, which limits glomerular filtration, traps the drug in the vascular spaces, and allows it to be delivered to the proximal convoluted tubule for secretion.[39] Diuretics act by inhibiting sodium reabsorption with an accompanying anion, usually chloride. The resultant natriuresis decreases the ECF volume. Despite administration of a diuretic causing a sustained net deficit in total body sodium, the time course of natriuresis is limited because renal mechanisms attenuate the sodium excretion. This phenomenon is known as *diuretic braking,* and its mechanism includes activation of the sympathetic nervous system and RAAS, decreased systemic and renal arterial blood pressure, hypertrophy of the distal nephron cells with increased expression of epithelial transporters, and perhaps alterations in natriuretic hormones (e.g., ANP).[41]

Adverse Effects

Many common diuretics are derived from sulfanilamide and may therefore induce allergy in susceptible patients, manifested as hypersensitivity reactions, usually as a rash or rarely acute interstitial nephritis. The most serious adverse effects of diuretics are electrolyte disturbances. By blocking sodium reabsorption in the loop of Henle and the distal tubule, loop and thiazide diuretics cause natriuresis and increased distal sodium delivery. The resultant negative sodium balance activates the RAAS. The effect of aldosterone to enhance distal K^+ and H^+ excretion can lead to hypokalemia and metabolic alkalosis. Patients should therefore be monitored, and oral supplementation or addition of a potassium-sparing diuretic may need to be considered.

Loop diuretics impair tubular reabsorption by abolishing the transepithelial potential gradient and thus increase excretion of magnesium and calcium. Thiazide diuretics exert the same effect on magnesium, but unlike loop diuretics, thiazide diuretics decrease urinary calcium losses and are therefore preferred in the treatment of hypercalciuric states and in subjects with osteoporosis. Thiazide diuretics interfere with urine-diluting mechanisms by blocking sodium reabsorption at the distal convoluted tubule, an effect that may risk hyponatremia. Acutely, loop and thiazide diuretics increase the excretion of uric acid, whereas chronic administration results in reduced uric acid excretion. The chronic effect may be caused by enhanced transport in the proximal convoluted tubule secondary to volume depletion, leading to increased uric acid reabsorption, or competition between the diuretic and uric acid for secretion in the proximal tubule, leading to reduced uric acid secretion. Other adverse effects with large doses may include ototoxicity with loop diuretics, particularly with aminoglycoside coadministration, and gynecomastia, which may develop with spironolactone.

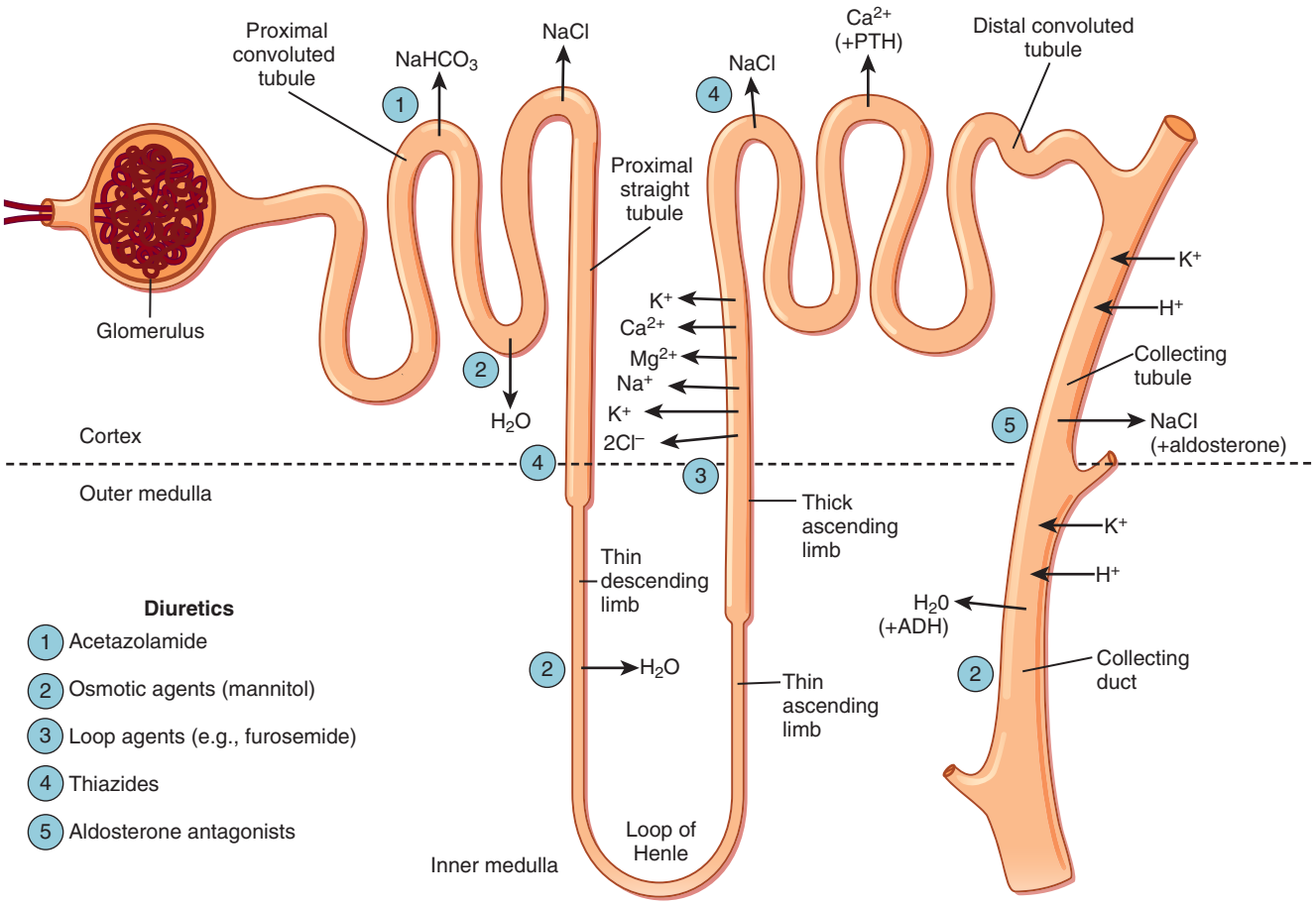

Figure 7-5 Tubule transport systems and sites of action of diuretics. *(Modified from reference 40.)*

Diuretic Tolerance and Resistance

Long-term loop diuretic *tolerance* refers to resistance of their action as a result of distal nephron segment hypertrophy and enhanced sodium reabsorption that follows increased exposure to solutes not absorbed proximally.[39] This problem can be addressed by combining loop and thiazide diuretics because the latter block the distal nephron sites responsible.

Diuretic *resistance* refers to edema that is or has become refractory to a given diuretic. Figure 7-6 outlines an algorithm for diuretic therapy in patients with edema caused by renal, hepatic, or cardiac disease. Diuretic resistance can result from several causes. Chronic kidney disease is associated with decreased tubular delivery and secretion of diuretics, which subsequently reduces drug concentration at the active site in the tubular lumen. In patients with nephrotic syndrome, the high protein content of tubular fluid was previously thought to increase protein binding of furosemide and other loop diuretics and therefore inhibit their action. However, more recent data suggest that urinary protein binding does not affect the response to furosemide.[42] As explained earlier, arterial underfilling in cirrhosis and CHF is associated with diminished nephron responsiveness to diuretics because of increased proximal tubular sodium reabsorption, leading to decreased delivery of sodium to the distal nephron segment sites of diuretic action. NSAIDs block prostaglandin-mediated increases in renal blood flow and increase the expression of Na^+-K^+-Cl^- cotransporters in the thick ascending limb (TAL).

Salt restriction is the key approach to lessening postdiuretic sodium retention. Secondary hyperaldosteronism also contributes to diuretic resistance. Further approaches to antagonize diuretic resistance include increasing the dose of loop diuretic, administering more frequent doses, and using combination therapy to block sequentially more than one site in the nephron, to cause a synergistic interaction between diuretics. It is reasonable to initiate aldosterone antagonist therapy before addition of a thiazide diuretic in patients with low or low-normal serum potassium level who are receiving only loop diuretic therapy, to enhance the diuresis and minimize the degree of potassium wasting. Highly resistant edematous patients may be treated with ultrafiltration.

Loop Diuretics

Loop diuretics such as furosemide, bumetanide, torsemide, and ethacrynic acid act by blocking the Na^+-K^+-Cl^- cotransporters at the apical surface of the TAL cells, thereby diminishing net reabsorption. Loop diuretics are the most potent of all diuretics because of the ability to inhibit the reabsorption of 25% of filtered sodium normally occurring at the TAL. Moreover, the nephron segment past the TAL does not possess the capacity to reabsorb completely the volume of fluid exiting the TAL. The oral bioavailability of furosemide varies between 10% and 100%; that of bumetanide and torsemide is comparatively higher. As a class, loop diuretics have a short elimination half-life, so the dosing interval needs to be short to maintain adequate levels in the lumen. Excessive prolongation of dosing interval may lead to avid sodium reabsorption by the nephron, which may result in postdiuretic sodium retention.

The intrinsic potency of a diuretic is defined by its dose-response curve, which is generally sigmoid. The steep dose-response is the reason that loop diuretics are often referred to as "threshold drugs."

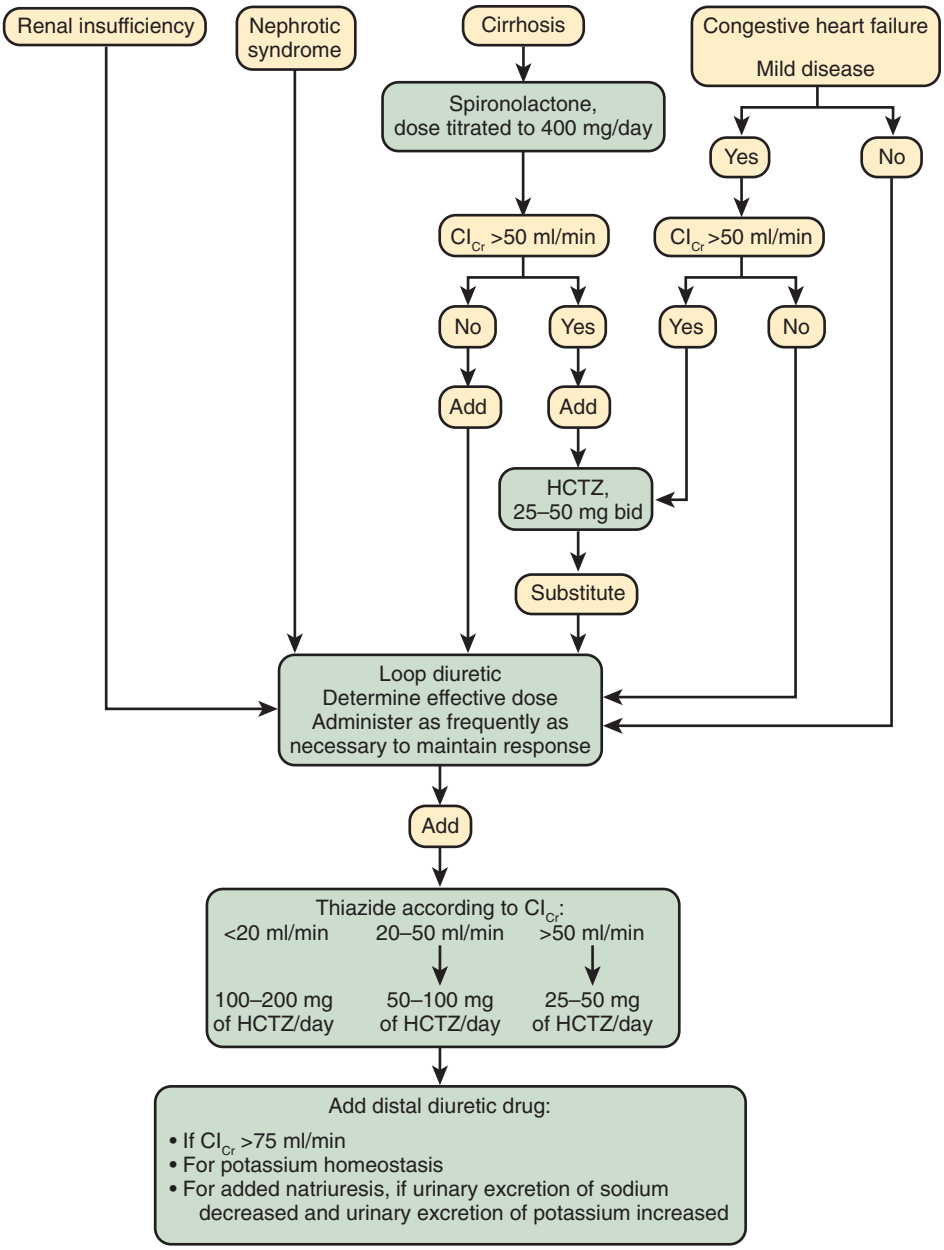

Figure 7-6 Diuretic therapy. Algorithm for diuretic therapy in patients with edema caused by renal, hepatic, or cardiac disease.*HCTZ*, Hydrochlorothiazide; *Cl_{cr}*, creatinine clearance. *(Modified from reference 39.)*

Therapeutic Regimens for Loop Diuretics

	Renal Impairment				Preserved Renal Function					
	Moderate		*Severe*		*Nephrotic Syndrome*		*Cirrhosis*		*Congestive Heart Failure*	
	PO	***IV***	***PO***	***IV***	***PO***	***IV***	***PO***	***IV***	***PO***	***IV***
Furosemide	80-160	80	240	200	240	120	80-160	40-80	160-240	40-80
Bumetanide	2-3	2-3	8-10	8-10	3	3	1-2	1	2-3	2-3
Torsemide	50	50	100	100	50	5	10-20	10-20	50	20-50

Table 7-5 Therapeutic regimens for loop diuretics. *(Modified from reference 46.)*

This is exemplified by furosemide, which can initiate diuresis in a person with normal renal function with an IV dose of 10 mg, and a maximal effect is seen with 40 mg. A larger dose provides minimal or no extra benefit, and side effects may increase. Furthermore, the effective diuretic dose is higher in patients with CHF, advanced cirrhosis, and renal failure (Table 7-5). Patients who respond poorly to intermittent doses of a loop diuretic may receive continuous IV infusion, which hypothetically enhances the response by virtue of maintaining an effective amount of drug at the site of action.[43] The benefit of continuous infusion, however, was not confirmed in a Cochrane review, which concluded that available data are insufficient to assess the merits of each approach (bolus or continuous) despite greater

diuresis and a better safety profile of the continuous infusion.[44] Furthermore, a recent prospective randomized trial was performed to compare bolus versus continuous IV infusion of furosemide, as well as high-dose versus low-dose therapy. The study found no difference in the primary end points—the global assessment of symptoms over the course of 72 hours and the change in serum creatinine from baseline to 72 hours—for continuous versus bolus infusion. High-dose diuretics were more effective than low-dose diuretics, without clinically important negative effects on renal function.[45]

Although having typical pharmacologic characteristics of other loop diuretics, ethacrynic acid has greater ototoxic potential and therefore is reserved for patients allergic to other loop diuretics.

Distal Convoluted Tubule Diuretics

The distal convoluted tubule group includes thiazide diuretics such as chlorothiazide, hydrochlorothiazide, and chlorthalidone, in addition to metolazone and indapamide. These diuretics inhibit NaCl absorption in the distal tubule, where up to 5% of filtered sodium and chloride is reabsorbed, and are therefore less potent than loop diuretics. Thiazides have a relatively long half-life and can be administered once or twice daily. Metolazone has pharmacologic characteristics similar to those of thiazide diuretics and is more often used in conjunction with other classes of diuretics. Metolazone has a longer elimination half-life (~2 days), and thus more rapidly acting and predictable thiazide agents may be preferred.

Thiazides may be used alone to induce diuresis in patients with mild CHF but more often are used in combination to synergize the effect of loop diuretics by blocking multiple nephron segment sites. Because thiazide diuretics must reach the lumen to be effective, higher doses are required in patients with impaired renal function. Thiazides (possibly excluding metolazone and indapamide) are ineffective in patients with advanced renal impairment (GFR <30 to 40 ml/min). In these patients, thiazides can enhance the diuretic effect of loop diuretics if they are coadministered in sufficient doses to attain effective nephron lumen concentration. If used, such combination therapy should be initiated under close monitoring because of a pronounced risk of hypokalemia and excessive ECF depletion.

Collecting Duct Diuretics

Amiloride, triamterene, and the aldosterone antagonists spironolactone and eplerenone act on the collecting duct. Amiloride and triamterene act primarily in the cortical collecting tubule or the connecting tubule and cortical collecting duct by interfering with sodium reabsorption through the apical ENaC. These agents inhibit potassium secretion indirectly by dissipating the electronegative gradient normally created by sodium reabsorption that favors potassium secretion. Spironolactone and eplerenone are competitive antagonists of aldosterone and cause natriuresis and potassium retention. Potassium-sparing diuretics are considered weak diuretics because they block only about 3% of the filtered sodium load reaching their site of action and thus are most often used with other diuretics to augment diuresis or to preserve potassium. If combination therapy is used, careful monitoring is essential to prevent dangerous hyperkalemia. Vulnerable patients include those with underlying renal dysfunction, those with CHF, diabetic patients, and those concurrently taking ACE inhibitors, ARBs, NSAIDs, or β-blockers. Collecting duct diuretics are considered first-line agents in certain conditions, for example, spironolactone in patients with liver cirrhosis with ascites and amiloride in the treatment of Liddle syndrome. Liddle syndrome is a rare autosomal dominant condition characterized by a primary increase in collecting tubule sodium epithelial channel function, leading to hypertension and, in some patients, hypokalemia and metabolic alkalosis (see Chapter 49).

Proximal Tubule Diuretics

Acetazolamide acts by blocking the activity of the Na^+-H^+ exchanger, thus increasing sodium bicarbonate excretion. Acetazolamide is a weak diuretic because proximal sodium reabsorption is mediated by other pathways and also because the loop of Henle has a large reabsorptive capacity that captures most of the sodium and chloride escaping from the proximal tubule. Acetazolamide generates a hyperchloremic metabolic acidosis, particularly with prolonged use. It may also cause hypokalemia because of increased distal sodium delivery; it may cause hypophosphatemia, but the mechanism of this is not well understood. Rarely used as a single agent, acetazolamide is most frequently used with other diuretics, in treatment of metabolic alkalosis accompanied by edematous states, and in chronic obstructive pulmonary disease (COPD).

Osmotic Diuretics

Osmotic diuretics are substances that are freely filtered at the glomerulus but are poorly reabsorbed. Mannitol is the prototype of osmotic diuretics. Mannitol produces diuresis by increasing the osmotic pressure within the lumen of the proximal tubule and Henle loop. This causes enhanced water diuresis and to a lesser extent sodium and potassium excretion.[47] Patients with reduced cardiac output may develop pulmonary edema when given mannitol because of an initial intravascular hypertonic phase. Therefore, mannitol is not a preferred agent for treatment of edematous states but rather is used to treat cerebral edema induced by trauma or neoplasms and to reduce intraocular pressure. Mannitol is also used in the treatment of dialysis disequilibrium syndrome, increasing the serum osmolality and thus decreasing the rapid rate of solute removal by dialysis, thought to be responsible for the symptoms.

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CHAPTER 8

Disorders of Water Metabolism

Tomas Berl and Chirag Parikh

PHYSIOLOGY OF WATER BALANCE

The maintenance of the tonicity of body fluids within a narrow physiologic range is made possible by homeostatic mechanisms that control the intake and excretion of water. Vasopressin, also known as arginine vasopressin (AVP) or antidiuretic hormone (ADH), governs the excretion of water by its effect on the renal collecting system. Osmoreceptors located in the hypothalamus control the secretion of vasopressin in response to changes in tonicity.

In the steady state, water intake matches water losses. Water intake is regulated by the need to maintain a physiologic serum osmolality of 285 to 290 mOsm/kg. Despite major fluctuations of solute and water intake, the total solute concentration (i.e., the tonicity) of body fluids is maintained virtually constant. The ability to dilute and to concentrate the urine allows wide flexibility in urine flow (see Chapter 2). During water loading, the diluting mechanisms permit excretion of 20 to 25 liters of urine daily, and during water deprivation, the urine volume may be as low as 0.5 l/day.[1,2]

VASOPRESSIN

Vasopressin plays a critical role in determining the concentration of urine. It is a 1099-d cyclic peptide and is synthesized and secreted by the specialized supraoptic and paraventricular magnocellular nuclei in the hypothalamus. Vasopressin has a short half-life of about 15 to 20 minutes and is rapidly metabolized in the liver and the kidney.

Osmotic Stimuli for Vasopressin Release

Substances restricted to the extracellular fluid (ECF), such as hypertonic saline and mannitol, decrease cell volume by acting as effective osmoles and enhancing osmotic water movement from the cell. This stimulates vasopressin release; in contrast, urea and glucose readily cross cell membranes and thus do not cause changes in cell volume. The "osmoreceptor" cells, located close to the supraoptic nuclei in the anterior hypothalamus, are sensitive to changes in plasma osmolality as small as 1% and bring about the release of vasopressin by a pathway that involves the activation of TRPV4 (transient receptor potential) channels. In humans, the osmotic threshold for vasopressin release is 280 to 290 mOsm/kg[2,3] (Fig. 8-1). This system is so efficient that plasma osmolality usually does not vary by more than 1% to 2% despite wide fluctuations in water intake.

Nonosmotic Stimuli for Vasopressin Release

There are several other nonosmotic stimuli for vasopressin secretion. Decreased effective circulating volume (e.g., heart failure, cirrhosis, vomiting) causes discharge from parasympathetic afferent nerves in the carotid sinus baroreceptors and increases vasopressin secretion. Other nonosmotic stimuli include nausea, postoperative pain, and pregnancy. Much higher vasopressin levels can be achieved with hypovolemia than with hyperosmolality, although a large (7%) decrease in blood volume is required before this response is elicited.

Mechanism of Vasopressin Action

Vasopressin binds three types of receptors coupled to G proteins: the V_{1a} (vascular and hepatic), V_{1b} (anterior pituitary), and V_2 renal receptors. The V_2 receptor is primarily localized in the collecting duct and leads to an increase in water permeability through aquaporin 2 (AQP2), which is a member of a family of cellular water transporters[4] (Fig. 8-2). AQP1 is localized in the apical and basolateral region of the proximal tubule epithelial cells and the descending limb of Henle loop and accounts for the high water permeability of these nephron segments. Because AQP1 is constitutively expressed, it is not subject to regulation by vasopressin. In contrast, AQP2 is found exclusively in apical plasma membranes and intracellular vesicles in the collecting duct principal cells. Vasopressin affects both the short-term and the long-term regulation of AQP2. The short-term regulation, also described as the "shuttle hypothesis," explains the rapid and reversible increase (within minutes) in collecting duct water permeability after vasopressin administration. This involves the insertion of water channels from subapical vesicles into the luminal membrane. Long-term regulation involves vasopressin-mediated increased transcription of genes involved in AQP2 production and occurs if circulating vasopressin levels are elevated for 24 hours or more. The maximal water permeability of the collecting duct epithelium is increased as a consequence of an increase in the total number of AQP2 channels per cell. This process is not readily reversible.

Aquaporins 3 and 4 are located on the basolateral membranes of the collecting duct (Fig. 8-2) and are probably involved in water exit from the cell. AQP3 is also urea permeable and, under the stimulus of vasopressin, increases the permeability of the collecting duct to urea, resulting in its movement into the interstitium. AQP4 is also found in the hypothalamus and is a candidate osmoreceptor for the control of vasopressin release.

THIRST AND WATER BALANCE

Hypertonicity is the most potent stimulus for thirst, with a change of only 2% to 3% in plasma osmolality producing a strong desire to drink. The osmotic threshold for thirst usually occurs at 290 to 295mOsm/kg H_2O and is above the threshold for vasopressin release (see Fig. 8-1). It closely approximates the level at which maximal concentration of urine is achieved. Hypovolemia, hypotension, and angiotensin II (Ang II) are also stimuli for thirst. Between the limits imposed by the osmotic thresholds for thirst and vasopressin release, plasma osmolality may be regulated more precisely by small,

osmoregulated adjustments in urine flow and water intake. The exact level at which balance occurs depends on various factors, such as insensible losses through skin and lungs, the gains incurred from drinking water and eating, and water generated from metabolism.

QUANTITATION OF RENAL WATER EXCRETION

Urine volume can be considered as having two components. The osmolar clearance (C_{osm}) is the volume needed to excrete solutes at the concentration of solutes in plasma. The free water clearance (C_{water}) is the volume of water that has been added to (positive C_{water}) or subtracted from (negative C_{water}) isotonic urine (C_{osm}) to create either hypotonic or hypertonic urine.

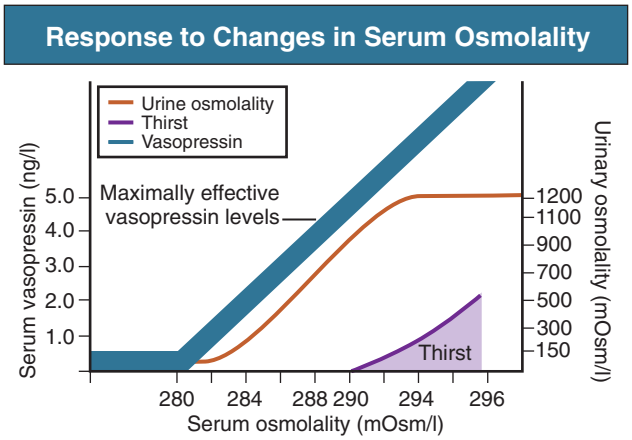

Figure 8-1 Mechanisms maintaining plasma osmolality. Thirst, vasopressin levels, and urinary osmolality in response to changes in serum osmolality. *(Modified from reference 2.)*

Urine volume flow (V) comprises the isotonic portion of urine (C_{osm}) plus the free water clearance (C_{water}).

$$V = C_{osm} + C_{water}$$

Therefore:

$$C_{water} = V - C_{osm}$$

The C_{osm}, solute clearance is determined by urine flow, urine osmolality, and plasma osmolality P_{osm} as follows:

$$C_{osm} = \left(\frac{U_{osm} \times V}{P_{osm}} \right)$$

Therefore:

$$C_{water} = V - \left(\frac{U_{osm} \times V}{P_{osm}} \right)$$
$$= V \left(1 - \frac{U_{osm}}{P_{osm}} \right)$$

This relationship reflects the following:

1. In hypotonic urine ($U_{osm} < P_{osm}$), C_{water} is positive.
2. In isotonic urine ($U_{osm} = P_{osm}$), C_{water} is zero.
3. In hypertonic urine ($U_{osm} > P_{osm}$), C_{water} is negative (i.e., water is retained).

If excretion of free water in a polyuric patient is unaccompanied by water intake, the patient will become hypernatremic. Conversely, failure to excrete free water with increased water intake can cause hyponatremia.

A limitation of the previous equation is that it fails to predict clinically important alterations in plasma tonicity and serum sodium concentration (serum [Na^+]) because it factors in urea. Urea is an important component of urinary osmolality; however, because it crosses cell membranes readily, urea does not establish a

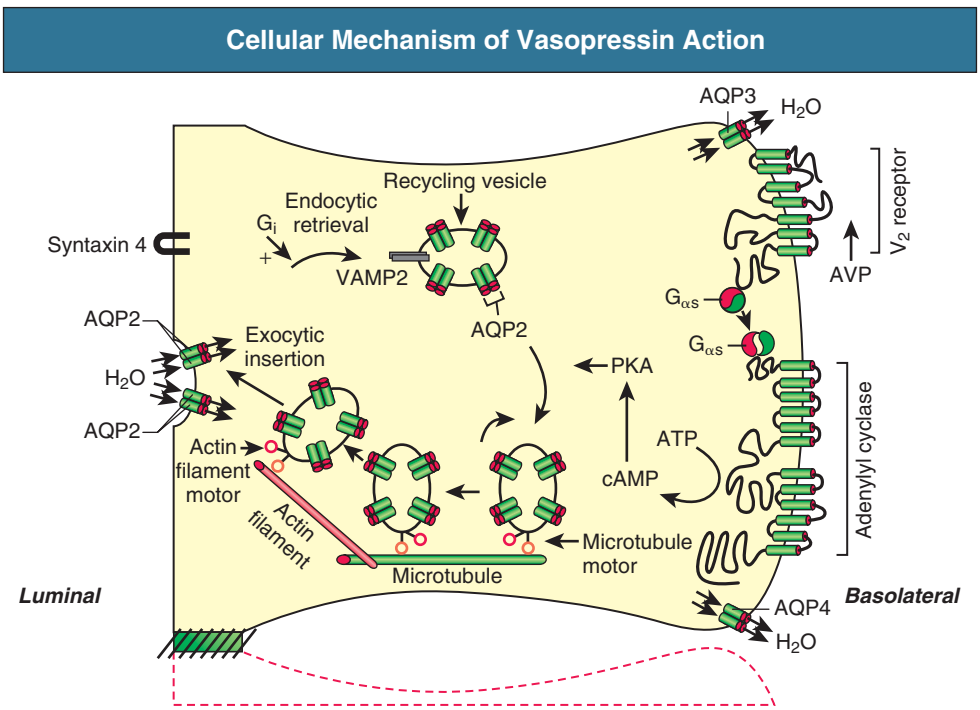

Figure 8-2 Cellular mechanism of vasopressin action. Vasopressin binds to V_2 receptors on the basolateral membrane and activates G proteins that initiate a cascade resulting in aquaporin 2 *(AQP2)* insertion in the luminal membrane. This then allows water uptake into the cell. *ATP,* Adenosine triphosphate; *AVP,* arginine vasopressin; *cAMP,* cyclic adenosine monophosphate; *PKA,* protein kinase A; *VAMP2,* vesicle-associated membrane protein 2. *(Modified from reference 3.)*

transcellular osmotic gradient and does not cause water movement between fluid compartments. Therefore, urea does not influence serum Na^+ concentration or the release of vasopressin. As a result, changes in serum $[Na^+]$ are better predicted by electrolyte free water clearance $[C_{water}(e)]$. The equation can be modified, replacing P_{osm} by plasma $[Na^+]$ (P_{Na}) and the urine osmolality by urine $[Na^+]$ and urine $[K^+]$, potassium concentration, $(U_{Na} + U_K)$:

$$C_{water}(e) = V\left(1 - \frac{U_{Na} + U_K}{P_{Na}}\right)$$

If $U_{Na} + U_K$ is less than P_{Na}, then $C_{water}(e)$ is positive and serum $[Na^+]$ increases. If $U_{Na} + U_K$ is greater than P_{Na}, then $C_{water}(e)$ is negative and serum $[Na^+]$ decreases. In the clinical setting, it is more appropriate to use the equation for electrolyte free clearance to predict if a patient's serum $[Na^+]$ will increase or decrease in the face of the prevailing water excretion. For example, in a patient with high urea excretion, the original equation would predict negative water excretion and a decrease in serum $[Na^+]$; but in fact, $[Na^+]$ increases, which is accurately predicted by the latter equation.

SERUM SODIUM CONCENTRATION, OSMOLALITY, AND TONICITY

The countercurrent mechanism of the kidneys, which allows urinary concentration and dilution, acts in concert with the hypothalamic osmoreceptors through vasopressin secretion to keep serum $[Na^+]$ and tonicity within a very narrow range[5] (Fig. 8-3). A defect in the urine-diluting capacity coupled with excess water intake leads to hyponatremia. A defect in urine-concentrating ability with inadequate water intake leads to hypernatremia.

Serum $[Na^+]$ along with its accompanying anions accounts for nearly all the osmotic activity of the plasma. Calculated serum osmolality is given by $2[Na^+]$ + BUN (mg/dl)/2.8 + glucose (mg/dl)/18, where BUN is blood urea nitrogen. The addition of other solutes to ECF results in an increase in measured osmolality (Table 8-1). Solutes that are permeable across cell membranes do not cause water movement and cause hypertonicity without cellular dehydration, as in uremia or ethanol intoxication. By contrast, in diabetic ketoacidosis with an increase in plasma glucose, which cannot move freely across cell membranes in the absence of insulin, water moves from the cells to the ECF, leading to cellular dehydration and lowering serum $[Na^+]$. This can be viewed as *translocational* because the decrease in serum $[Na^+]$ does not reflect change in total body water but rather the movement of water from intracellular to extracellular space. A correction whereby a decrease in serum $[Na^+]$ of 1.6 mmol/l for every 100 mg/dl (5.6 mmol/l) of glucose is used, but this may somewhat underestimate the impact of glucose to decrease serum $[Na^+]$.

Pseudohyponatremia occurs when the solid phase of plasma (usually 6% to 8%) is increased by large increments in either lipids or proteins (e.g., in hypertriglyceridemia and paraproteinemias). Serum osmolality is normal in pseudohyponatremia. This false result occurs because the usual method that measures the concentration of sodium uses whole plasma and not just the liquid phase, in which the concentration of sodium is 150 mmol/l. Many laboratories are now moving to direct ion-selective potentiometry, which will give the true aqueous sodium activity. In the absence of a direct-reading potentiometer, an estimate of plasma water can be obtained from the following well-validated formula[6]:

$$\text{Plasma water content (\%)} = 99.1 - (0.1 \times L) - (0.07 \times P)$$

where L and P refer to the total lipid and protein concentration (in g/l), respectively. For example, if the formula reveals that plasma water is 90% of the plasma sample rather than the normal 93% (which yields a serum sodium concentration of 140 mmol/l as 150 × 0.93 = 140), the concentration of measured sodium would be expected to decrease to 135 mmol/l (150 × 0.90).

ESTIMATION OF TOTAL BODY WATER

In normal individuals, total body water is approximately 60% of body weight (50% in women and obese individuals). With hyponatremia or hypernatremia, the change in total body water can be calculated from the serum $[Na^+]$ by the following formula:

$$\text{Water excess} = 0.6W \times \left(1 - \frac{[Na^+]_{obs}}{140}\right)$$

$$\text{Water deficit} = 0.6W \times \left(\frac{[Na^+]_{obs}}{140} - 1\right)$$

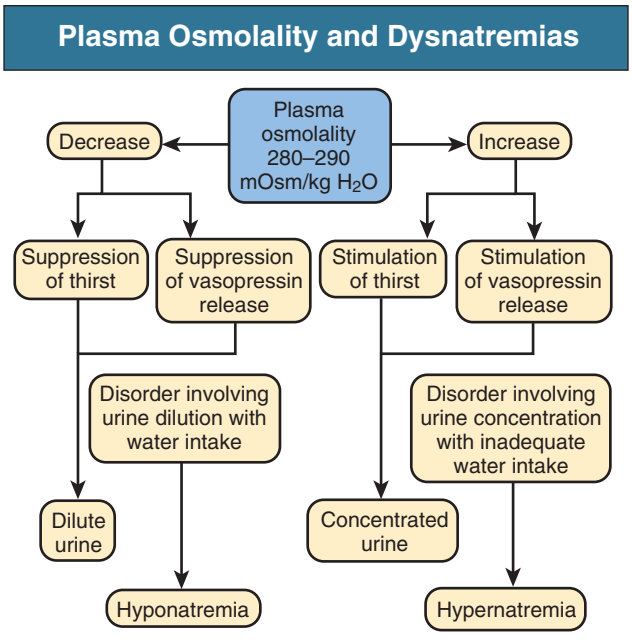

Figure 8-3 Maintenance of plasma osmolality and pathogenesis of dysnatremias. *(Modified from reference 5.)*

Effects of Osmotically Active Substances on Serum Sodium Levels

Substances that Increase Osmolality Without Changing Serum Na^+	*Substances that Increase Osmolality and Decrease Serum Na^+ (Translocational Hyponatremia)*
Urea	Glucose
Ethanol	Mannitol
Ethylene glycol	Glycine
Isopropyl alcohol	Maltose
Methanol	

Table 8-1 Effects of osmotically active substances on serum sodium ion (Na^+) levels.

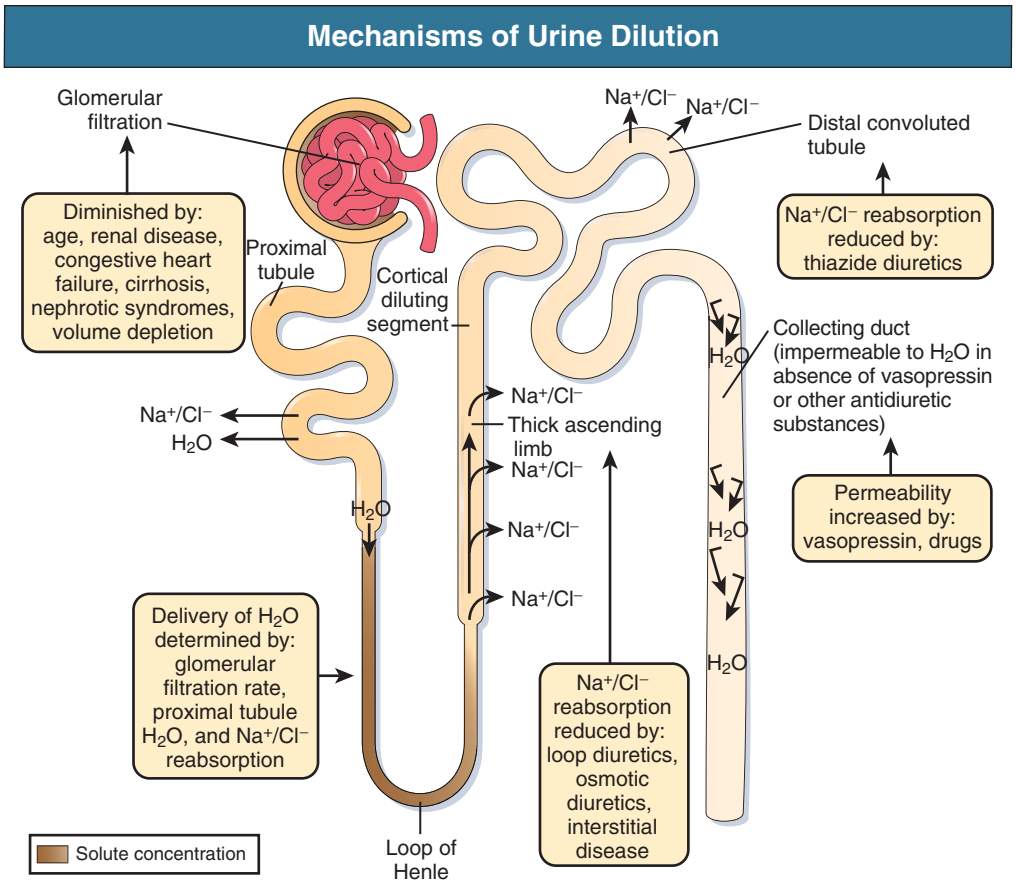

Figure 8-4 Mechanisms of urine dilution. Normal determinants of urinary dilution and disorders causing hyponatremia. *(Modified from reference 7.)*

where $[Na^+]_{obs}$ is observed sodium concentration (in mmol/l) and W is body weight (in kilograms). By use of this formula, a change of 10 mmol/l in the serum $[Na^+]$ in a 70-kg individual is equivalent to a change of 3 liters in free water.

HYPONATREMIC DISORDERS

Hyponatremia is defined as serum $[Na^+]$ of less than 135 mmol/l and equates with a low serum osmolarity once translocational hyponatremia and pseudohyponatremia are ruled out. True hyponatremia develops when normal urine-diluting mechanisms are disturbed[7] (Fig. 8-4). Hyponatremia may result from intrarenal factors, such as a diminished glomerular filtration rate (GFR) and an increase in proximal tubular fluid and Na^+ reabsorption, which decrease distal delivery of filtrate to the diluting segments of the nephron. Also, hyponatremia may result from a defect in Na^+-Cl^- transport out of the water-impermeable segments of the nephrons (thick ascending limb of Henle loop [TAL] or distal convoluted tubule). Most frequently, hyponatremia results from continued vasopressin secretion by nonosmotic mechanisms despite the presence of serum hypo-osmolality.

Etiology and Classification of Hyponatremia

Once pseudohyponatremia and translocational hyponatremia are ruled out and the patient is established as truly hypo-osmolar, the next step is to classify the patient as hypovolemic, euvolemic, or hypervolemic (Fig. 8-5).

Hypovolemia: Hyponatremia Associated with Decreased Total Body Sodium

A patient with hypovolemic hyponatremia has both a total body Na^+ and a water deficit, with the Na^+ deficit exceeding the water deficit. This occurs in patients with high gastrointestinal and renal losses of water and solute accompanied by free water or hypotonic fluid intake. The underlying mechanism is the nonosmotic release of vasopressin stimulated by volume contraction, which maintains vasopressin secretion despite the hypotonic state. Measurement of urine $[Na^+]$ is a useful tool in helping to diagnose these conditions (Fig. 8-5).

Gastrointestinal and Third-Space Sequestered Losses In the patient with diarrhea or vomiting, the kidney responds to volume contraction by conserving Na^+ and Cl^-. A similar pattern is observed in burn victims and patients with sequestration of fluids in third spaces, as in the peritoneal cavity with peritonitis or pancreatitis or in the bowel lumen with ileus. In all these patients, urine $[Na^+]$ is usually less than 10 mmol/l, and the urine is hyperosmolar. An exception to this is in patients with vomiting and metabolic alkalosis. Here, the increased bicarbonate ion (HCO_3^-) excretion obligates simultaneous cation excretion such that urine $[Na^+]$ may exceed 20 mmol/l despite severe volume depletion, but in this clinical setting the urine $[Cl^-]$ is lower than 10 mmol/l. Likewise, in chronic renal insufficiency, renal salt conservation is impaired and urine $[Na^+]$ may be high.

Diuretics Diuretic use is one of the most common causes of hypovolemic hyponatremia associated with a high urine $[Na^+]$. Loop diuretics inhibit Na^+-Cl^- reabsorption in the TAL. This interferes with the generation of a hypertonic medullary interstitium.

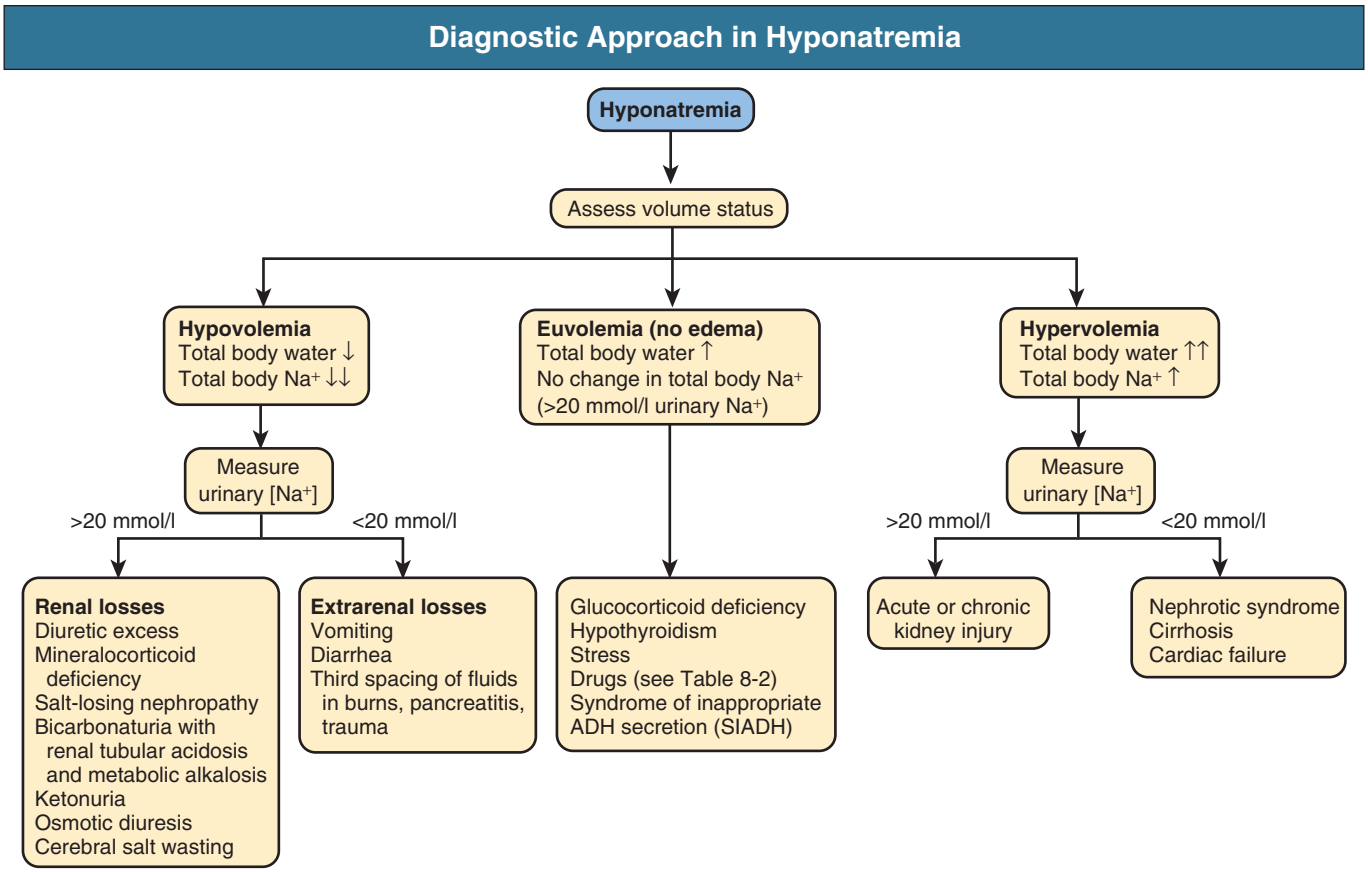

Figure 8-5 Algorithm for diagnostic assessment of the patient with hyponatremia. *(Modified from reference 5.)*

Therefore, even though volume contraction leads to increased vasopressin secretion, responsiveness to vasopressin is diminished and free water is excreted. In contrast, thiazide diuretics act in the distal tubule by interfering with urine dilution rather than with urine concentration, limiting free water excretion. Hyponatremia usually occurs within 14 days of initiation of therapy, although one third of patients present within 5 days. Underweight women and elderly patients appear to be most susceptible. Postulated mechanisms for diuretic-induced hyponatremia include the following:

- Hypovolemia-stimulated vasopressin release and decreased fluid delivery to the diluting segment
- Impaired water excretion through interference with maximal urinary dilution in the cortical diluting segment
- K^+ depletion, directly stimulating water intake by alterations in osmoreceptor sensitivity and increasing thirst

Water retention can mask the physical findings of hypovolemia, thereby making the patients with diuretic-induced hyponatremia appear euvolemic.

Salt-Losing Nephropathy A salt-losing state may occur in patients with advanced chronic renal impairment (GFR <15 ml/min), particularly from interstitial disease. It is characterized by hyponatremia and hypovolemia. In proximal type 2 renal tubular acidosis, there is renal Na^+ and K^+ wastage despite only moderate renal impairment, and bicarbonaturia obligates urine Na^+ excretion.

Mineralocorticoid Deficiency Mineralocorticoid deficiency is characterized by hyponatremia with ECF volume contraction, urine [Na^+] above 20 mmol/l, and high serum K^+, urea, and creatinine. Decreased ECF volume provides the nonosmotic stimulus for vasopressin release.

Osmotic Diuresis An osmotically active, non-reabsorbable solute obligates the renal excretion of Na^+ and results in volume depletion. In the face of continuing water intake, the diabetic patient with severe glycosuria, the patient with a urea diuresis after relief of urinary tract obstruction, and the patient with mannitol diuresis all undergo urinary losses of Na^+ and water, leading to hypovolemia and hyponatremia. Urine [Na^+] is typically above 20 mmol/l. The ketone bodies β-hydroxybutyrate and acetoacetate also obligate urinary electrolyte losses and aggravate the renal Na^+ wasting seen in diabetic ketoacidosis, starvation, and alcoholic ketoacidosis.

Cerebral Salt Wasting Cerebral salt wasting is a syndrome described primarily in patients with subarachnoid hemorrhage. The primary defect is salt wasting from the kidneys with subsequent volume contraction, which stimulates vasopressin release. The exact mechanism is not understood, but it is postulated that brain natriuretic peptide increases urine volume and Na^+ excretion. The diagnosis requires evidence of inappropriate sodium losses and reduced effective blood volume. These criteria are rarely fulfilled, suggesting that cerebral salt wasting is overdiagnosed.[8]

Hypervolemia: Hyponatremia Associated with Increased Total Body Sodium

In hypervolemia, if the total body water is increased more than total body Na^+ hyponatremia occurs, as in congestive heart failure (CHF), nephrotic syndrome, and cirrhosis, all of which are associated with impaired water excretion (see Fig. 8-5 and Chapter 7).

Congestive Heart Failure Edematous patients with CHF have reduced effective intravascular volume as a result of decreased systemic mean arterial pressure and cardiac output. This reduction is

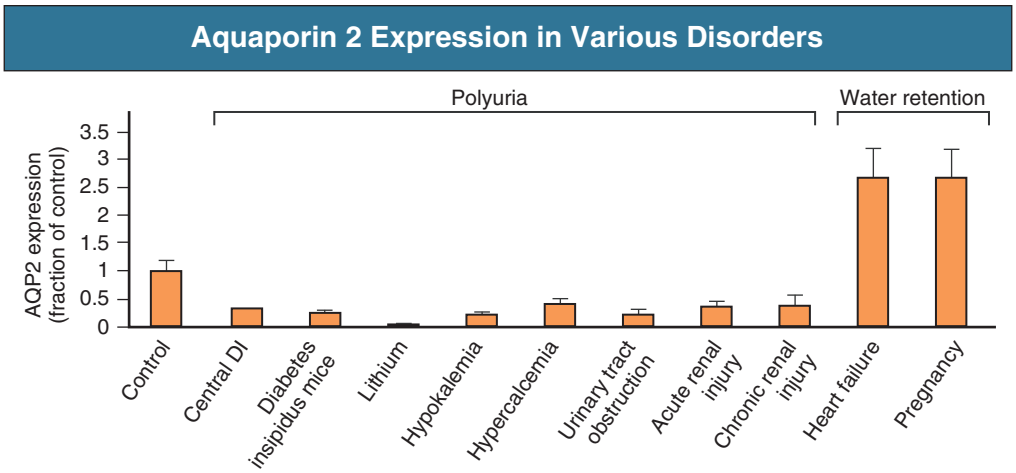

Figure 8-6 Changes in aquaporin 2 (AQP2) expression seen in association with different water balance disorders. Levels are expressed as a fraction (percentage) of control levels. AQP2 expression is reduced, sometimes dramatically, in a wide range of hereditary and acquired forms of diabetes insipidus *(DI)* characterized by different degrees of polyuria. Conversely, congestive heart failure and pregnancy are conditions associated with increased expression of AQP2 levels and excessive water retention. *(Modified from reference 9.)*

sensed by aortic and carotid baroreceptors activating nonosmotic pathways, and vasopressin is released. In addition, the relative "hypovolemic" state stimulates the renin-angiotensin axis and increases norepinephrine production, which in turn decreases GFR. The decrease in GFR leads to an increase in proximal tubular reabsorption and a decrease in water delivery to the distal tubule.

The neurohumorally mediated decrease in delivery of tubular fluid to the distal nephron and an increase in vasopressin secretion mediate hyponatremia by limiting Na^+-Cl^- and water excretion. In addition, low cardiac output and high Ang II levels are potent stimuli of thirst. There is also excessive intracellular targeting of AQP2 to the apical cell membrane of the collecting duct (Fig. 8-6).[9] These effects most likely result from high circulating levels of vasopressin.

As cardiac function improves with afterload reduction, plasma vasopressin decreases, with concomitant improvement in water excretion. The degree of hyponatremia has also been correlated with the severity of cardiac disease and with patient survival; serum [Na^+] of less than 125 mmol/l reflects severe CHF.

Hepatic Failure Patients with cirrhosis and hepatic insufficiency also have increased ECF volume (ascites, edema). Because of splanchnic venous dilation, these patients have increased plasma volume. Unlike patients with CHF, cirrhotic patients have an increased cardiac output because of multiple arteriovenous fistulas in their alimentary tract and skin. Vasodilation and arteriovenous fistulas lead to a decrease in mean arterial blood pressure. As the severity of cirrhosis increases, there are progressive increases in plasma renin, norepinephrine, vasopressin, and endothelin. There is also an associated decline in mean arterial pressure and serum [Na^+]. In experimental models of cirrhosis, there is increased expression of vasopressin-regulated AQP2 in collecting ducts.[4]

Nephrotic Syndrome In some patients with nephrotic syndrome, especially children with minimal change disease, hypoalbuminemia and lowered plasma oncotic pressure alter Starling forces, leading to intravascular volume contraction. Most patients with nephrotic syndrome appear to have a renal defect in sodium excretion resulting in increased effective circulating volume. In experimental models of nephrotic syndrome, expression of AQP2 and AQP3 in the renal collecting ducts is downregulated.[4]

Advanced Chronic Renal Impairment Patients with advanced renal impairment, either acute or chronic, have a profound increase in fractional excretion of Na^+ to maintain normal salt balance given the overall decreased number of functioning nephrons. Edema usually develops when the Na^+ ingested exceeds the kidneys' capacity to excrete this load. Likewise, if water intake exceeds threshold, there is positive water balance and hyponatremia. At a GFR of 5 ml/min, only 7.2 liters of filtrate is formed daily. Approximately 30%, or 2.2 liters, of this filtered fluid will reach the diluting segment of the nephron, which is therefore the maximum solute-free water that can be excreted daily.

Euvolemia: Hyponatremia Associated with Normal Total Body Sodium

Euvolemic hyponatremia is the most common dysnatremia in hospitalized patients. In these patients, no physical signs of increased total body Na^+ are detected.

Glucocorticoid Deficiency Glucocorticoid deficiency causes impaired water excretion in patients with primary and secondary adrenal insufficiency. Elevation of vasopressin accompanies the water excretion defect resulting from anterior pituitary and adrenocorticotropic hormone (ACTH, corticotropin) deficiency. This can be corrected by physiologic doses of corticosteroids. In addition, implicated vasopressin-independent factors are impaired renal hemodynamics and decreased distal fluid delivery to the diluting segments of the nephron.

Hypothyroidism Hyponatremia occurs in patients with severe hypothyroidism, who usually meet the clinical criteria for myxedema coma. A decrease in cardiac output leads to nonosmotic release of vasopressin. A reduction in the GFR leads to diminished free water excretion through decreased distal delivery to the distal nephron. The exact mechanisms are unclear. In patients with untreated myxedema, a vasopressin-independent mechanism is suggested by normal suppression of vasopressin after water loading, but in patients with advanced hypothyroidism, elevated vasopressin levels are reported in the basal state and after a water load. Hyponatremia is readily reversed by treatment with levothyroxine sodium (thyroxine).

Psychosis Patients with acute psychosis may develop hyponatremia. Some psychogenic drugs are associated with hyponatremia, but psychosis can cause hyponatremia independently. The pathophysiologic process involves an increased thirst perception, a mild defect in osmoregulation that causes vasopressin to be secreted at

lower osmolality, and an enhanced renal response to vasopressin. Individuals with self-induced water intoxication may also be more prone to development of rhabdomyolysis.[10]

Postoperative Hyponatremia Postoperative hyponatremia mainly is a result of excessive infusion of electrolyte-free water (hypotonic saline or 5% dextrose in water) and the presence of vasopressin, which prevents water excretion. Hyponatremia can also occur despite near-isotonic saline infusion within 24 hours of induction of anesthesia, mostly through the generation of electrolyte-free water by the kidneys in the presence of vasopressin.[11] In young women, hyponatremia is rarely accompanied by cerebral edema, leading to seizures and hypoxia with catastrophic neurologic events, particularly after gynecologic surgery. The mechanism has not been fully elucidated, and the patients at highest risk cannot be prospectively identified. Nevertheless, hypotonic fluids should be avoided after surgery, isotonic fluids minimized, and serum [Na^+] checked if hyponatremia is suspected.

Exercise-Induced Hyponatremia Hyponatremia is increasingly seen in long-distance runners. A study at a marathon race associated increased risk of hyponatremia with body mass index (BMI) less than 20 kg/m^2, running time exceeding 4 hours, and greatest weight gain.[12] A study in ultramarathon runners showed elevated vasopressin despite normal or low serum [Na^+].[13]

Drugs Causing Hyponatremia Drug-induced hyponatremia is becoming the most common cause of hyponatremia.[14] Thiazide diuretics are the most common cause, probably followed by selective serotonin reuptake inhibitors (SSRIs). Hyponatremia can be mediated by vasopressin analogues such as desmopressin (brand name DDAVP, 1-desamino-D-arginine vasopressin), drugs that enhance vasopressin release, and agents potentiating the action of vasopressin.[15] In other cases, the mechanism is unknown (Table 8-2). The increased use of desmopressin for nocturia in elderly patients and enuresis in young persons has resulted in a marked increase of reported cases of hyponatremia in these patients.[16] With the increasing use of intravenous immune globulin (IVIG) as a therapeutic modality in many disorders, cases of hyponatremia associated with its use have been described.[17] The mechanism of IVIG-associated hyponatremia is multifactorial, involving pseudohyponatremia as the protein concentration increases, translocation because of the sucrose in the solution, and true dilutional hyponatremia related to retention of water, particularly in those with associated acute kidney injury.[17]

Syndrome of Inappropriate Antidiuretic Hormone Secretion Despite being the most common cause of hyponatremia in hospitalized patients, the syndrome of inappropriate ADH secretion (SIADH) is a diagnosis of exclusion. A defect in osmoregulation causes vasopressin to be inappropriately stimulated, leading to urine concentration (Table 8-3). A few causes deserve special mention. Central nervous system (CNS) disturbances such as hemorrhage, tumors, infections, and trauma cause SIADH by excess vasopressin secretion. Small cell lung cancers, cancer of the duodenum and pancreas, and olfactory neuroblastoma cause ectopic production of vasopressin. Idiopathic cases of SIADH are unusual except in elderly patients, in whom hyponatremia is frequently multifactorial,[18] but in whom as

Drugs Associated with Hyponatremia*

Vasopressin Analogues	*Drugs that Potentiate Renal Action of Vasopressin*
Desmopressin (DDAVP)	Chlorpropamide
Oxytocin	Cyclophosphamide
	Nonsteroidal anti-inflammatory drugs (NSAIDs)
	Acetaminophen
Drugs that Enhance Vasopressin Release	***Drugs that Cause Hyponatremia by Unknown Mechanisms***
Chlorpropamide	*Haloperidol*
Clofibrate	Fluphenazine
Carbamazepine-oxcarbazepine	Amitriptyline
Vincristine	Thioridazine
Nicotine	Fluoxetine
Narcotics	*Methamphetamine* (MDMA, "ecstasy")
Antipsychotics/antidepressants (SSRIs)	Intravenous immune globulin (IVIG)
Ifosfamide	

Table 8-2 Drugs associated with hyponatremia. Terms in italics are the most common causes. *MDMA,* 3,4- Methylenedioxymethamphetamine; *SSRIs,* selective serotonin reuptake inhibitors. *Not including diuretics. *(From reference 15.)*

Causes of Syndrome of Inappropriate ADH Secretion

Carcinomas	Pulmonary Disorders	Nervous System Disorders	Other
Bronchogenic carcinoma	*Viral pneumonia*	*Encephalitis (viral, bacterial)*	*Human immunodeficiency virus (HIV) infection; acquired immunodeficiency syndrome (AIDS)*
Carcinoma of duodenum	*Bacterial pneumonia*	*Meningitis (viral, bacterial, tuberculous, fungal)*	*Idiopathic (elderly)*
Carcinoma of pancreas	*Pulmonary abscess*	*Head trauma*	Prolonged exercise
Thymoma	*Tuberculosis*	*Brain abscess*	
Carcinoma of stomach	Aspergillosis	*Brain tumors*	
Lymphoma	Positive-pressure ventilation	Guillain-Barré syndrome	
Ewing sarcoma	Asthma	Acute intermittent porphyria	
Carcinoma of bladder	Pneumothorax	Subarachnoid hemorrhage or subdural hematoma	
Carcinoma of prostate	Mesothelioma	Cerebellar and cerebral atrophy	
Oropharyngeal tumor	Cystic fibrosis	Cavernous sinus thrombosis	
Carcinoma of ureter		Neonatal hypoxia	
		Hydrocephalus	
		Shy-Drager syndrome	
		Rocky Mountain spotted fever	
		Delirium tremens	
		Cerebrovascular accident (stroke; cerebral thrombosis or hemorrhage)	
		Acute psychosis	
		Peripheral neuropathy	
		Multiple sclerosis	

Table 8-3 Causes of syndrome of inappropriate antidiuretic hormone secretion (SIADH). Terms in italics are the most common causes. *(From reference 15.)*

many as 10% have abnormal vasopressin secretion without known cause.

Several patterns of abnormal vasopressin release have emerged from studies of patients with clinical SIADH.[19] In one third of patients with SIADH, vasopressin release varies appropriately with serum [Na^+] but begins at a lower threshold of serum osmolality, implying a "resetting of the osmostat." Ingestion of free water then leads to water retention to maintain the serum [Na^+] at a new lower level, usually 125 to 130 mmol/l. In two thirds of patients, vasopressin release does not correlate with serum [Na^+], but a solute-free urine cannot be excreted. Therefore ingested water is retained, giving rise to moderate nonedematous volume expansion and dilutional hyponatremia. In about 10% of patients, vasopressin levels are not measurable, suggesting that the *syndrome of inappropriate antidiuresis* (SIAD) is a more accurate term.[19] Such patients may have a nephrogenic syndrome of antidiuresis, and a gain-of-function mutation in the vasopressin receptor may be a mechanism.[20]

The diagnostic criteria for SIADH are summarized in Box 8-1.[21] Plasma vasopressin may be in the "normal" range (up to 10 ng/l), but this is inappropriate given the hypo-osmolar state. In clinical practice, the measurement of plasma vasopressin is rarely needed because the urinary osmolality provides an excellent surrogate bioassay. Thus, a hypertonic urine (>300 mOsm/kg) provides strong evidence for the presence of vasopressin in the circulation because such urinary tonicities are unattainable in its absence. Likewise, a urinary osmolality lower than 100 mOsm/kg reflects the virtual absence of the hormone. Urinary osmolalities in the range of 100 to 300 mOsm/kg can occur in the presence or absence of vasopressin. A decrease in uric acid concentration is frequently encountered in the SIADH patient.

Clinical Manifestations of Hyponatremia

Most patients with a serum [Na^+] above 125 mmol/l are asymptomatic. Below 125 mmol/l, headache, yawning, lethargy, nausea, reversible ataxia, psychosis, seizures, and coma may occur as a result of cerebral edema. Rarely, hypotonicity leads to cerebral edema so severe that there is increased intracerebral pressure, tentorial herniation, respiratory depression, and death. Hyponatremia-induced cerebral edema usually occurs with rapid development of hyponatremia, typically in hospitalized postoperative patients receiving diuretics or hypotonic fluids. In patients with untreated severe hyponatremia, mortality is as high as 50%. Neurologic symptoms in a hyponatremic patient call for immediate attention and treatment.

Criteria for Syndrome of Inappropriate ADH Release

Essential Diagnostic Criteria

- Decreased extracellular fluid effective osmolality (270 mOsm/kg H_2O)
- Inappropriate urine concentration (>100 mOsm/kg H_2O)
- Clinical euvolemia
- Elevated urine Na^+ concentration under conditions of normal salt and water intake
- Absence of adrenal, thyroid, pituitary, or renal insufficiency or diuretic use

Supplemental Criteria

- Abnormal water-load test (inability to excrete at least 90% of a 20-ml/kg water load in 4 hours and/or failure to dilute urine osmolality to <100 mOsm/kg)
- Plasma vasopressin level inappropriately elevated relative to the plasma osmolality
- No significant correction of plasma Na^+ level with volume expansion, but improvement after fluid restriction

Box 8-1 Diagnostic criteria for syndrome of inappropriate antidiuretic hormone secretion (SIADH). *(Modified from reference 21.)*

Cerebral Edema

The development of cerebral edema largely depends on the cerebral adaptation to hypotonicity. Decreases in extracellular osmolality cause movement of water into cells, increasing intracellular volume and causing tissue edema. The water channel AQP4 appears to play a key role in the movement of water across the blood-brain barrier. Knockout mice for AQP4 are protected from hyponatremic brain swelling,[22] whereas animals overexpressing the water channel have exaggerated brain swelling.[23] Cellular edema within the fixed confines of the cranium causes an increase in intracranial pressure, leading to the neurologic syndrome. In most hyponatremic patients, mechanisms of volume regulation prevent cerebral edema.

Early in the course of hyponatremia, within 1 to 3 hours, a decrease in cerebral extracellular volume occurs by movement of fluid into the cerebrospinal fluid, which is then shunted back into the systemic circulation. Loss of extracellular solutes Na^+ and Cl^- occurs as early as 30 minutes after the onset of hyponatremia (Fig. 8-7). If hyponatremia persists for longer than 3 hours, the brain

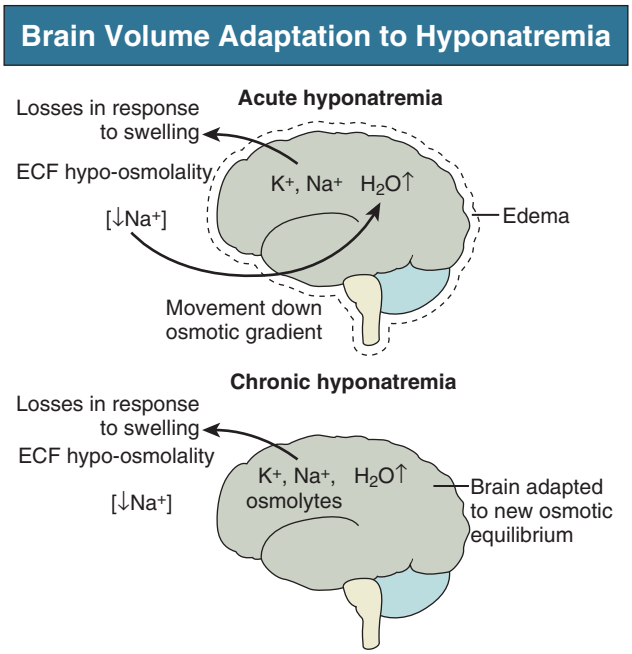

Figure 8-7 Brain volume adaptation to hyponatremia. During acute hyponatremia, water enters the brain to establish osmotic equilibrium with the ECF. As an acute adaptive change, NaCl exits from the brain interstitial space, followed by loss of potassium from cells several hours later. In chronic hyponatremia, the brain loses osmolytes, which lead to further water losses from the brain and an almost full restoration of brain water to levels marginally greater than baseline. *(Modified from reference 21.)*

Hyponatremic Patients at Risk for Neurologic Complications	
Acute Cerebral Edema	**Osmotic Demyelination Syndrome (Central Pontine Myelinolysis)**
Postoperative menstruating women	Liver transplant recipients
Elderly women taking thiazides	Alcoholic patients
Children	Malnourished patients
Patients with polydipsia secondary to psychiatric disorders	Hypokalemic patients
Hypoxemic patients	Burn victims
Marathon runners	Elderly women taking thiazides
	Hypoxemic patients
	Severe hyponatremia ($[Na^+]$ < 105 mmol/l)

Table 8-4 Neurologic risk in patients with hyponatremia. Patient groups at risk for acute cerebral edema and central pontine myelinolysis (osmotic demyelination). *(From reference 24.)*

adapts by losing cellular osmolytes, including K^+ and organic solutes, which tends to lower the osmolality of the brain, resulting in concomitant water losses. Thereafter, if hyponatremia persists, other organic osmolytes, such as phosphocreatine, myoinositol, and amino acids (e.g., glutamine, taurine), are lost, greatly decreasing cerebral swelling. As a result of these adaptations, some patients, particularly elderly, may have minimal symptoms despite severe hyponatremia ($[Na^+]$ <125 mmol/l).

Certain patients are at increased risk for development of acute cerebral edema in the course of hyponatremia[24] (Table 8-4). Hospitalized premenstrual women with hyponatremia are more symptomatic and more likely to have complications of therapy than postmenopausal women or men. This increased risk of cerebral edema is independent of the rate of development or the magnitude of hyponatremia. The best management of these patients is to avoid the administration of hypotonic fluids in the postoperative setting. Hyponatremia may occur in the postoperative state even if isotonic fluid is being used if urine $[Na^+]$ and $[K^+]$ exceed serum concentrations; the hyponatremia is mild and not associated with cerebral dysfunction.[11] Children are particularly vulnerable to the development of acute cerebral edema, perhaps because of a relatively high ratio of brain to skull volume.

Osmotic Demyelination

Another neurologic syndrome can occur in hyponatremic patients as a complication of correction of hyponatremia. Osmotic demyelination most often affects the central pons of the brainstem and is therefore also termed *central pontine myelinolysis.* It occurs at all ages; Table 8-4 lists patients most at risk. Osmotic demyelination syndrome is especially common after liver transplantation, with a reported incidence of 13% to 29% at autopsy. The risk of central pontine myelinolysis is related to the severity and chronicity of the hyponatremia. It rarely occurs with serum $[Na^+]$ above 120 mmol/l or acute onset of hyponatremia (<48 hours). The symptoms are biphasic. Initially, there is a generalized encephalopathy associated with rapid correction of serum $[Na^+]$. At 2 to 3 days after correction, the patient displays behavioral changes, cranial nerve palsies, and progressive weakness, culminating in quadriplegia and a locked-in syndrome. T2-weighted magnetic resonance imaging shows nonenhancing and hyperintense pontine and extrapontine lesions. These lesions may not appear until 2 weeks after development, so a diagnosis of myelinolysis should not be excluded if the imaging is initially normal.

The pathogenesis of osmotic demyelination syndrome is uncertain; one suggestion is that sodium-coupled amino acid transporters (e.g., SNAT2) are downregulated by hypotonicity, thereby delaying the return of osmolytes to the brain, rendering it more sensitive to the correction of hyponatremia.[16] Although serum $[Na^+]$ and $[K^+]$ return to normal in a few hours, osmotically active solutes in the brain require several days to reach normal levels. This temporary imbalance causes cerebral dehydration and can lead to a potential breakdown of the blood-brain barrier. Astrocytes appear to be an early target of the disease process, leading to their activation of microglial cells and the expression of proinflammatory cytokines.[25]

Whereas central pontine myelinolysis was originally considered to be uniformly fatal, evidence now shows that a substantial number of patients can have some neurologic recovery, even with severe symptoms at onset, and that milder forms of osmotic demyelination occur as well.[26]

Treatment of Hyponatremia

Symptoms and duration of hyponatremia determine treatment. Acutely hyponatremic patients (hyponatremia developing within 48 hours) are at great risk for development of permanent neurologic sequelae from cerebral edema if the hyponatremia remains uncorrected. Patients with chronic hyponatremia are at risk for osmotic demyelination if the hyponatremia is corrected too rapidly.

Acute Symptomatic Hyponatremia

Acute symptomatic hyponatremia almost always develops in hospitalized patients receiving hypotonic fluids, especially when associated with seizures or other neurologic manifestations (Fig. 8-8). Treatment should be prompt because the risk of acute cerebral edema far exceeds the risk of osmotic demyelination. Serum $[Na^+]$ should be ideally corrected by 2 mmol/l/h until symptoms resolve. It is not necessary to correct the serum $[Na^+]$ completely, although this appears to pose no risk. Correction may be achieved by administration of hypertonic saline (3% NaCl) at the rate of 1 to 2 ml/h/kg.[24,27] Administration of a loop diuretic enhances free water excretion and hastens the normalization of serum $[Na^+]$. If the patient presents with severe neurologic symptoms, such as seizures, obtundation, or coma, 3% NaCl may be infused at higher rates (4 to 6 ml/h/kg). Various formulas have been proposed to estimate an increase in serum $[Na^+]$ after administration of intravenous fluids,[19] but these tend to underestimate the rate of correction.[28] Therefore, during treatment with hypertonic saline, the patient should be monitored carefully for changes in neurologic and pulmonary status, and serum electrolytes should be checked frequently, about every 2 hours.

Chronic Symptomatic Hyponatremia

If the hyponatremia has taken more than 48 hours to evolve or if the duration is not known, correction should be undertaken with caution (Fig. 8-8). Controversy exists as to whether it is the rate of correction or the magnitude of correction of hyponatremia that predisposes to neurologic complications. In clinical practice, it is difficult to dissociate these two variables because a rapid correction rate is usually accompanied by a greater absolute magnitude of correction during a given time. Three important principles guide treatment, as follows[26]:

1. Because cerebral water is increased only by approximately 10% in severe chronic hyponatremia, the goal is to increase the serum Na^+ level by 10%, or about 10 mmol/l.
2. Do not exceed a correction rate of 1.0 to 1.5 mmol/l in any given hour.
3. The goal of treatment is 6 to 8 mmol/l, but do not increase serum sodium by more than 12 mmol/l/24 h.

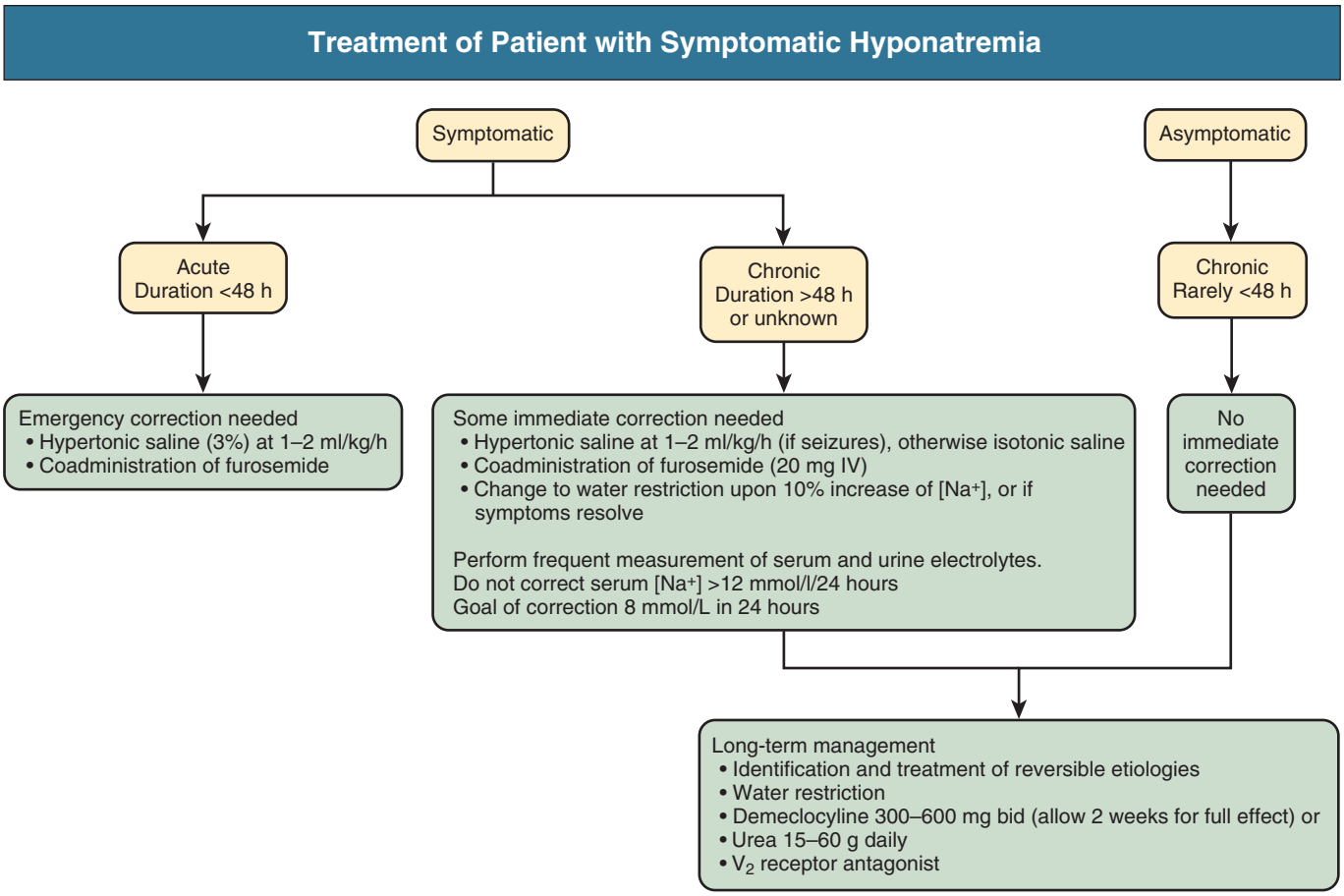

Figure 8-8 Algorithm for management of the patient with symptomatic (and "asymptomatic") hyponatremia. *(Modified from reference 24.)*

It is important to take into account the rate and electrolyte content of infused fluids and the rate of production and electrolyte content of urine. Once the desired increment in serum Na^+ concentration is obtained, treatment should consist of water restriction.

If correction has proceeded more rapidly than desired, usually because of excretion of hypotonic urine, the risk of osmotic demyelination may be decreased by relowering serum Na^+ concentration with intravenous or subcutaneous desmopressin or administration of 5% dextrose.[29]

Chronic "Asymptomatic" Hyponatremia

Although many patients with chronic hyponatremia appear to be asymptomatic, formal neurologic testing frequently reveals subtle impairments, including gait disturbances comparable to those seen in subjects with toxic levels of alcohol that reverse with correction of the hyponatremia. This results in an increased risk for falls and fractures.[30] This increased risk was observed even in patients with mild or asymptomatic hyponatremia (mean serum sodium, 131 mmol/l). Therefore, even "asymptomatic" patients should be treated in an attempt to restore serum sodium to near-normal levels, particularly if they display gait instability or have sustained a fall. These patients should also be evaluated for hypothyroidism, adrenal insufficiency, and SIADH and should have their medications reviewed.

Fluid Restriction Fluid restriction is the first-line therapy in patients with chronic asymptomatic hyponatremia (Table 8-5). This approach is usually successful if patients are compliant. It involves a calculation of the fluid restriction that will maintain a specific serum $[Na^+]$. The daily osmolar load (OL) and the minimal urinary osmolality $(U_{osm})_{min}$ determine a patient's maximal urine volume (V_{max}), as follows:

$$V_{max} = \frac{OL}{(U_{osm})_{min}}$$

The value of $(U_{osm})_{min}$ is a function of the severity of the diluting disorder. In the absence of circulating vasopressin, it can be as low as 50 mOsm. In a normal North American diet, the daily osmolar load is approximately 10 mOsm/kg (700 mOsm for 70-kg person). Assuming that a patient with SIADH has U_{osm} that cannot be lowered to less than 500 mOsm, the same osmolar load of 700 mOsm allows only 1.4 liters of urine to be excreted daily. Therefore if the patient drinks more than 1.4 l/day, the serum Na^+ concentration will decrease. Measurement of urine $[Na^+]$ and $[K^+]$ can indicate the degree of water restriction required in a given patient.[31] If the diluting defect is so severe that fluid restriction to less than 1 liter is necessary or if the patient's serum Na^+ concentration remains low (<130 mmol/l), an alternative approach to treatment, such as increasing solute excretion or pharmacologic inhibition of vasopressin, should be considered.

Maneuvers that Increase Solute Excretion If the patient remains unresponsive to fluid restriction, solute intake can be increased to facilitate an obligatory increase in excretion of solute

Treatment of Chronic Asymptomatic Hyponatremia				
Treatment	**Mechanism of Action**	**Dose**	**Advantages**	**Limitations**
Fluid restriction	Decreases availability of free water	Variable	Effective and inexpensive; not complicated	Noncompliance
Pharmacologic Inhibition of Vasopressin Action				
Lithium	Inhibits kidney's response to vasopressin	900-1200 mg/day	Unrestricted water intake	Polyuria, narrow therapeutic range, neurotoxicity
Demeclocycline	Inhibits kidney's response to vasopressin	300-600 mg twice daily	Effective; unrestricted water intake	Neurotoxicity, polyuria, photosensitivity, nephrotoxicity
V_2 receptor antagonist	Antagonizes vasopressin action	—	Addresses underlying mechanisms	Limited clinical experience
Increased Solute (Salt) Intake				
With furosemide	Increases free water clearance	Titrate to optimal dose; coadminister 2-3 g NaCl	Effective	Ototoxicity, K^+ depletion
With urea	Osmotic diuresis	30-60 g/day	Effective; unrestricted water intake	Polyuria, unpalatable, gastrointestinal symptoms

Table 8-5 Treatment of patients with chronic "asymptomatic" hyponatremia.

and free water.[32] This can be achieved by increasing oral salt and protein intake in the diet to increase the C_{osm} of the urine. Loop diuretics combined with high sodium intake (2 to 3 g of additional salt) are effective in the management of hyponatremia. A single diuretic dose (40 mg furosemide) is usually sufficient but should be doubled if the diuresis induced in the first 8 hours is less than 60% of the total daily urine output.

The administration of urea increases urine flow by causing an osmotic diuresis. This permits a more liberal water intake without worsening the hyponatremia and without altering urine concentration. The dose for urea is usually 30 to 60 g/day. The major limitations are gastrointestinal distress and unpalatability.

Pharmacologic Inhibition of Vasopressin *Vaptans* are novel oral V_2 receptor antagonists that block vasopressin binding to the collecting duct tubular epithelial cells and increase free water excretion without significantly altering electrolyte excretion. Vaptans are effective in the treatment of hyponatremia in euvolemic and hypervolemic patients.[33,34] Conivaptan, a V_2 and V_{1a} antagonist, is the only vaptan available for intravenous use.[35] It is used in the treatment of hyponatremia in hospitalized patients with transient SIADH, but treatment should be limited to 4 days because it is a potent cytochrome P-450 3A4 (CYP3A4) inhibitor. Tolvaptan, an oral V_2 antagonist, is now available in some countries at doses of 15 to 60 mg/day. In the Tolvaptan trials in patients with polycystic kidney disease (TEMPO), higher doses were used and some cases of hepatic toxicity, as well as rhabdomyolysis, were encountered. This has led to a U.S. Food and Drug Administration (FDA) warning requiring careful monitoring of liver function tests and creatine kinase (CK, CPK) levels.

An alternative pharmacologic treatment is demeclocycline, 600 to 1200 mg/day given 1 to 2 hours after meals; calcium-, aluminum-, and magnesium-containing antacids should be avoided. Onset of action is usually 3 to 6 days after initiation of treatment. Dose should be titrated to the minimum to keep serum $[Na^+]$ within the desired range with unrestricted water intake. Skin photosensitivity may develop and tooth or bone abnormalities may occur in children. Polyuria leads to noncompliance, and nephrotoxicity may occur, especially in patients with underlying liver disease. Lithium was previously used to block vasopressin action in the collecting duct but has been superseded by the vaptans and demeclocycline.

Hypovolemic Hyponatremia

When thiazides are prescribed, especially in elderly women, serum $[Na^+]$ should be monitored and water intake restricted. If hyponatremia develops, the thiazide needs to be discontinued.

Neurologic syndromes directly related to hyponatremia are unusual in hypovolemic hyponatremia because both Na^+ and water loss limits any osmotic shifts in the brain. Restoration of ECF volume with crystalloids or colloids interrupts the nonosmotic release of vasopressin. Vasopressin antagonists should not be used in these patients.[34]

Hypervolemic Hyponatremia

Congestive Heart Failure In patients with CHF, sodium and water restriction is critical. Patients may be treated with a combination of angiotensin-converting enzyme (ACE) inhibitors and diuretics. The resulting increase in cardiac output decreases the neurohumorally mediated processes that limit water excretion. Loop diuretics diminish the action of vasopressin on the collecting tubules, thereby decreasing water reabsorption. Thiazides should be avoided because they impair urinary dilution and may worsen hyponatremia. V_2 antagonists increase serum $[Na^+]$ in patients with heart failure,[33,36] and correction of serum $[Na^+]$ is associated with better long-term outcomes.[37] However, in the much larger randomized controlled EVEREST trial in patients with decompensated heart failure, treatment with tolvaptan did not alter any long-term clinical outcomes. In principle, a vaptan with V_1 antagonist activity could have additional benefit in the CHF patient, but this is unproven.

Cirrhosis In patients with cirrhosis, water and sodium restriction is the mainstay of therapy. Loop diuretics increase C_{water} once a negative sodium balance has been achieved. V_2 antagonists increase water excretion, accompanied by an increase in serum $[Na^+]$.[36] In one study, satavaptan led to a mean increase in serum $[Na^+]$ of 6.6. mmol/l,[38] but this drug has not yet gained FDA approval. The response to vaptans in cirrhosis is more attenuated than in patients with SIADH or CHF, which suggests that vasopressin-independent mechanisms may also contribute to their hyponatremia. The administration of V_2 antagonists to patients with liver failure is not associated with decrements in blood pressure. Combined V_1 and V_2 antagonists (e.g., conivaptan) should not be used in these patients.

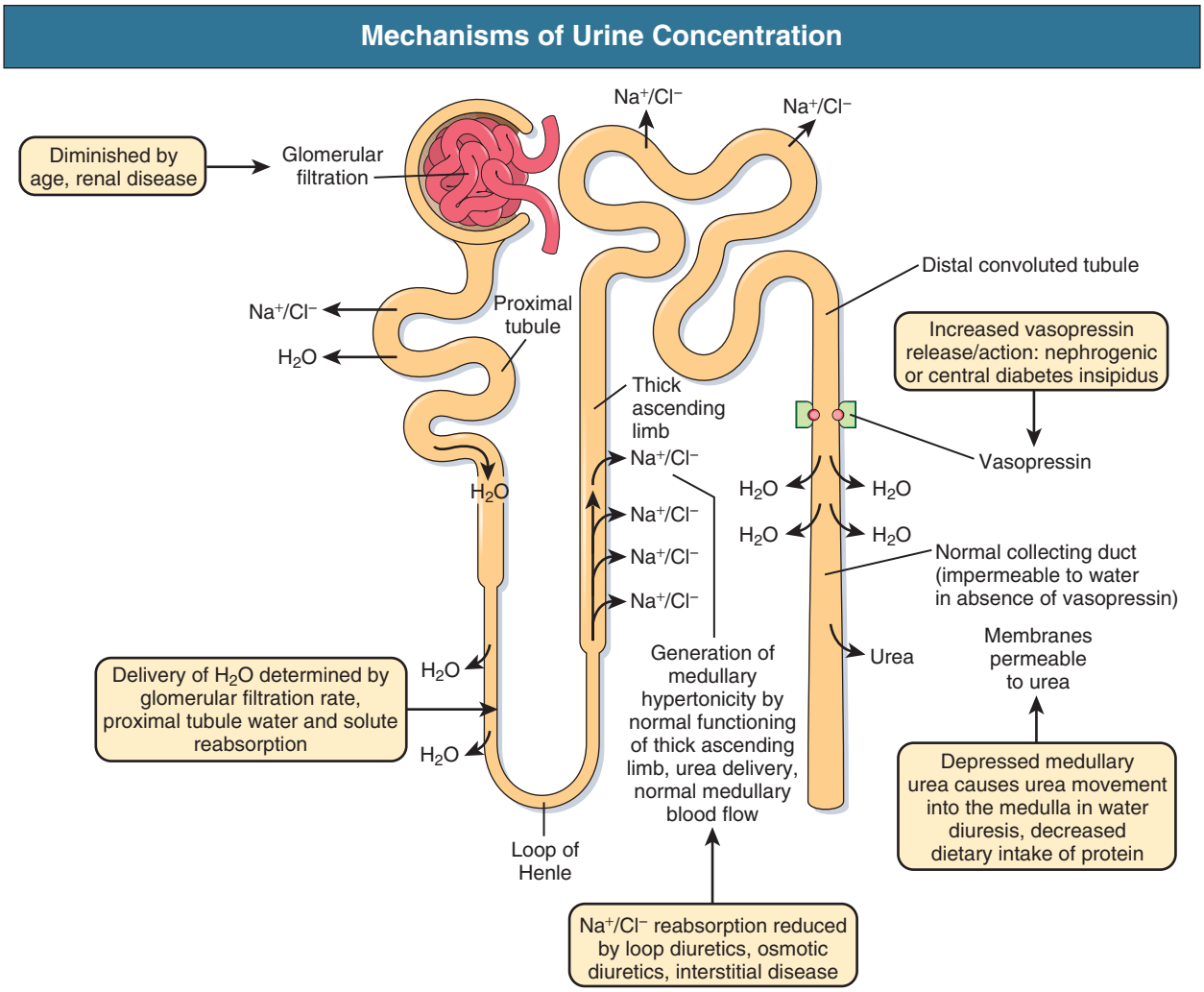

Figure 8-9 Urine-concentrating mechanisms. Determinants of normal urine concentration and disorders causing hypernatremia. *(Modified from reference 7.)*

HYPERNATREMIC DISORDERS

Hypernatremia is defined as serum [Na^+] above 145 mmol/l and reflects serum hyperosmolarity. The renal concentrating mechanism provides the first defense mechanism against water depletion and hyperosmolarity. The components of the normal concentrating mechanism are shown in Figure 8-9. Disorders of urine concentration may result from decreased delivery of solute (with decreasing GFR) or the inability to generate interstitial hypertonicity because of decreased Na^+ and Cl^- reabsorption in the ascending limb of Henle loop (loop diuretics), decreased medullary urea accumulation (poor dietary intake), or alterations in medullary blood flow. Hypernatremia may also result from failure to release or respond to AVP. Thirst is the first and most important defense mechanism in preventing hypernatremia.

Etiology and Classification of Hypernatremia

As with hyponatremia, patients with hypernatremia fall into three broad categories based on volume status.[15] A diagnostic algorithm is helpful in the evaluation of these patients (Fig. 8-10).

Hypovolemia: Hypernatremia Associated with Low Total Body Sodium

Patients with hypovolemic hypernatremia sustain losses of both Na^+ and water, but with a relatively greater loss of water. On physical examination, there are signs of hypovolemia, including orthostatic hypotension, tachycardia, flat neck veins, and poor skin turgor; some patients have altered mental status. Patients generally have hypotonic water loss from the kidneys or the gastrointestinal tract; in the GI tract, the urine [Na^+] will be low.

Hypervolemia: Hypernatremia Associated with Increased Total Body Sodium

Hypernatremia with increased total body Na^+ is the least common form of hypernatremia. It results from the administration of hypertonic solutions such as 3% NaCl and $NaHCO_3$ for the treatment of metabolic acidosis, hyperkalemia, and cardiorespiratory arrest. It may also result from inadvertent dialysis against a dialysate with a high Na^+ concentration or from consumption of salt tablets. Therapeutic hypernatremia is also becoming common as hypertonic saline solutions have emerged as an alternative to mannitol for treatment of increased intracranial pressure.[39] Hypernatremia is also increasingly recognized in hypoalbuminemic hospitalized patients with

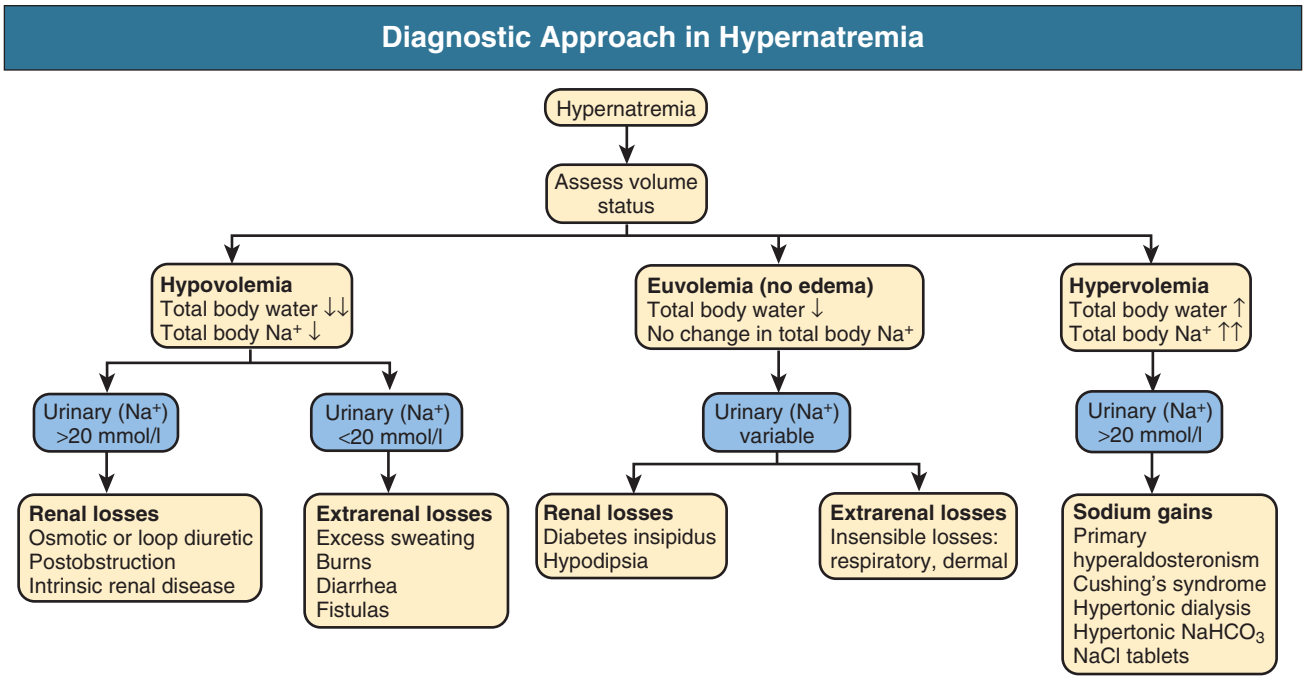

Figure 8-10 Algorithm for diagnostic assessment of the patient with hypernatremia. *(Modified from reference 5.)*

renal failure who are edematous and unable to concentrate their urine.

Euvolemia: Hypernatremia Associated with Normal Body Sodium

Most patients with hypernatremia secondary to water loss appear euvolemic with normal total body Na^+ because loss of water without Na^+ does not lead to overt volume contraction. Water loss need not result in hypernatremia unless unaccompanied by water intake. Because hypodipsia is uncommon, hypernatremia usually develops only in those who have no access to water and in very young children and old persons, who may have an altered perception of thirst. Extrarenal water loss occurs from the skin and respiratory tract in febrile or other hypermetabolic states and is associated with a high urine osmolality because the osmoreceptor-vasopressin-renal response is intact. The urine Na^+ concentration varies with the intake. Renal water loss leading to euvolemic hypernatremia results either from a defect in vasopressin production or release (central diabetes insipidus) or from a failure of the collecting duct to respond to the hormone (nephrogenic diabetes insipidus). Defense against the development of hyperosmolality requires the appropriate stimulation of thirst and the patient's ability to respond by drinking water.

Polyuric disorders can result from either an increase in C_{osm} or an increase in C_{water}. An increase in C_{osm} occurs with diuretic use, renal salt wasting, excess salt ingestion, vomiting (bicarbonaturia), alkali administration, and administration of mannitol (as a diuretic, for bladder lavage, or for the treatment of cerebral edema). An increase in C_{water} occurs with excess ingestion of water (psychogenic polydipsia) or in abnormalities of the renal concentrating mechanism (diabetes insipidus).

Diabetes Insipidus

Diabetes insipidus (DI) is characterized by polyuria and polydipsia and is caused by defects in vasopressin action. Patients with central and nephrogenic DI and primary polydipsia present with polyuria and polydipsia. These entities can be differentiated by clinical evaluation, with measurements of vasopressin levels and response to a water deprivation test, followed by vasopressin administration (Table 8-6).[40]

Water Deprivation Test

Condition	Urinary Osmolality with Water Deprivation (mOsm/kg H_2O)	Plasma Vasopressin after Dehydration (pg/ml)	Increase in Urinary Osmolality with Exogenous Vasopressin
Normal	>800	>2	Little or no increase
Complete central diabetes insipidus	<300	Undetectable	Substantially increased
Partial central diabetes insipidus	300-800	<1.5	Increase of >10% of urinary osmolality after water deprivation
Nephrogenic diabetes insipidus	<300-500	>5	Little or no increase
Primary polydipsia	>500	<5	Little or no increase

Table 8-6 Water deprivation test. Test procedure: Water intake is restricted until the patient loses 3% to 5% of body weight or until three consecutive hourly determinations of urinary osmolality are within 10% of each other. (Caution must be exercised to ensure that patient does not become excessively dehydrated.) Aqueous vasopressin is given, 5 U subcutaneously, and urinary osmolality is measured after 60 minutes. Expected responses are outlined in the table. *(From reference 40.)*

Central Diabetes Insipidus

Clinical Features Central DI usually has an abrupt onset. Patients have a constant need to drink, have a predilection for cold water, and typically have nocturia. By contrast, the compulsive water drinker may give a vague history of the onset and has large variations in

Etiology of Central Diabetes Insipidus

Congenital Causes
Autosomal dominant
Autosomal recessive

Acquired Causes
Post-traumatic
Iatrogenic (postsurgical)
Tumors (metastatic from breast, craniopharyngioma, pinealoma)
Histiocytosis
Granuloma (tuberculosis, sarcoid)
Aneurysm
Meningitis
Encephalitis
Guillain-Barré syndrome
Idiopathic

Box 8-2 Causes of central diabetes insipidus. Entries in italics are the common causes.

water intake and urine output. Nocturia is unusual in compulsive water drinkers. A plasma osmolality of more than 295 mOsm/kg suggests central DI, and less than 270 mOsm/kg suggests compulsive water drinking.

Causes Central DI is caused by infection, tumors, granuloma, and trauma affecting the CNS in 50% of patients; in the other 50% it is idiopathic (Box 8-2). In a survey of 79 children and young adults, central DI was idiopathic in half the patients. The other half had tumors and Langerhans cell histiocytosis; these patients had an 80% risk for development of anterior pituitary hormone deficiency compared with the patients with idiopathic disease.[41]

Autosomal dominant DI is caused by point mutations in a precursor gene for vasopressin that cause "misfolding" of the provasopressin peptide, preventing its release from the hypothalamic and posterior pituitary neurons.[42] Patients present with a mild polyuria and polydipsia in the first year of life. These children have normal physical and mental development. There is a rare autosomal recessive central DI associated with diabetes mellitus, optic atrophy, and deafness (Wolfram syndrome).[43] DI is usually partial and gradual in onset in Wolfram syndrome. It is linked to chromosome 4 and involves abnormalities in mitochondrial DNA.

A rare clinical entity involving the combination of central DI and deficient thirst has been reported in a total of 70 patients in 41 studies.[44] When vasopressin secretion and thirst are both impaired, affected patients are vulnerable to recurrent episodes of hypernatremia. Formerly called essential hypernatremia, the disorder is now called central DI with deficient thirst, or *adipsic* DI.

Differential Diagnosis Measurement of circulating vasopressin by radioimmunoassay is preferred to the tedious water deprivation test. Under basal conditions, vasopressin levels are unhelpful because there is a significant overlap among the polyuric disorders. Measurement after a water deprivation test is more useful (Table 8-6).

Treatment Central DI is treated with hormone replacement or pharmacologic agents (Table 8-7). In acute settings, when renal water losses are extensive, aqueous vasopressin (Pitressin) is useful. It has a short duration of action, allows careful monitoring, and avoids complications such as water intoxication. Aqueous vasopressin should be used with caution in patients with underlying coronary artery disease and peripheral vascular disease because it may cause vascular spasm and prolonged vasoconstriction. For chronic central DI, desmopressin acetate is the agent of choice. It has a long half-life and none of the significant vasoconstrictive effects of aqueous vasopressin. Desmopressin is administered at the dose of 10 to 20 µg intranasally every 12 to 24 hours. It is tolerated well, safe to use in pregnancy, and resistant to degradation by circulating vasopressinase. Oral desmopressin (0.1 to 0.8 mg every 12 hours) is available as second-line therapy. In patients with partial DI, in addition to desmopressin itself, agents that potentiate the release of vasopressin may be used, including chlorpropamide, clofibrate, and carbamazepine.

Treatment of Central Diabetes Insipidus

Disease	Drug	Dose	Interval
Complete central diabetes insipidus	Desmopressin (DDAVP)	10-20 µg intranasally	12-24 hours
	Desmopressin (DDAVP)	0.1-0.8 mg orally	Every 12 hours
Partial central diabetes insipidus	Desmopressin (DDAVP)	10-20 µg intranasally	12-24 hours
	Aqueous vasopressin	5-10 U subcutaneously	4-6 hours
	Chlorpropamide	250-500 mg	24 hours
	Clofibrate	500 mg	6 or 8 hours
	Carbamazepine	400-600 mg	24 hours

Table 8-7 Treatment of central diabetes insipidus.

Congenital Nephrogenic Diabetes Insipidus Inherited forms of DI are caused by mutations in genes for aquaporins or vasopressin receptors. Urine volumes are typically very high, and there is a risk for severe hypernatremia if patients do not have free access to water. These entities are discussed further in Chapter 49.

Acquired Nephrogenic Diabetes Insipidus Acquired nephrogenic DI is more common than congenital nephrogenic DI but rarely as severe. In patients with acquired DI, the ability to elaborate a maximal concentration of urine is impaired, but urine-concentrating mechanisms are partially preserved. For this reason, urine volumes are less than 3 to 4 l/day, which contrasts with the much higher volumes seen in patients with congenital or central DI or compulsive water drinking. Table 8-8 outlines the causes and mechanisms of acquired nephrogenic DI.

Chronic Kidney Disease A defect in urine-concentrating ability may develop in patients with chronic kidney disease of any etiology, but this defect is most prominent in tubulointerstitial diseases, particularly medullary cystic disease. Disruption of inner medullary structures and diminished medullary concentration are thought to play a role; alterations in V_2 receptor and AQP2 expression also contribute (see Fig. 8-6). To achieve daily osmolar clearance, an amount of fluid commensurate with the severity of the concentrating defect is necessary in patients who still make urine. Patients should be advised to maintain a fluid intake that matches their urine volume.

Electrolyte Disorders Hypokalemia causes a reversible abnormality in urine-concentrating ability. Hypokalemia stimulates water intake and reduces interstitial tonicity, which relates to the decreased Na^+-Cl^- reabsorption in the TAL. Hypokalemia resulting from diarrhea, chronic diuretic use, and primary aldosteronism also decreases intracellular cyclic adenosine monophosphate accumulation and causes a reduction in vasopressin-sensitive AQP2 expression (see Fig. 8-6).

Hypercalcemia also impairs urine-concentrating ability, resulting in mild polydipsia. The pathophysiologic mechanism is multifactorial and includes a reduction in medullary interstitial tonicity caused by decreased vasopressin-stimulated adenylate cyclase in the TAL and a defect in adenylate cyclase activity with decreased AQP2 expression in the collecting duct.

Acquired Nephrogenic Diabetes Insipidus: Causes and Mechanisms				
Disease State	**Defect in Medullary Interstitial Tonicity**	**Defect in cAMP Generation**	**Downregulation of Aquaporin 2**	**Other**
Chronic kidney disease	Yes	Yes	Yes	Downregulation of V_2 receptor message
Hypokalemia	Yes	Yes	Yes	—
Hypercalcemia	Yes	Yes	—	—
Sickle cell disease	Yes	—	—	—
Protein malnutrition	Yes	—	Yes	—
Demeclocycline therapy	—	Yes	—	—
Lithium therapy	—	Yes	Yes	—
Pregnancy	—	—	—	Placental secretion of vasopressinase

Table 8-8 Acquired nephrogenic diabetes insipidus: causes and mechanisms. *cAMP,* Cyclic adenosine monophosphate.

Pharmacologic Agents Lithium is the most common cause of nephrogenic DI, occurring in up to 50% of patients receiving long-term lithium therapy. Lithium causes downregulation of AQP2 in the collecting duct; experimentally, it also increases cyclooxygenase-2 (COX-2) expression and urinary prostaglandins, which may contribute to the polyuria.[45] The concentrating defect of lithium may persist even when the drug is discontinued. The epithelial sodium channel (ENaC) is the entrance pathway for lithium into collecting duct principal cells. Amiloride inhibits lithium uptake through ENaC and has been used clinically to treat nephrogenic DI caused by lithium. Aldosterone administration dramatically increased urine production in experimental nephrogenic DI caused by lithium[46] (an effect associated with decreased expression of AQP2 on luminal membranes of collecting duct), whereas administration of the mineralocorticoid receptor blocker spironolactone decreased urine output and increased AQP2 expression.[47] It is not yet known if spironolactone is a useful treatment for humans with lithium-induced nephrogenic DI.

Other drugs impairing urine-concentrating ability include amphotericin, foscarnet, and demeclocycline, which reduces renal medullary adenylate cyclase activity, thereby decreasing the effect of vasopressin on the collecting ducts.

Sickle Cell Anemia Patients with sickle cell disease and trait often have a urine-concentrating defect. In the hypertonic medullary interstitium, the "sickled" red cells cause occlusion of the vasa recta and papillary damage. The resultant medullary ischemia may impair Na^+-Cl^- transport in the ascending limb and diminish medullary tonicity. Although initially reversible, medullary infarcts occur with longstanding sickle cell disease, and the concentrating defects become irreversible.

Dietary Abnormalities Extensive water intake or a marked decrease in salt and protein intake leads to impairment of maximal urine-concentrating ability through a reduction in medullary interstitial tonicity. On a low-protein diet with excessive water intake, there is a decrease in vasopressin-stimulated osmotic water permeability that is reversed with feeding.

Gestational Diabetes Insipidus In gestational DI, there is an increase in circulating vasopressinase, which is produced by the placenta. Patients are typically unresponsive to vasopressin but respond to desmopressin, which is resistant to vasopressinase.

Clinical Manifestations of Hypernatremia

Certain patients are at increased risk for development of severe hypernatremia (Box 8-3). Signs and symptoms mostly relate to the CNS and include altered mental status, lethargy, irritability, restlessness, seizures (usually in children), muscle twitching, hyperreflexia, and spasticity. Fever, nausea or vomiting, labored breathing, and intense thirst can also occur. In children, mortality of acute hypernatremia ranges from 10% to 70%. As many as two thirds of survivors have neurologic sequelae. In contrast, mortality in patients with chronic hypernatremia is 10%. In adults, serum [Na^+] above 160 mmol/l is associated with 75% mortality, although this may reflect associated comorbidities rather than hypernatremia.

Patients at Risk for Severe Hypernatremia

- Elderly patients
- Infants
- Hospitalized patients
  - Hypertonic infusions
  - Tube feedings
  - Osmotic diuretics
  - Lactulose
  - Mechanical ventilation
- High-risk patient groups
  - Altered mental status
  - Uncontrolled diabetes mellitus
  - Underlying polyuric disorders

Box 8-3 Patient groups at risk for development of severe hypernatremia. *(From reference 24.)*

Treatment of Hypernatremia

Hypernatremia occurs in predictable clinical settings, allowing opportunities for prevention. Elderly and hospitalized patients are at high risk because of impaired thirst and inability to access free water independently.[48] Certain clinical situations, such as recovery from acute kidney injury, catabolic states, therapy with hypertonic solutions, uncontrolled diabetes, and burns, should prompt close attention to serum sodium concentration and increased administration of free water.

Hypernatremia always reflects a hyperosmolar state. The primary goal in the treatment of these patients is the restoration of serum tonicity. Figure 8-11 outlines specific management options.[24] Since restoration of volume takes precedence over restoration of tonicity, in hypovolemic hypernatremic patients, sodium-containing solutions should be used until euvolemia is achieved. Thereafter, dextrose

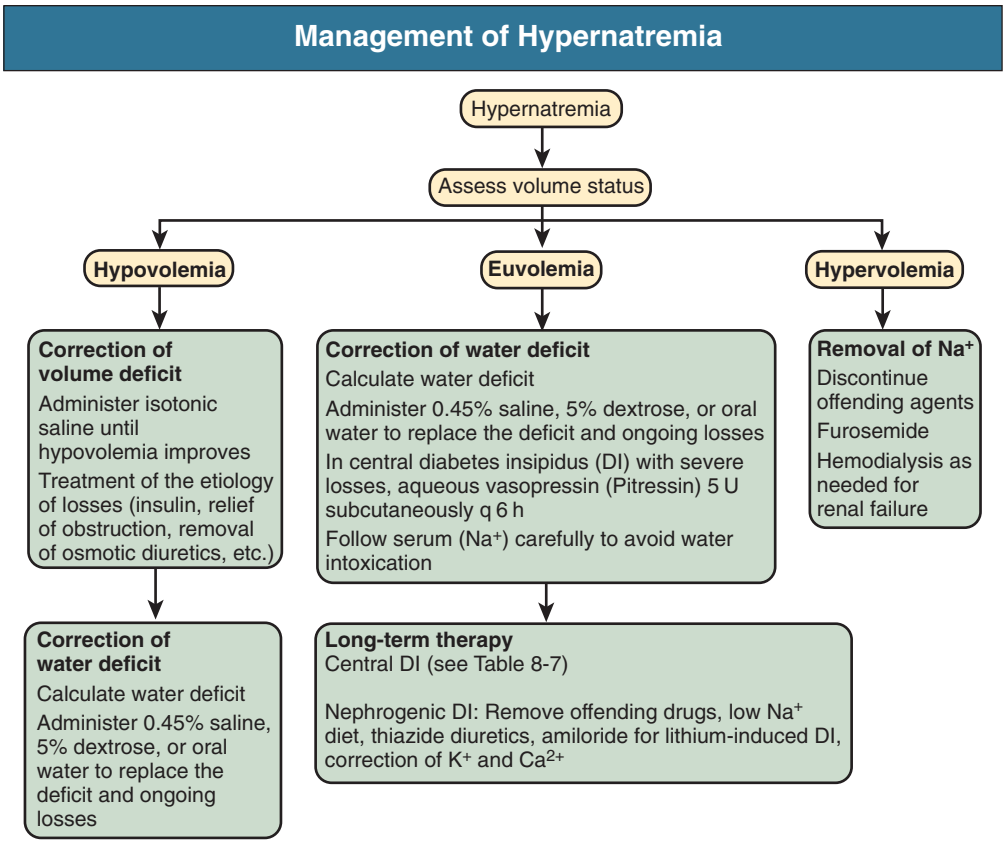

Figure 8-11 Algorithm for management of the patient with hypernatremia. *(From reference 24.)*

in water or oral water intake should be given to decrease serum sodium concentration.

The rapidity with which hypernatremia should be corrected is controversial. Some animal studies and case series in pediatric patients suggest that a correction rate of more than 0.5 mmol/l/h in [Na^+] can cause seizures. Cerebral edema also can be caused by rapid correction of hypernatremia by the net movement of water into the brain. Most clinicians believe that even in adults, correction should be achieved during 48 hours at a rate no greater than 2 mmol/l/h.

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CHAPTER 9

Disorders of Potassium Metabolism

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Potassium disorders are some of the most frequently encountered fluid and electrolyte abnormalities in clinical medicine. Patients with disorders of potassium metabolism may be asymptomatic or they may have symptoms ranging from mild weakness to sudden death. When the serum potassium level is verified as abnormal, correction is essential, but inappropriate treatment can worsen symptoms and even lead to death.

NORMAL PHYSIOLOGY OF POTASSIUM METABOLISM

Potassium Intake

Potassium is essential for many cellular functions, is present in most foods, and is excreted primarily by the kidney. The typical Western diet contains about 70 to 150 mmol of potassium daily. The gastrointestinal (GI) tract efficiently absorbs potassium, and total dietary potassium intake varies the composition of the diet. Table 9-1 shows the potassium content of several foods high in potassium.[1]

Potassium Distribution

After absorption from the GI tract, potassium distributes into the extracellular fluid (ECF) and intracellular fluid (ICF) compartments. Potassium is the major intracellular cation, with K^+ concentrations from about 100 to 120 mmol/l in the cytosol. Total intracellular K^+ content is 3000 to 3500 mmol in healthy adults, found primarily in muscle (70%), with a lesser amount in bone, red blood cells, liver, and skin (Table 9-2). Only 1% to 2% total body potassium is present in the ECF. The electrogenic sodium pump, Na^+-K^+-ATPase, which is present in virtually all cells, affects this asymmetric potassium distribution by active cellular K^+ uptake. Na^+-K^+-ATPase transports two potassium ions into cells in exchange for extrusion of three sodium ions, which results in high intracellular potassium concentration (high $[K^+]$) and low intracellular sodium concentration (low $[Na^+]$). Potassium-selective ion channels are the predominant determinant of the resting membrane potential. Therefore, the intracellular/extracellular $[K^+]$ ratio largely determines the resting cell membrane potential and the intracellular electronegativity. Normal maintenance of this ratio and membrane potential is critical for normal nerve conduction and muscular contraction.

Serum potassium is tightly regulated through multiple mechanisms. Recent studies support a "feed forward" regulatory system involving gut or portal potassium sensors. This system adjusts renal potassium excretion through mechanisms independent of serum potassium and aldosterone.[2,3] This reflex system, which is still not understood fully, allows the kidney to "sense" dietary intake and alter renal potassium excretion despite no discernible changes in serum potassium or aldosterone concentration.

In addition, several hormones and factors can induce potassium shifts between the extracellular and intracellular potassium pools (Fig. 9-1). The most common causes include acid-base disorders, specific hormones, plasma osmolality, and exercise.

Acidosis caused by inorganic anions (e.g., NH_4Cl, HCl) can cause hyperkalemia, but the mechanism is not fully understood. In contrast, organic acids (e.g., lactic acid) generally do not cause transcellular potassium shifts. Insulin and β_2-adrenergic receptor activation induce cellular potassium uptake by stimulating Na^+-K^+-ATPase. Stimulation of Na^+-K^+-ATPase by insulin occurs through a mechanism separate from its stimulation of glucose entry. β_2-Adrenoceptor activation increases intracellular cAMP production, which stimulates Na^+-K^+-ATPase-mediated potassium uptake, whereas α-adrenergic receptor activation has the opposite effect. The effects of insulin and β_2-adrenoceptor activation are synergistic, as expected given the differing cellular mechanisms.

Aldosterone lowers serum potassium by two major mechanisms. First, aldosterone stimulates potassium movement into cells through stimulation of Na^+-K^+-ATPase (i.e., redistribution). Second, it can increase potassium excretion by the kidney and, to a lesser extent, by the GI tract. In the kidney, aldosterone stimulates sodium reabsorption in both the distal convoluted tubule and the collecting duct, and if there is sufficient sodium delivery to the collecting duct, this increased sodium reabsorption promotes potassium secretion. Mineralocorticoids can also stimulate potassium absorptive pumps, which may explain the equivocal effects of mineralocorticoids on potassium excretion despite their consistent effect on sodium absorption.[4,5]

Another important factor that alters cellular potassium uptake is plasma osmolality. Increased plasma osmolality, or hyperosmolality, when resulting from "effective osmoles," can cause hyperkalemia. The likely mechanism is that increased plasma osmolality induces water movement out of the cells, which decreases cell volume and increases intracellular $[K^+]$. This in turn results in feedback inhibition of Na^+-K^+-ATPase, decreasing cellular potassium uptake and normalizing intracellular $[K^+]$. The clinician should remember that this occurs only with effective osmoles, such as with mannitol, or with hyperglycemia in diabetic patients. Both glucose in patients with intact insulin secretion and urea are "ineffective osmoles" because they rapidly cross plasma membranes and therefore do not alter cell volume. Importantly, administration of a glucose load to a nondiabetic patient, through stimulation of endogenous insulin secretion, can cause insulin-induced cellular potassium uptake and result in hypokalemia.

Exercise may result in hyperkalemia due to α-adrenergic receptor activation that shifts potassium out of the skeletal muscle cells. The increased serum potassium induces arterial dilation, which increases skeletal muscle blood flow and acts as an adaptive mechanism during exercise. Simultaneous β_2-adrenoceptor activation stimulates

Potassium Content of Select High-Potassium Foods					
Food	**Common Serving Size**	**Serving Size (g)**	**K^+ per Serving (mg)**	**K^+ per Serving (mmol)**	**mmol K^+/100 g**
Apricots, dried	10 halves	35	407	10	30
Banana	1 banana	118	422	11	9
Cabbage, Chinese (pak-choi)	1 cup	170	631	16	10
Chickpeas or garbanzo beans	1 cup	164	477	12	7
Chocolate, semisweet	1 cup	168	613	16	9
Dates	~5 dates	42	272	7	17
French fried potato	1 large	169	979	25	15
Lentils, boiled without salt	1 cup	198	731	19	9
Lima beans, boiled without salt	1 cup	188	955	24	13
Papaya	1 papaya	304	553	14	5
Plantains, raw	1 medium	179	893	23	13
Potatoes, baked	1 medium potato	202	1081	28	14
Raisins, seedless	1 cup	145	1086	28	19
Refried beans, traditional style	1 cup	252	847	22	9
Sauce, pasta, spaghetti/marinara, ready-to-serve	1 cup	250	798	20	8
Soybeans, green, cooked, boiled, drained	1 cup	180	970	25	14
Sweet potato, canned	1 cup	255	796	20	8
Tomato sauce, canned	1 cup	245	811	21	8
Yogurt, plain, low fat	8 oz	227	579	15	7

Table 9-1 Amount of potassium (K^+) in select foods with high potassium content. *(Data from reference 1.)*

Distribution of Total Body Potassium in Organs and Body Compartments			
Organ/Fluid	**Total K^+ Amount**	**Body Compartment**	**K^+ Concentration**
Muscle	2650 mmol	Intracellular fluid (ICF)	100-120 mmol/l
Liver	250 mmol	Extracellular fluid (ECF)	~4 mmol/l
Interstitial fluid	35 mmol		
Red blood cells	350 mmol		
Plasma	15 mmol		

Table 9-2 Distribution of total body potassium in organs and body compartments

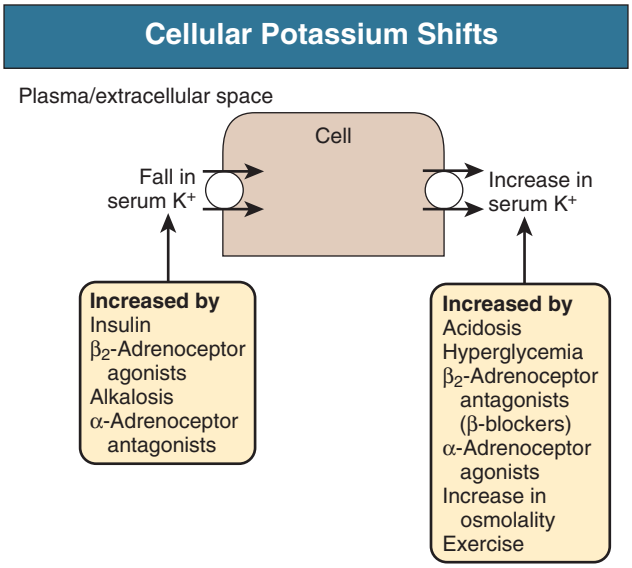

Figure 9-1 Regulation of extracellular/intracellular potassium shifts.

skeletal muscle cellular potassium uptake and minimizes the severity of exercise-induced hyperkalemia, but this can lead to hypokalemia after cessation of exercise. In patients with preexisting potassium depletion, postexercise hypokalemia may be severe and can cause rhabdomyolysis.[6]

Renal Potassium Handling with Normal Renal Function

Long-term potassium homeostasis is accomplished primarily through changes in renal potassium excretion, almost entirely through regulated collecting duct potassium transport. Serum potassium is almost completely ionized, is not bound to plasma proteins, and is filtered efficiently by the glomerulus (Fig. 9-2). The proximal tubule reabsorbs the majority (~65% to 70%) of filtered potassium, but there is relatively little variation in proximal tubule potassium reabsorption in response to hypokalemia or hyperkalemia. In the loop of Henle, potassium is secreted in the descending loop, at least in deep nephrons, and is reabsorbed in the ascending loop through the action of the Na^+-K^+-$2Cl^-$ cotransporter (Fig. 9-3, *A*). However, the majority of K^+ transported by this protein is recycled back into the tubular lumen through an apical K^+ channel. As a result, there is only modest net potassium reabsorption in the Henle loop. This absorption can be reversed to secretion, however, by administration of a loop diuretic or by substantial potassium

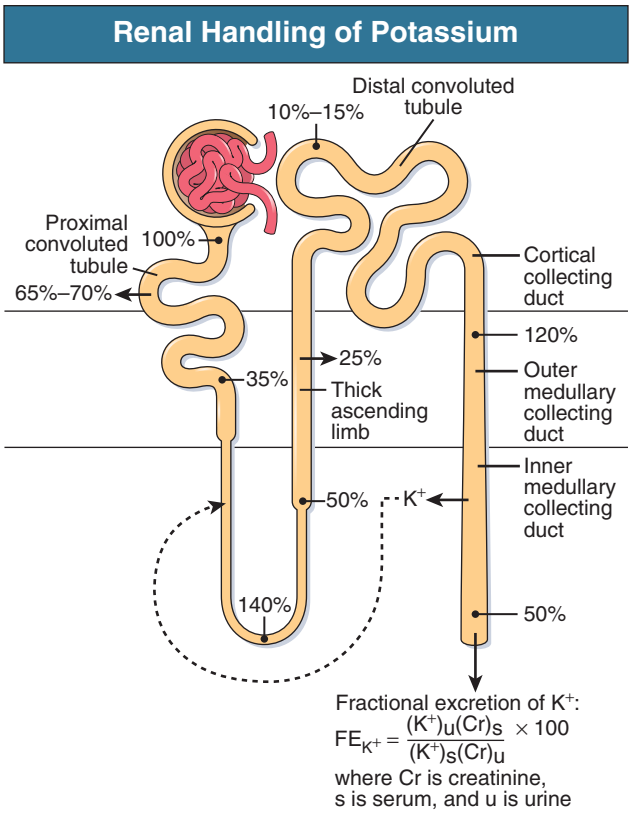

Figure 9-2 **Renal handling of potassium.**

loading. However, the magnitude of the change in Henle loop potassium transport in various physiologic conditions is rather small. Consequently, potassium excretion is regulated under most conditions through variations in distal convoluted tubule and collecting duct potassium transport.

The collecting duct consists of two fundamentally different cell types with distinctly different roles in potassium transport. The principal cell in the cortical collecting duct secretes potassium, whereas intercalated (IC) cells appear to reabsorb potassium. In the principal cell, sodium is reabsorbed through the apical epithelial sodium channel (ENaC), which stimulates basolateral Na^+-K^+-ATPase (Fig. 9-3, *B*); active potassium uptake by this protein maintains a high intracellular [K^+]. Subsequent to basolateral potassium uptake, K^+ is secreted across the apical plasma membrane of principal cells into the luminal fluid by apical potassium channels and KCl cotransporters. IC cells, in contrast, reabsorb potassium through an apical H^+-K^+-ATPase[7] (Fig. 9-3, *C*); this protein actively secretes H^+ into the luminal fluid in exchange for reabsorption of luminal potassium. The presence of two separate potassium transport processes, secretion by principal cells and reabsorption by IC cells, enables rapid and effective regulation of renal potassium excretion.

Several factors regulate principal cell potassium secretion and, in relative order of importance, include luminal flow rate, distal sodium delivery, aldosterone, extracellular potassium, and extracellular pH. An increase in luminal flow rate reduces luminal [K^+], thereby increasing the concentration gradient across the apical membrane, which stimulates potassium secretion. In addition, flow rate directly influences cellular potassium secretion, possibly by modulating the activity of potassium channels. Conversely, reduced luminal flow, such as occurs in pre-renal azotemia and obstruction, may result in hyperkalemia. Decreased sodium reabsorption, whether from reduced luminal sodium delivery or sodium channel inhibitors, decreases K^+ secretion by altering electrochemical forces for K^+ secretion. "Potassium-sparing diuretics" function by blocking principal cell ENaC-mediated sodium reabsorption, which inhibits principal cell potassium secretion. Conversely, increased sodium delivery to the collecting duct, as may occur with loop or thiazide diuretics, increases principal cell sodium reabsorption and causes a secondary increase in potassium secretion. Aldosterone has many effects that increase principal cell potassium secretion, including increases in Na^+-K^+-ATPase expression and increased apical expression of eNaC. The net effect is increased K^+ secretion. Increasing extracellular potassium directly stimulates Na^+-K^+-ATPase activity, leading to increased K^+ secretion. Metabolic acidosis decreases K^+ secretion, both through direct effects on potassium channels and through changes in interstitial ammonia concentration, which decreases K^+ secretion.[8] Respiratory acidosis has minimal effect on K^+ secretion, whereas chronic respiratory alkalosis causes marked increases in K^+ excretion because of increases in urinary bicarbonate excretion.

Potassium reabsorption, which occurs in parallel with potassium secretion, decreases net renal K^+ excretion, and occurs through the action of the potassium-reabsorbing protein, H^+-K^+-ATPase. The major factors regulating H^+-K^+-ATPase expression and activity include potassium balance, aldosterone, and acid-base status. Potassium depletion increases H^+-K^+-ATPase expression, resulting in increased active potassium reabsorption and decreased potassium excretion. Aldosterone also increases H^+-K^+-ATPase expression and activity and, by decreasing net potassium excretion, may function to minimize the hypokalemia that otherwise results from aldosterone's effect on both potassium redistribution and principal cell–mediated K^+ secretion. Metabolic acidosis has both direct and indirect effects, mediated through alterations in ammonia metabolism, that increase H^+-K^+-ATPase potassium transport. In some patients, this may contribute to the hyperkalemia that can occur with metabolic acidosis.

An important class of intracellular signaling proteins have been identified that are fundamental in the regulation of renal K^+ transport in the distal nephron. The "with no lysine" or "WNK" kinases are a family of proteins expressed in many cells of the body including the kidney. Under basal conditions, WNK kinases inhibit Na^+ reabsorption as well as decreasing potassium secretion, in part by inhibiting the rectifying renal outer medulla potassium (ROMK) channel. Genetic defects that inactivate WNK kinases result in enhanced Na^+ reabsorption and reduced K^+ secretion.

Renal Potassium Handling in Chronic Kidney Disease

Potassium homeostasis is relatively well preserved and serum potassium usually remains in the normal range until glomerular filtration rate is reduced substantially. This adaptation is due largely to increased rates of per nephron potassium excretion in the connecting segment and the collecting duct. Both aldosterone and an increase in serum potassium may contribute to this adaptation. Intestinal potassium secretion increases, also, although quantitatively this is less important.

Patients with chronic kidney disease (CKD) have more difficulty handling an acute potassium load, even when they have a normal serum [K^+]. Because these patients have decreased nephron number, their maximal capacity for K^+ secretion is limited. Patients with CKD are also routinely treated with medications that alter renal potassium handling, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and β-blockers. These can decrease renal potassium sensitivity and result in higher serum potassium concentrations.

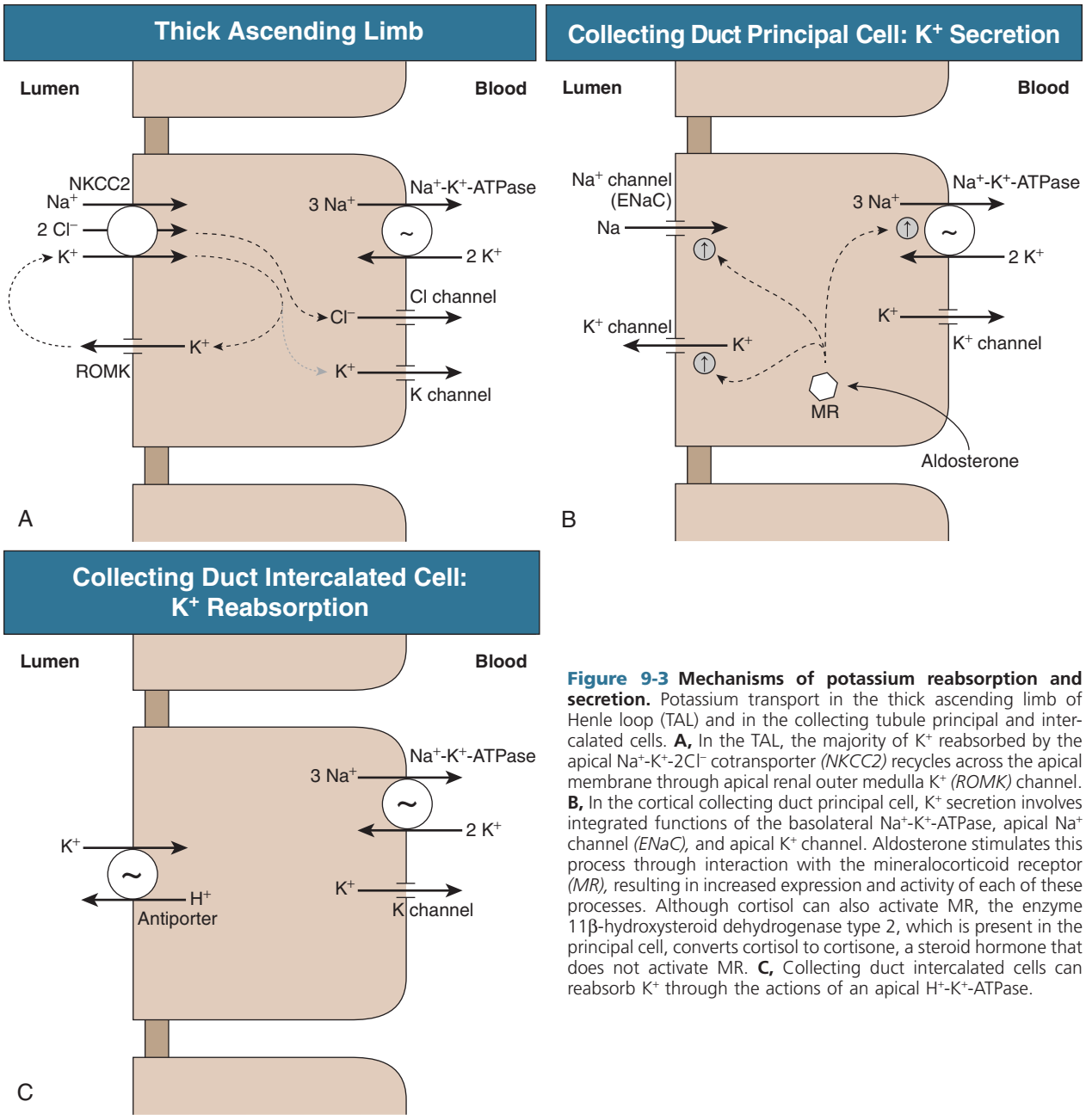

Figure 9-3 Mechanisms of potassium reabsorption and secretion. Potassium transport in the thick ascending limb of Henle loop (TAL) and in the collecting tubule principal and intercalated cells. **A,** In the TAL, the majority of K^+ reabsorbed by the apical Na^+-K^+-$2Cl^-$ cotransporter *(NKCC2)* recycles across the apical membrane through apical renal outer medulla K^+ *(ROMK)* channel. **B,** In the cortical collecting duct principal cell, K^+ secretion involves integrated functions of the basolateral Na^+-K^+-ATPase, apical Na^+ channel *(ENaC),* and apical K^+ channel. Aldosterone stimulates this process through interaction with the mineralocorticoid receptor *(MR),* resulting in increased expression and activity of each of these processes. Although cortisol can also activate MR, the enzyme 11β-hydroxysteroid dehydrogenase type 2, which is present in the principal cell, converts cortisol to cortisone, a steroid hormone that does not activate MR. **C,** Collecting duct intercalated cells can reabsorb K^+ through the actions of an apical H^+-K^+-ATPase.

Patients with CKD generally tolerate hyperkalemia with fewer cardiac and electrocardiographic (ECG) abnormalities than do patients with normal renal function. The mechanism of this adaptation is incompletely understood. In particular, patients with CKD appear to tolerate serum [K^+] of 5.0 to 5.5 mmol/l with no significant adverse effect, and levels of 5.5 to 6.0 mmol/l are associated with lower mortality than [K^+] of 3.5 to 3.9 mmol/l.[9] Nevertheless, severe hyperkalemia (>6.0 mmol/l or presence of ECG changes) can have lethal effects and should be treated aggressively.

HYPOKALEMIA

Epidemiology

The incidence of potassium disorders depends greatly on the patient population. Less than 1% of adults with normal renal function who are not receiving medicines develop hypokalemia or hyperkalemia; however, diets with high sodium and low potassium content may lead to potassium depletion. Thus, identification of hypokalemia or hyperkalemia should suggest either that an underlying disease is present or that the individual is taking medications that alter potassium handling. For example, hypokalemia may be present in as many as half of patients taking diuretics[10] and is present frequently in patients with primary or secondary hyperaldosteronism.

Clinical Manifestations

Potassium deficiency, because it alters the ratio of extracellular to intracellular potassium, alters the resting membrane potential, which can impair normal functioning of almost every cell in the body. This particularly is true for cells in the heart and blood vessels, nerves, muscles, gut, and kidneys. Overall, children and young adults

tolerate hypokalemia better than elderly persons. Prompt correction is warranted in patients with coronary heart disease or in patients receiving digitalis glycosides, because of an increased risk of lethal cardiac arrhythmias.

Cardiovascular

Epidemiologic studies link hypokalemia and a low-potassium diet with an increased prevalence of hypertension. Experimental studies show that hypokalemia increases blood pressure by 5 to 10 mm Hg, and that potassium supplementation can lower blood pressure by a similar amount.[11] Potassium deficiency increases blood pressure through multiple mechanisms, including stimulating sodium retention and causing intravascular volume expansion, and by sensitizing the vasculature to endogenous vasoconstrictors.[11] In part, sodium retention is related to decreased expression of the kidney-specific isoform of WNK1, which leads to increased NaCl cotransporter (NCC)–mediated and ENaC-mediated sodium reabsorption in the distal convoluted tubule and cortical collecting duct, respectively.[12]

Hypokalemia increases the risk of a variety of ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation.[13] Diuretic-induced hypokalemia is of particular concern, because sudden cardiac death may occur more frequently in those treated with thiazide diuretics.[13] Ventricular arrhythmias are also more common in patients receiving digoxin.

Hormonal

Hypokalemia both impairs insulin release and induces insulin resistance, resulting in worsened glucose control in diabetic patients.[14] The insulin resistance that usually occurs with thiazide diuretic therapy is caused by endothelial dysfunction mediated by thiazide-induced hypokalemia and hyperuricemia.[15,16]

Muscular

Hypokalemia hyperpolarizes skeletal muscle cells, thereby impairing muscle contraction. Hypokalemia also reduces skeletal muscle blood flow, possibly by impairing local nitric oxide release; this effect can predispose patients to rhabdomyolysis during vigorous exercise.[17]

Renal

Hypokalemia leads to several important disturbances of renal function. Reduced medullary blood flow and increased renal vascular resistance may predispose to hypertension, tubulointerstitial and cystic changes, alterations in acid-base balance, and impairment of renal concentrating mechanisms.

Potassium depletion causes tubulointerstitial fibrosis that is generally greatest in the outer medulla. The degree of reversibility is related to the duration of hypokalemia, and if prolonged, hypokalemia may result in renal failure. Experimental studies suggest increased risk for irreversible renal injury when hypokalemia is present during the neonatal period.[18] Longstanding potassium depletion also causes renal hypertrophy and predisposes to renal cyst formation, particularly when there is increased mineralocorticoid activity.

Metabolic alkalosis is a common acid-base consequence of potassium depletion and results from increased renal net acid excretion caused by increased renal ammonia excretion.[19] Conversely, *metabolic alkalosis* may increase renal potassium excretion and cause potassium depletion. Severe hypokalemia can lead to respiratory muscle weakness and development of respiratory acidosis.

Severe hypokalemia also impairs concentrating ability, causing mild polyuria, typically 2 to 3 l/day. Both increased thirst and mild nephrogenic diabetes insipidus contribute to the polyuria.[20] The nephrogenic diabetes insipidus is caused by decreased expression of several proteins, such as the water transporter aquaporin 2 (AQP2), and the urea transporters UT-A1, UT-A3, and UT-B, which are involved in urine concentration and water reabsorption.

Hypokalemia has substantial effects to increase renal ammonia production. Some ammonia is excreted in the urine, increasing net acid excretion and leading to development of metabolic alkalosis. In addition, approximately half of this increase returns to the systemic circulation via the renal veins. In patients with acute or chronic liver disease, this increased ammonia delivery may exceed hepatic ammonia clearance capacity, increase plasma ammonia levels, and either precipitate or worsen hepatic encephalopathy.[21]

Etiology

Hypokalemia results typically from one of four etiologies: pseudohypokalemia, redistribution, extrarenal potassium loss, or renal potassium loss. However, multiple etiologies may coexist in the specific patient.

Pseudohypokalemia

Pseudohypokalemia refers to the condition in which serum potassium decreases, artifactually, following phlebotomy. The most common cause is acute leukemia; the large numbers of abnormal leukocytes take up potassium when the blood is stored in a collection vial for prolonged periods at room temperature. Rapid separation of plasma and storage at 4°C is used to confirm this diagnosis and should be used for subsequent testing once pseudohypokalemia is diagnosed, to avoid this artifact leading to inappropriate treatment.

Redistribution

Because less than 2% of total body potassium is in the ECF compartment, quantitatively small potassium shifts from the ECF to the ICF compartment can result in substantial hypokalemia. As previously discussed, many hormones, particularly including insulin, aldosterone, and β_2-adrenergic agonists, stimulate transcellular potassium uptake.

A rare but important cause of redistribution-induced hypokalemia is *hypokalemic periodic paralysis*.[22] In this condition, attacks characterized by flaccid paralysis or severe muscular weakness typically occur during the night or the early morning, or after a carbohydrate-rich meal, and persist for 6 to 24 hours. A genetic defect in a dihydropyridine-sensitive calcium channel has been identified in some patients,[23] whereas other cases are associated with hyperthyroidism.

Nonrenal Potassium Loss

The skin and the GI tract excrete small amounts of potassium under normal circumstances. Occasionally, excessive sweating or chronic diarrhea results in substantial potassium loss and leads to hypokalemia.[24] Vomiting or nasogastric suction may also result in loss of potassium, although gastric fluids typically contain only 5 to 8 mmol/l of potassium. However, the concomitant metabolic alkalosis and the intravascular volume depletion results in secondary hyperaldosteronism that can increase urinary potassium loss and contribute to development of hypokalemia.[24]

Renal Potassium Loss

The most common cause of hypokalemia is renal potassium loss, resulting from medications, endogenous hormone production, or rarely intrinsic renal defects.

Medications Both thiazide and loop diuretics increase urinary potassium excretion, and the incidence of diuretic-induced hypokalemia is related to both dose and treatment duration. If the effect of

loop and thiazide diuretics on sodium excretion is compared and adjusted, thiazide diuretics actually cause more urinary potassium loss than loop diuretics. Certain antibiotics increase urinary potassium excretion. Some penicillin analogues, such as piperacillin/tazobactam, increase distal tubular delivery of a non-reabsorbable anion, which obligates the presence of a cation such as potassium, thereby increasing urinary potassium excretion.[25] The antifungal agent amphotericin B directly increases collecting duct potassium secretion.[26] Aminoglycosides may cause hypokalemia either with or without simultaneous nephrotoxicity. The mechanism is incompletely understood but may relate to magnesium depletion (see later discussion). Cisplatin is a common antineoplastic agent that can induce hypokalemia. Toluene exposure, from sniffing certain glues, can also cause renal tubular acidosis with renal potassium wasting, leading to hypokalemia.[27] In addition, certain herbal products, including herbal cough mixtures, licorice tea, licorice root, and gan cao, contain glycyrrhizic and glycyrrhetinic acids, which have mineralocorticoid-like effects.[28]

Endogenous Hormones Endogenous hormones are important and common causes of hypokalemia. Aldosterone is the most important hormone regulating total body potassium homeostasis. Aldosterone causes hypokalemia both by stimulating potassium uptake into cells and by stimulating renal potassium excretion. Primary aldosteronism is a common cause of hypokalemia (see Chapter 40).

Genetic Causes Genetic defects leading to excessive aldosterone production are occasionally seen as causes of renal potassium wasting (see Chapter 49). *Glucocorticoid-remediable aldosteronism* (GRA) is a condition in which a corticotropin (ACTH)–regulated promoter is linked to the gene for aldosterone synthase, the rate-limiting enzyme for aldosterone synthesis.[29] As a result, aldosterone synthase expression is regulated by ACTH, leading to excessive aldosterone synthase expression and the development of severe hyperaldosteronism. In *congenital adrenal hyperplasia,* there is persistent adrenal synthesis of 11-deoxycorticosterone, a potent mineralocorticoid.[30] This condition can be recognized by the associated effects on sex steroid production.

Genetic defects can also lead to abnormal activation of the mineralocorticoid receptor, resulting in the same clinical manifestations as excessive aldosterone production. The glucocorticoid hormone cortisol can activate the mineralocorticoid receptor. Under normal conditions, the enzyme 11β-hydroxysteroid dehydrogenase, type 2 (11β-HSDH-2) rapidly metabolizes cortisol to cortisone, thereby preventing inappropriate mineralocorticoid receptor activation.[31] If this does not occur, glucocorticoid hormones are able to activate mineralocorticoid receptors. Genetic deficiency of 11β-HSDH-2 is rare, but leads to severe hypertension and hypokalemia. Some compounds, such as glycyrrhetinic acid, found in some chewing tobacco and licorice preparations, inhibit 11β-HSDH-2, allowing cortisol to exert mineralocorticoid-like effects.[32] Also, in severe Cushing syndrome circulating cortisol levels can exceed the metabolic capacity of 11β-HSDH-2, resulting in mineralocorticoid receptor activation and hypokalemia.[33]

Magnesium Depletion Magnesium deficiency inhibits renal potassium retention and causes inappropriately high renal potassium excretion despite hypokalemia.[34] This occurs most frequently as a complication of prolonged diuretic use and can also result from aminoglycoside- and cisplatin-induced renal toxicity. Magnesium deficiency should be suspected when potassium replacement does not correct hypokalemia; treatment with magnesium replacement generally reverses the potassium wasting.

Intrinsic Renal Defect Intrinsic renal potassium transport defects leading to hypokalemia are rare but have led to important advances in our understanding of renal solute transport. *Bartter syndrome* is characterized by hypokalemia, reduced blood pressure, hyperreninemia, metabolic alkalosis, and hypercalciuria. Patients with Bartter syndrome typically develop clinical manifestations at a young age, which include severe volume depletion and growth retardation. Bartter syndrome results from genetic abnormalities in any of several proteins involved in sodium and potassium transport in the thick ascending limb of the loop of Henle.[35] *Gitelman syndrome* is similar to Bartter syndrome, except patients have hypocalciuria and milder clinical manifestations and are usually diagnosed later in life. Gitelman syndrome results from genetic abnormalities in the proteins involved in distal convoluted tubule sodium and potassium transport.[36] When Bartter or Gitelman syndrome is suspected, it is critical to evaluate the patient for surreptitious diuretic use, because loop and thiazide diuretics give the same clinical phenotype as Bartter and Gitelman syndrome, respectively. *Liddle syndrome* is characterized by severe hypertension, hypokalemia and suppressed renin and aldosterone levels. Liddle syndrome is caused by a mutation that increases collecting duct ENaC expression and activity, leading to excessive sodium reabsorption, potassium excretion, volume expansion, and hypertension.[37] (See Chapter 49.)

Bicarbonaturia Bicarbonaturia can result from metabolic alkalosis, distal renal tubular acidosis, or treatment of proximal renal tubular acidosis. In each case, the increased distal tubular bicarbonate delivery increases potassium secretion.

Diagnostic Evaluation

The evaluation of hypokalemia is summarized in Figure 9-4. The nephrologist should first consider the possibility of either pseudohypokalemia or potassium redistribution from the extracellular to the intracellular space. Insulin, aldosterone, and its synthetic analogue, fludrocortisone, and sympathomimetic agents such as theophylline and β_2-adrenoceptor agonists are common causes of potassium redistribution. In the hypertensive patient, frank hypokalemia in the absence of diuretic use or substantial hypokalemia with diuretic use should suggest primary aldosteronism.

If neither pseudohypokalemia nor potassium redistribution is present, the hypokalemia represents total body potassium depletion caused by renal, GI, or skin losses. Renal potassium loss is most frequently caused by diuretics or metabolic alkalosis. Hypomagnesemia-induced hypokalemia causes renal potassium wasting and is frequently a complication of diuretic use. Rarer causes of renal potassium loss include renal tubular acidosis, diabetic ketoacidosis, and ureterosigmoidostomy. Primary aldosteronism, surreptitious diuretic use or vomiting, concomitant magnesium depletion, and Bartter or Gitelman syndrome should be considered when the cause of the hypokalemia is not obvious. Lastly, excessive potassium loss may result from the skin through excessive sweating or from diarrhea, vomiting, nasogastric suction, or GI fistula. Occasionally, patients are reluctant to admit to self-induced diarrhea, and the diagnosis may need to be confirmed by sigmoidoscopy or direct testing of the stool for cathartic agents.

Treatment

As with any condition, the risks associated with untreated or slowly treated hypokalemia must be balanced against the risks of therapy. Usually, the primary short-term risks are cardiovascular arrhythmias and neuromuscular weakness. Overaggressive therapy can cause acute hyperkalemia, which can cause ventricular fibrillation and sudden death.

Conditions requiring urgent therapy are rare. The clearest indications are hypokalemic periodic paralysis, severe hypokalemia in a

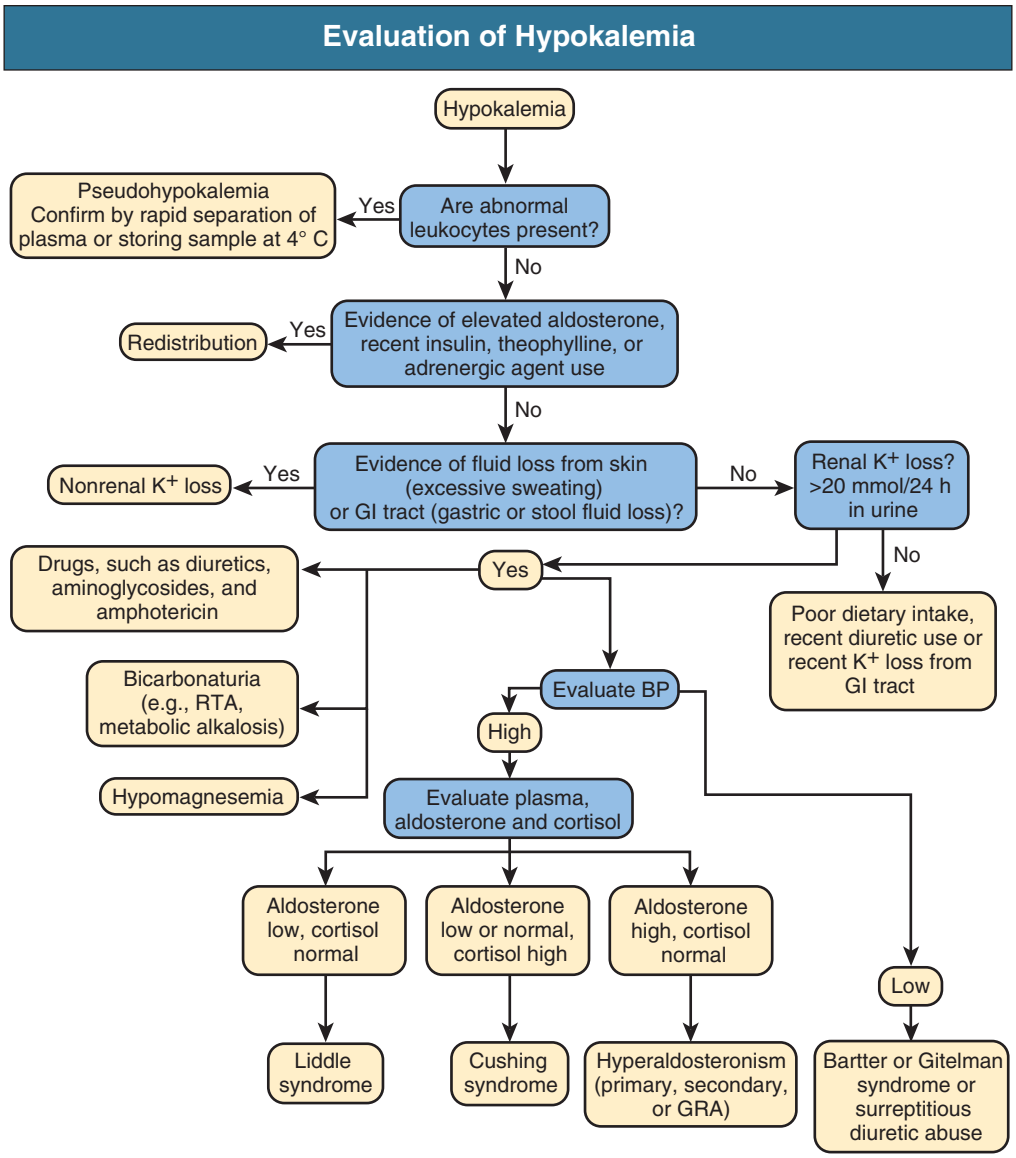

Figure 9-4 Diagnostic evaluation of hypokalemia. *BP,* Blood pressure; *GI,* gastrointestinal; *GRA,* glucocorticoid-remediable aldosteronism; *RTA,* renal tubular acidosis.

patient requiring urgent surgery, and the patient with an acute myocardial infarction and significant ventricular ectopy. In these patients, potassium chloride (KCl) can be administered intravenously at a dose of 5 to 10 mmol over 15 to 20 minutes. This dose can be repeated as needed. Close, continuous monitoring of the serum [K^+] and the electrocardiogram are necessary to reduce the risk of potentially lethal acute hyperkalemia.

In the great majority of hypokalemic patients, emergency therapy is not necessary, and instead a slower approach to replacing the potassium deficit is appropriate. In doing so, it is important to recognize that the amount of potassium required may be much greater than predicted from the deficit in serum potassium concentration. This occurs because the body responds to chronic hypokalemia resulting from potassium losses by shifting potassium from ICF to ECF compartment, thereby minimizing the change in extracellular [K^+]. Consequently, the amount of potassium replacement needed is much greater than predicted by the change in extracellular [K^+] and the ECF volume (Fig. 9-5).

Potassium replacement can be given through the intravenous (IV) or oral (PO) route. Oral or enteral administration is preferred if the patient can take oral medication and has normal GI tract function. Acute hyperkalemia is highly unusual when potassium is given orally. This reflects several factors, most prominently gut sensors that minimize changes in serum potassium levels. When potassium is given intravenously, acute hyperkalemia can occur if the IV rate is too rapid and can cause sudden cardiac death. IV replacement can be given safely at a rate of 10 mmol KCl/h. Although significant variations can occur between patients, IV administration of 20 mmol KCl typically increases the serum potassium by about 0.25 mmol/l.[38] If more rapid replacement is necessary, 20 or 40 mmol/h can be administered through a central venous catheter, but continuous ECG monitoring should be used under these circumstances.

The parenteral fluids used for potassium administration can affect the response. In patients without diabetes mellitus, dextrose administration increases serum insulin levels, which causes redistribution

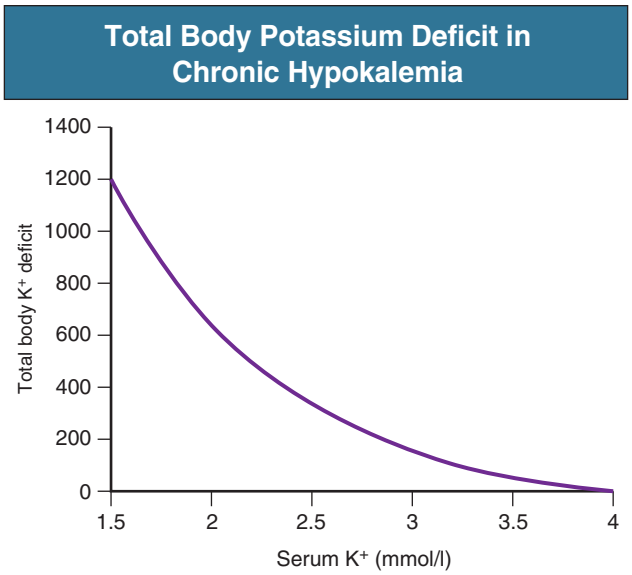

Figure 9-5 Total body potassium deficit in hypokalemia. Because of shift of potassium from the intracellular fluid (ICF) to the extracellular fluid (ECF) compartment during chronic potassium depletion, the magnitude of deficiency can be masked and is generally much larger than would be calculated solely from the ECF volume and the change in serum potassium.

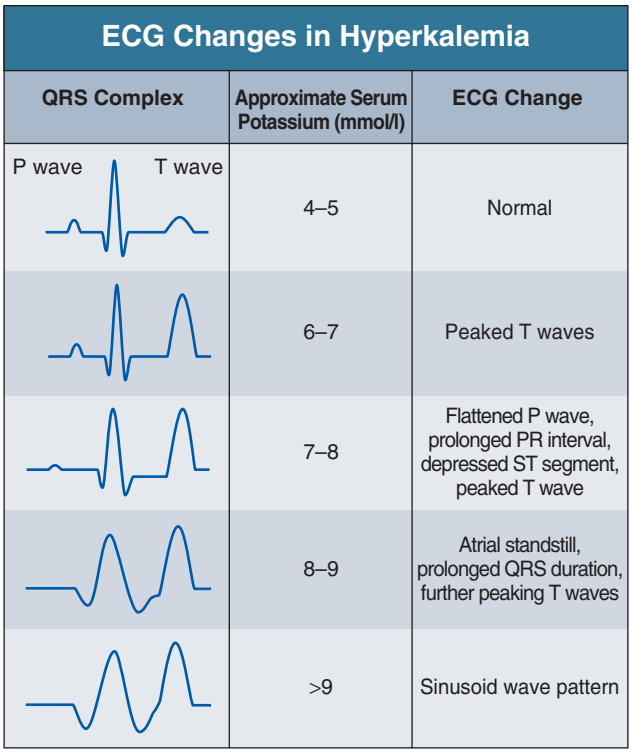

Figure 9-6 Electrocardiographic (ECG) changes in hyperkalemia. Progressive hyperkalemia results in identifiable changes in the electrocardiogram. These include peaking of the T wave, flattening of the P wave, prolongation of the PR interval, depression of the ST segment, prolongation of the QRS complex, and eventually, progression to a sine wave pattern. Ventricular fibrillation may occur at any time during this ECG progression.

of potassium from ECF to ICF compartment. As a result, if KCl is administered in dextrose-containing solutions such as 5% dextrose in water (D5W), the dextrose load may actually stimulate cellular potassium uptake to an extent that exceeds the KCl replacement rate, resulting, paradoxically, in worsening of the hypokalemia.[39] Consequently, parenteral KCl should be administered in dextrose-free solutions.

The underlying condition should be treated whenever possible. If patients with diuretic-induced hypokalemia require ongoing diuretic administration, addition of potassium-sparing diuretics may be considered. When oral replacement therapy is required, KCl is the preferred drug in all patients, except those with metabolic acidosis, in whom potassium citrate may be considered as a concomitant alkali source. If clinically indicated for other reasons, the use of β-blockers, ACE inhibitors, or ARBs can assist in maintaining serum potassium levels.

Hypomagnesemia can lead to refractoriness to potassium replacement because of inability of the kidneys to decrease potassium excretion.[34] Correction of the hypokalemia may not occur until the hypomagnesemia is corrected. Patients with unexplained hypokalemia or with diuretic-induced hypokalemia should have serum magnesium checked and, if indicated, magnesium replacement therapy instituted, usually with $MgSO_4$, and periodic measurement of serum $[Mg^{2+}]$.

HYPERKALEMIA

Epidemiology

Hyperkalemia is distinctly unusual in healthy individuals, with less than 1% of normal healthy adults developing hyperkalemia in the absence of significant underlying disease or medication use. This low frequency is a testament to the potent renal mechanisms for potassium excretion. Accordingly, hyperkalemia should suggest an underlying impairment of renal potassium excretion. Rarely, pseudohyperkalemia or a condition that shifts potassium from intracellular to extracellular space is present.

Clinical Manifestations

Hyperkalemia can be asymptomatic, can cause mild symptoms, or can be life threatening. Importantly, the mortality risk of hyperkalemia is independent of the patient's clinical symptoms and reflects acute effects of hyperkalemia on cardiac conduction. This is demonstrable on the electrocardiogram (Fig. 9-6). The initial effect of hyperkalemia is a generalized increase in the height of the T waves, most evident in the precordial leads, but typically present in all leads, which is known as "tenting." More severe hyperkalemia is associated with delayed electrical conduction, resulting in an increased PR interval and a widened QRS complex. This is followed by progressive flattening and eventual absence of the P waves. Under extreme conditions, the QRS complex widens sufficiently that it merges with the T wave, resulting in a sine-wave pattern. Finally, ventricular fibrillation develops. Although the ECG findings correlate generally with the degree of hyperkalemia, the rate of progression from mild to severe cardiac effects may be unpredictable and may not correlate well with changes in the serum potassium concentration.

Hyperkalemia also affects muscular contraction. Skeletal muscle cells are particularly sensitive to hyperkalemia, causing weakness ("rubbery" or "spaghetti" legs). In patients with severe hyperkalemia, respiratory failure may occur from paralysis of the diaphragm.

Etiology

Hyperkalemia can result from pseudohyperkalemia, potassium redistribution from intracellular to extracellular space, or imbalances between potassium intake and renal potassium excretion. A diagnostic approach is shown in Figure 9-7.

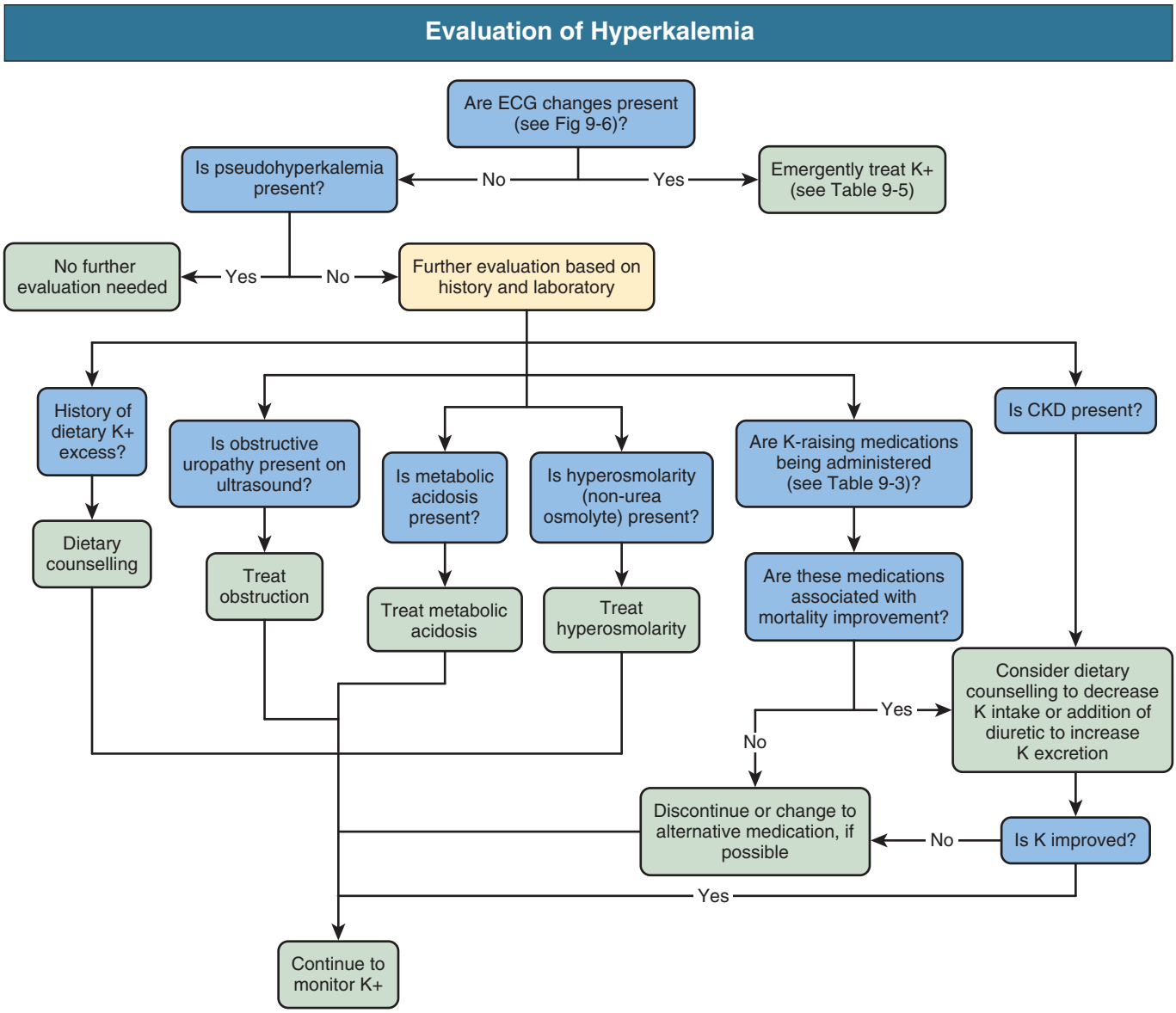

Figure 9-7 Workup of hyperkalemia. *CKD,* Chronic kidney disease.

Pseudohyperkalemia

Pseudohyperkalemia refers to the condition of potassium release from cellular elements in the blood occurring after the phlebotomy procedure. The most common cause of pseudohyperkalemia is potassium release from damaged erythrocytes. This is identified clinically by the presence of free hemoglobin in the plasma, reported as "hemolysis" by most clinical laboratories. If hemolysis is present, the serum $[K^+]$ cannot be accurately assessed, and a repeat measurement is necessary. Ischemia from prolonged tourniquet time or exercise of the limb in the presence of a tourniquet can also lead to abnormally increased potassium values. Pseudohyperkalemia may also occur with hemolysis in patients with rheumatoid arthritis or infectious mononucleosis, as well as in families who have abnormal red blood cell (RBC) membrane potassium permeability. Potassium can also be released from the other cellular elements present in blood during clotting. This can occur in patients with severe leukocytosis (>70,000/cm^3) or thrombocytosis. About one third of patients with platelet counts of 500 to 1000 × 10^9/l exhibit pseudohyperkalemia.

Pseudohyperkalemia is diagnosed by showing that the serum $[K^+]$ is more than 0.3 mmol/l higher than in a simultaneous plasma sample. If not caused by hemolysis, future potassium levels may need to be measured in plasma samples to allow accurate measurement of extracellular $[K^+]$.

Redistribution

Redistribution of potassium from ICF to ECF compartment can result in rapid development of hyperkalemia. This may occur with severe hyperglycemia (from development of hyperosmolarity), in association with severe nonorganic acidosis, and rarely with β-blockers. Patients who have received mannitol may also develop hyperosmolarity-induced hyperkalemia. Digoxin overdose can block cellular potassium uptake and lead to hyperkalemia that requires rapid treatment.

Excess Intake

Excessive potassium ingestion generally does not lead to hyperkalemia unless other contributing factors are present. Under normal conditions, the kidney has the capacity to excrete several multiples of the mean daily potassium intake. However, if renal potassium excretion is impaired, as from medications, acute kidney injury

Medications Associated with Hyperkalemia		
Class	**Mechanism**	**Representative Example(s)**
Potassium-containing drugs	Increased potassium intake	KCl, PCN G, Na citrate, K citrate
β-Adrenergic receptor blockers (β-blockers)	Inhibit renin release	Propranolol, metoprolol, atenolol
Angiotensin-converting enzyme (ACE) inhibitors	Inhibit conversion of angiotensin I to angiotensin II	Captopril, lisinopril
Angiotensin receptor blockers (ARBs)	Inhibit activation of AT_1 receptor by angiotensin II	Losartan, valsartan, irbesartan
Direct renin inhibitors	Inhibit renin activity, leading to decreased angiotensin II production	Aliskiren
Heparin	Inhibit aldosterone synthase, rate-limiting enzyme for aldosterone synthesis	Heparin sodium
Aldosterone receptor antagonists	Block aldosterone receptor activation	Spironolactone, eplerenone
Potassium-sparing diuretics	Block collecting duct apical ENaC Na channel, decreasing gradient for K^+ secretion	Amiloride, triamterene; certain antibiotics, specifically trimethoprim and pentamidine
NSAIDs and COX-2 inhibitors	Inhibit prostaglandin stimulation of collecting duct K^+ secretion; inhibit renin release	Ibuprofen
Digitalis glycosides	Inhibit Na^+, K^+-ATPase necessary for collecting duct K^+ secretion and regulation of K^+ distribution into cells	Digoxin
Calcineurin inhibitors	Inhibit Na^+, K^+-ATPase necessary for collecting duct K^+ secretion	Cyclosporine, tacrolimus

Table 9-3 Classes of medications associated with hyperkalemia. *NSAIDs,* Nonsteroidal anti-inflammatory drugs, *COX-2,* cyclooxygenase-2.

(AKI), or CKD, excessive potassium intake can contribute to the development of hyperkalemia.

Common sources of excess potassium intake are potassium supplements, salt substitutes, enteral nutrition products, and several common foods. As many as 4% of patients receiving potassium supplements develop hyperkalemia. "Salt substitutes" contain an average of 10 to 13 mmol K/g. Many enteral nutrition products contain 40 mmol/l or more of KCl; administration of 100 ml/h of such products can result in a potassium intake of about 100 mmol/day. Also, many food products are particularly high in potassium (see Table 9-1). In some countries, pharmacies routinely label medication bottles containing diuretics with recommendations to increase intake of high-potassium dietary sources such as bananas.

Impaired Renal Potassium Secretion

The normal kidney possesses a remarkable ability to excrete potassium, so chronic hyperkalemia is difficult to produce unless renal potassium secretion is impaired. Factors that affect renal potassium excretion are classified into those resulting from reduced nephron number and those from intrinsic impairment of renal potassium handling.

Because the kidney is the primary organ regulating potassium excretion, impaired renal function decreases maximal potassium excretion. In the absence of other contributing factors, renal potassium excretion is moderately well preserved until glomerular filtration rate (GFR) is reduced to 10 to 20 ml/min. However, both CKD and AKI limit maximal renal potassium excretion. This factor is particularly important to consider in patients who are elderly or cachectic or have limb amputation, in whom low serum creatinine production rates lead to underestimation of the degree of renal impairment.

Obstructive uropathy leads frequently to hyperkalemia,[40] at least in part from decreased Na^+-K^+-ATPase expression and activity.[41] In many patients, hyperkalemia may persist for weeks following relief of the obstruction.

Specific Medicine The renin-angiotensin system (RAS) is the primary hormonal system regulating renal potassium excretion. Accordingly, medications that interfere with the RAS or that inhibit the cellular mechanisms of renal potassium excretion are frequent causes of hyperkalemia. Table 9-3 summarizes classes of medications that inhibit potassium secretion and their mechanism of action.

Intrinsic Renal Defect A rare genetic disorder, pseudohypoaldosteronism type 2 (PHA2), also known as *Gordon syndrome,* is characterized by hypertension, hyperkalemia, non–anion gap metabolic acidosis and normal GFR.[42] Mutations in either of two proteins, WNK1 or WNK4, increase sodium absorption and inhibit potassium secretion in the distal convoluted tubule and collecting duct and lead to this phenotype.[12,43] Recognizing this diagnosis can be particularly beneficial because patients typically respond to low doses of thiazide diuretics, with dramatic clinical improvement in both hyperkalemia and hypertension.

Distinguishing Between Renal and Nonrenal Mechanisms of Hyperkalemia

In most patients, a careful history and a 24-hour urine K^+ excretion rate will distinguish renal (K^+ <20 to 30 mmol/day) from extrarenal (K^+ >40 mmol/day) causes of hyperkalemia. In selected patients, assessment of the urine potassium–creatinine ratio in a random urine specimen may be used, with potassium excretion less than 20 to 30 mmol/g creatinine suggesting inadequate renal excretion in the patient with hyperkalemia. However, urinary K^+ measurements may be difficult to interpret, since K^+ excretion depends on multiple factors, including GFR, tubule lumen flow, and water reabsorption in the distal tubule and collecting duct. When urine K^+ is equivocal, the transtubular K^+ gradient (TTKG) may be informative (Table 9-4).

Treatment

Acute Therapy

Acute therapies for hyperkalemia are divided into those that minimize the cardiac effects of hyperkalemia, those that induce potassium uptake by cells resulting in a decrease in serum potassium, and those that remove potassium from the body (Table 9-5). Treatment

of hyperkalemia should not include sodium bicarbonate ($NaHCO_3$) therapy unless the patient is frankly acidotic (pH <7.2) or unless substantial endogenous renal function is present. Administering hypertonic $NaHCO_3$ (e.g., 50 mmol in 50 ml of sterile water) can worsen intravascular volume overload, as frequently seen in the patient with oliguric AKI; can cause acute hypernatremia; and in general, has minimal effect on serum potassium.[44]

Blocking Cardiac Effects Intravenous calcium administration specifically antagonizes the effects of hyperkalemia on the myocardial conduction system and on myocardial repolarization. Calcium is the most rapid way to stabilize the membrane voltage and treat the cardiac effects of hyperkalemia. Calcium should be given intravenously if unambiguous ECG changes of hyperkalemia are present. If the electrocardiogram is ambiguous, comparison to a previous ECG may be helpful. Patients with a prolonged PR interval, a widened QRS complex, or the absence of P waves should receive IV calcium without delay. Responses can occur within 1 to 3 minutes, but typically last for only 30 to 60 minutes. The dose may be repeated as needed if ECG changes persist or they recur. If a delay in more definitive therapy, such as institution of dialysis, is anticipated, a continuous calcium infusion can be used since the effect of a calcium bolus is transient.

Intravenous calcium is relatively safe if certain precautions are taken. IV calcium should not be administered in $NaHCO_3$-containing solutions because calcium carbonate ($CaCO_3$) precipitation can occur. Hypercalcemia, which occurs during rapid calcium infusion, can potentiate the myocardial toxicity of digoxin. Patients taking digoxin, particularly if they have evidence of digoxin toxicity as a contributing cause of hyperkalemia, should be given calcium as a slow infusion over 20 to 30 minutes. Calcium should be administered with caution in patients with advanced CKD or end-stage renal disease because these patients frequently have hyperphosphatemia, and increases in calcium could result in calcium phosphate deposition in many tissues, including the cardiac conduction system. The preferred calcium preparation is calcium gluconate. However, calcium chloride ($CaCl_2$) should be used in patients who have undergone cardiac arrest from hyperkalemia, because the active calcium is released immediately on infusion, unlike calcium gluconate, which requires liver metabolism to release the calcium.

Cellular Potassium Uptake The second most rapid way to treat hyperkalemia is to stimulate cellular potassium uptake, with either insulin or β_2-adrenergic agonist administration. Insulin rapidly stimulates cellular potassium uptake and should be administered through the IV, not the subcutaneous (SC), route to ensure rapid and predictable bioavailability. Insulin's effects on serum [K^+] are seen generally within 10 to 20 minutes and can last for 4 to 6 hours. Glucose is coadministered to avoid hypoglycemia but may not be needed if hyperglycemia coexists. This is particularly important because extracellular glucose in patients with diabetes mellitus can function as an "ineffective osmole" and can increase serum potassium. Conversely, in patients with impaired renal function, there is delayed insulin clearance, and hypoglycemia can result from IV insulin administration, even if glucose is coadministered, because glucose uptake may occur more rapidly than insulin clearance. Accordingly, patients given IV insulin for treatment of hyperkalemia should be closely monitored for the development of hypoglycemia. If dialysis is indicated and a delay in its initiation is anticipated, administering a continuous infusion of insulin, 4 to 10 U/h (with D10W) may be beneficial; periodic monitoring of serum glucose and potassium is required.

β_2-Adrenoceptor agonists directly stimulate cellular potassium uptake and can be administered through the IV, inhaled, or SC route.

Transtubular Potassium Gradient

TTKG is a measurement of net K^+ secretion by the distal nephron after correcting for changes in urinary osmolality and is often used to determine whether hyperkalemia is caused by aldosterone deficiency/resistance or whether the hyperkalemia is secondary to nonrenal causes. As with all diagnostic aids, clinical correlation is indicated, and potassium intake should be assessed.

TTKG = $(K_u/K_s) \times (S_{osm}/U_{osm})$, where K_u and K_s are the concentration of K^+ in urine and serum, respectively, and U_{osm} and S_{osm} are the osmolalities of urine and serum, respectively.

TTKG Value		Indication
6 to 12		Normal
>10		Suggests normal aldosterone action and extrarenal cause of hyperkalemia
<5 to 7		Suggests aldosterone deficiency or resistance
After 0.05 mg 9α-fludrocortisone	>10 No change	Hypoaldosteronism is likely. Suggests a renal tubule defect from either K^+-sparing diuretics (amiloride, triamterene, spironolactone), aldosterone resistance (interstitial renal disease, sickle cell disease, urinary tract obstruction, PHA1), or increased distal K^+ reabsorption (PHA2, urinary tract obstruction)

Table 9-4 Transtubular potassium gradient. *PHA1, PHA2,* Pseudohypoaldosteronism types 1 and 2.

Treatment of Hyperkalemia

Mechanism	Therapy	Dose	Onset	Duration
Antagonize membrane effects	Calcium	Calcium gluconate, 10% solution, 10 ml IV over 10 min	1-3 min	30-60 min
Cellular potassium uptake	Insulin	Regular insulin, 10 U IV, with dextrose 50%, 50 ml, if plasma glucose <250 mg/dl	30 min	4-6 hr
	β_2-Adrenergic agonist	Nebulized albuterol, 10 mg	30 min	2-4 hr
Potassium removal	Sodium polystyrene sulfonate or calcium polystyrene sulfonate (calcium resonium)	30-60 g PO in 20% sorbitol *or* 30-60 g in water, per retention enema	1-2 hr	4-6 hr
	Hemodialysis	—	Immediate	Until dialysis completed

Table 9-5 Treatment of hyperkalemia

However, β_2-agonist therapy frequently induces substantial tachycardia, and as many as 25% of patients do not respond to β-blocker given by nebulizer.[45] A frequent mistake when administering nebulized β_2-adrenoceptor agonists is underdosage; the dose required is two to eight times that usually given by nebulizer for bronchodilation and is 50 to 100 times greater than the dose administered by metered dose inhalers.

Potassium Removal Most patients with severe hyperkalemia have increased total body potassium content. Definitive treatment of these patients requires potassium elimination, through the kidneys, GI route, or dialysis.

In select patients, treatment that focuses on increasing renal potassium elimination may be adequate. With chronic or mild hyperkalemia, loop or thiazide diuretics increase renal potassium excretion; loop diuretics may be the therapy of choice for patients with hyperkalemic renal tubular acidosis.[46] With life-threatening hyperkalemia, diuretics should be avoided because the rate of renal potassium excretion usually will not be adequate, and most patients will have renal impairment, which decreases the response to diuretic therapy. Although synthetic mineralocorticoids such as fludrocortisone increase renal potassium excretion, the accompanying renal sodium retention, intravascular volume expansion, and increased blood pressure are relative contraindications to their use. Furthermore, mineralocorticoids can increase the rate of progression of CKD. If a rapidly reversible cause of renal failure is identified, such as obstructive uropathy, or pre-renal failure from volume depletion, treating the underlying condition, along with close observation of serum potassium and continuous ECG observation, may be sufficient therapy.

A second mode of potassium elimination is with cation exchange resins such as sodium polystyrene sulfonate (Kayexalate) or calcium polystyrene sulfonate (calcium resonium). These resins exchange sodium or calcium, respectively, for potassium in the GI tract, enabling potassium elimination. It can be administered orally or rectally as a retention enema. The rate of potassium removal is relatively slow, requiring about 4 hours for full effect, although administering the resin as a retention enema results in more rapid onset of action. When given orally, cation exchange resins are generally administered with 20% sorbitol to avoid constipation. If given as an enema, sorbitol should be avoided, because rectal administration of cation exchange resins with sorbitol can cause colonic perforation.[47] Questions have been raised recently as to the efficacy of these compounds and whether the risk of colonic perforation exceeds their benefits.[48]

Acute hemodialysis is the primary method of potassium removal when renal function is significantly impaired, either from AKI or advanced CKD, and hyperkalemia is severe. Serum potassium can decrease as much as 1.2 to 1.5 mmol/h with a low potassium (1 mmol/l) dialysate. In general, the more severe the hyperkalemia, the more rapid should be the reduction in serum potassium and the lower the dialysate potassium concentration. However, care should be taken to avoid rapidly reducing the serum potassium in patients with coronary heart disease or severe cardiac arrhythmias. In these patients, it may be necessary to dialyze for a longer period with dialysate potassium of 3 mmol/l, because serum potassium can equilibrate to these levels during the dialysis. Continuous dialysis modalities, such as peritoneal dialysis and continuous venovenous hemodialysis, generally do not remove potassium sufficiently quickly for use in patients with life-threatening hyperkalemia.

If dialysis is delayed, as when access to equipment or nursing support is not immediate, or while vascular access is established, other therapies should be instituted and continued until hemodialysis is begun.

Specific therapies are available for certain causes of hyperkalemia. For example, digoxin-specific Fab fragments are beneficial in patients with severe digitalis glycoside toxicity.[49] Patients with acute urinary tract obstruction and hyperkalemia may be treated with relief of the obstruction, but the rate of potassium excretion afterward is variable, and frequent measurement of serum potassium is necessary.

Chronic Treatment

Management of chronic hyperkalemia is a common and often challenging problem, particularly in the CKD patient. Patients with CKD have impaired capacity to excrete potassium and are often treated with many medications, including ACE inhibitors, ARBs, β-blockers, and mineralocorticoid receptor antagonists. All these medicines have, as a well-recognized side effect, further increase in serum potassium concentration.

The optimal serum potassium level for patients with CKD and the serum potassium level that requires management may differ from the laboratory's report of the normal range of serum potassium. As noted previously, CKD patients tolerate hyperkalemia with fewer cardiac side effects than do most patients with normal renal function. Recent studies have suggested that serum potassium levels of up to 5.5 mmol/l or associated with optimal reduction of cardiovascular risk, and that levels between 5.5 and 6.0 mmol/l are associated with only minimal risk.[9]

Although the majority of patients with chronic hyperkalemia are receiving medicines associated with the development of hyperkalemia, discontinuing all medications that can cause hyperkalemia may not be the correct approach. Many medicines, such as ACE inhibitors, ARBs, β-blockers, and mineralocorticoid receptor blockers, have significant renoprotective and cardioprotective benefits. Discontinuing these medications simply because of hyperkalemia prevents the patient from receiving these important benefits, and this is not recommended in the first-line management of these patients. However, if the patient is receiving combined therapy with ACE inhibitor and ARB, discontinuing one of these medications may decrease the risk of further hyperkalemia, and this does not appear to be associated with adverse renal effects. Similarly, if a patient is receiving combination therapy of either an ACE inhibitor or an ARB with a direct renin inhibitor, such as aliskiren, the direct renin inhibitor may be discontinued.

Instead of immediately discontinuing such beneficial drugs without review, a careful assessment should be made for medicines that cause hyperkalemia but are not necessary for renoprotective or cardioprotective benefits and therefore can be discontinued, such as nonsteroidal anti-inflammatory agents (NSAIDs), COX-2 inhibitors, potassium-sparing diuretics (e.g., amiloride, triamterene), and oral KCl or potassium citrate supplementation. If hyperkalemia persists, the addition of diuretics to increase renal potassium excretion should be considered. Thiazide diuretics may be preferred, because when adjusted for their effect on sodium excretion, thiazide diuretics are associated with a greater increase in renal potassium excretion than loop diuretics. In the patient with CKD, the thiazide diuretic metolazone may be effective.[50]

A dietary history should be obtained, and if the patient is ingesting a diet with potassium-rich foods, instruction on avoidance of these foods should be provided. However, routine instruction in a low-potassium diet for CKD patients is not recommended. Recent studies have suggested that a diet higher in potassium-rich foods may be associated with slower progression of CKD.[51]

Finally, intermittent administration of exchange resins may be necessary for patients with persistent hyperkalemia. This should be limited to intermittent use because of the risk of bowel infarction.

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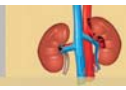
CHAPTER 10



Disorders of Calcium, Phosphate, and Magnesium Metabolism

Bryan Kestenbaum and Tilman B. Drüeke

CALCIUM HOMEOSTASIS AND DISORDERS OF CALCIUM METABOLISM

Distribution of Calcium in the Organism

Most calcium is bound and associated with bony structures (99%). The majority of free calcium, either in diffusible (ultrafilterable) nonionized form or in ionized form (Ca^{2+}), is found in the intracellular fluid (ICF) and extracellular fluid (ECF) compartments. Similar to potassium, there is a steep concentration gradient between Ca^{2+} in the ICF versus ECF milieu (Fig. 10-1).

The serum concentration of Ca^{2+} is tightly regulated within a narrow range by the actions of parathyroid hormone (PTH, parathormone) and calcitriol (1,25-dihydroxycholecalciferol). The physiologic role of other calcium regulatory hormones, such as calcitonin, estrogens, and prolactin, is less clear. Figure 10-2 demonstrates the physiologic defense mechanisms used to counter changes in serum Ca^{2+} levels.[1] Serum Ca^{2+} levels are also influenced by acid-base status, with alkalosis causing a decrease in Ca^{2+} and acidosis an increase in Ca^{2+}. Long-term maintenance of calcium homeostasis depends on (1) the adaptation of intestinal Ca^{2+} absorption to the needs of the organism, (2) the balance between bone accretion and resorption, and (3) urinary excretion of calcium (Fig. 10-3).

Intestinal, Skeletal, and Renal Handling of Calcium

Gastrointestinal (GI) calcium absorption is a selective process; only about 25% of total dietary calcium is absorbed. Ca^{2+} transport across the intestinal wall occurs in two directions: absorption and secretion. Absorption can be subdivided into transcellular and paracellular flow (Fig. 10-4). Transcellular calcium flux takes place through the transient receptor potential TRPV6 calcium channel.[2] Calcitriol is calcium's most important hormonal regulatory factor. After binding to and activating the vitamin D receptor (VDR), calcitriol increases active transport by inducing the expression of TRPV6, calbindin-D_{9k}, and Ca^{2+}-ATPase (PMCA1b).[3] Other hormones, including estrogens, prolactin, growth hormone, and PTH, also stimulate Ca^{2+} absorption, either directly or indirectly. The amount of dietary calcium intake also regulates the proportion of calcium absorbed through the GI tract (Fig. 10-5).[4]

Cutaneous synthesis on exposure to ultraviolet (UV) light converts 7-dehydrocholesterol into vitamin D substrate (cholecalciferol). Vitamin D substrate is also obtained through the diet and supplementation. Cholecalciferol (and ergocalciferol) have minimal inherent biologic activity and require two hydroxylation steps for full hormonal activity. 25-Hydroxylation occurs in the liver, is thought to be non–rate limiting, and is widely accepted as a summary measure of vitamin D stores. Further hydroxylation to 1,25-dihydroxyvitamin D (calcitriol) occurs predominantly in the kidney; however, other tissues can also perform this hydroxylation step, in particular macrophages and parathyroid tissue.

Increased calcium absorption is required in puberty, pregnancy, and lactation. In each of these states, calcitriol synthesis is increased to enhance GI calcium absorption. Intestinal Ca^{2+} absorption is also increased in states of vitamin D excess and acromegaly. Rarely, ingestion of calcium and alkali in large quantities can overwhelm GI checks on calcium absorption, resulting in hypercalcemia (milk-alkali syndrome). However, innate limitations on GI calcium absorption prevent this condition from occurring in most individuals. A decrease in intestinal Ca^{2+} transport occurs in advanced age, chronic kidney disease (CKD), gastrectomy, intestinal malabsorption syndromes, diabetes mellitus, corticosteroid treatment, and estrogen deficiency and with dietary factors such as high vegetable fiber and fat content, low Ca^{2+}–phosphate ratio in food, and fructose ingestion. The decrease in Ca^{2+} absorption in older adults probably results from multiple factors in addition to lower serum calcitriol and intestinal VDR levels.[5]

The net balance between Ca^{2+} entry and exit fluxes is positive during skeletal growth in children, zero in young adults, and negative in the elderly. Exchangeable skeletal Ca^{2+} contributes to maintaining extracellular Ca^{2+} homeostasis. Several growth factors, hormones, and genetic factors participate in the differentiation from the mesenchymal precursor cell to the osteoblast and the maturation of the osteoclast from its granulocyte-macrophage precursor cell (Fig. 10-6). The regulation of bone formation and resorption involves many hormones, growth factors, and mechanical factors[6,7] (Fig. 10-7).

The kidneys play a major role in the minute-by-minute regulation of calcium, and the intestine and skeleton ensure homeostasis in the midterm and long term. To perform its task, the kidney uses a complex system of filtration and reabsorption (Fig. 10-8).[8] Moreover, the kidney controls conversion of substrate 25-hydroxyvitamin D to calcitriol, which then regulates GI calcium absorption through the TRPV6 channel. Renal calcitriol production is stimulated by PTH and inhibited by hyperphosphatemia and fibroblast growth factor 23 (FGF-23).The adjustment of blood Ca^{2+} is mainly achieved by modulation of tubular Ca^{2+} reabsorption in response to the body's needs, perfectly compensating minor increases or decreases in the filtered load of calcium at the glomerular level, which is normally about 220 mmol (8800 mg) in 24 hours (see Fig. 10-3). In the proximal tubule, Ca^{2+} reabsorption follows the convective flow of salt and water, whereas the transport mechanisms are more complex in the distal segments.

States of excess volume delivery to the kidney, such as a high-sodium diet, diminish the concentration gradient between proximal tubule and peritubular capillary, reducing calcium absorption and

increasing calcium in the urine. This mechanism likely plays a role in the pathogenesis of calcium-based kidney stones. On the other hand, volume depletion increases salt, water, and (by convection) calcium reabsorption in the proximal tubule, exacerbating states of hypercalcemia. For this reason, intravascular volume repletion is an essential component of the treatment for hypercalcemia. In the thick ascending limb of Henle loop (TAL), Ca^{2+} transport is linked with activity of the Na^+-K^+-$2Cl^-$ transporter. Stimulation of the Ca^{2+}-sensing receptor (CaR_G) on the basolateral membrane decreases activity of rectifying outer medulla potassium (ROMK) channels located on apical cell surfaces, impeding activity of the Na^+-K^+-$2Cl^-$ cotransporter. The result is dissipation of the electrochemical gradient and decreased calcium reabsorption through claudin-16 in the tight junction. In contrast, understimulation of CaR_G because of lower serum calcium levels enhances ROMK activity, resulting in greater calcium reabsorption. In the distal tubule, active Ca^{2+} transport

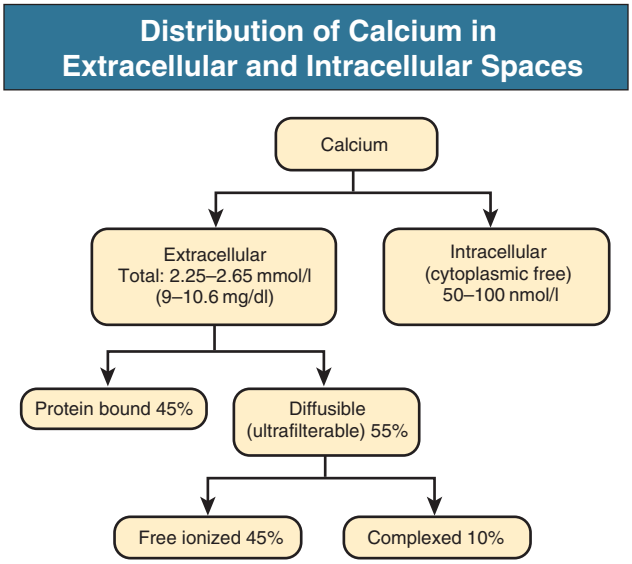


Figure 10-1 Calcium distribution in extracellular and intracellular spaces.

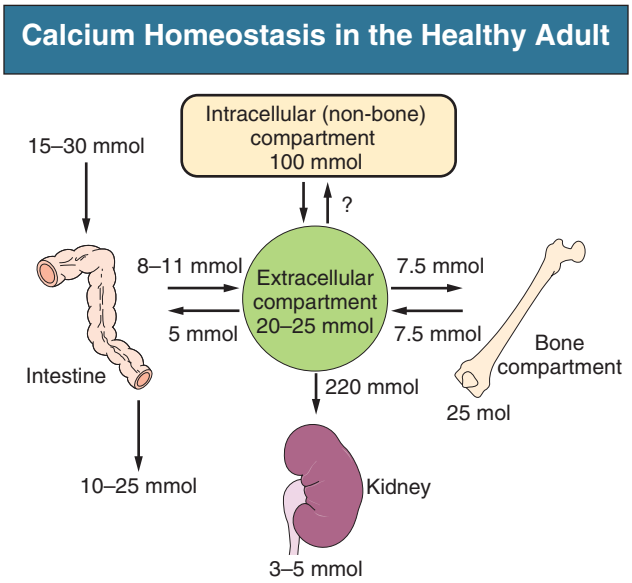


Figure 10-3 Calcium homeostasis in healthy adults. Net zero Ca^{2+} balance is the result of net intestinal absorption (absorption minus secretion) and urinary excretion, which by definition are the same. After its passage into the extracellular fluid, Ca^{2+} enters the extracellular space, is deposited in bone, or is eliminated via the kidneys. Entry and exit fluxes between the extracellular and intracellular spaces (skeletal and nonskeletal compartments) are also of identical magnitude under steady-state conditions.

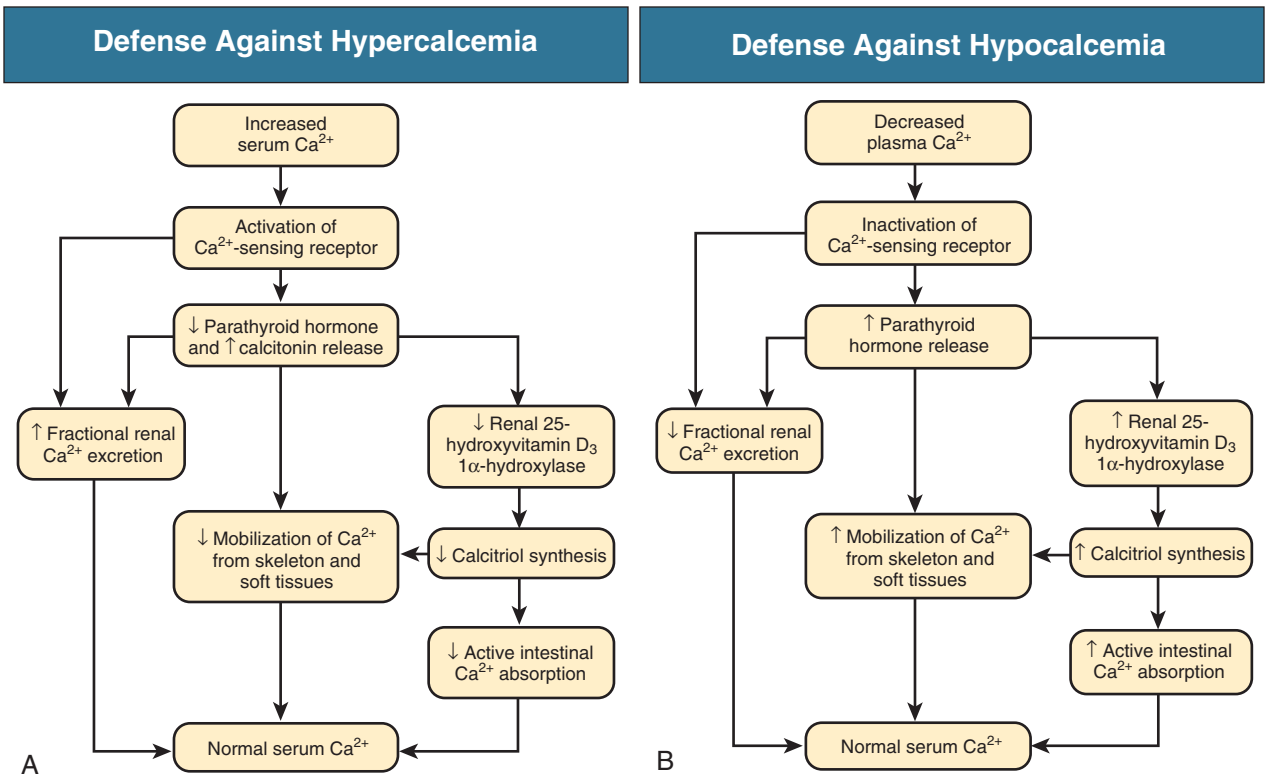


Figure 10-2 Calcium regulation. Physiologic defense mechanisms against increases or decreases in serum calcium levels. **A**, Hypercalcemia; **B**, hypocalcemia. *(Adapted from reference 1.)*

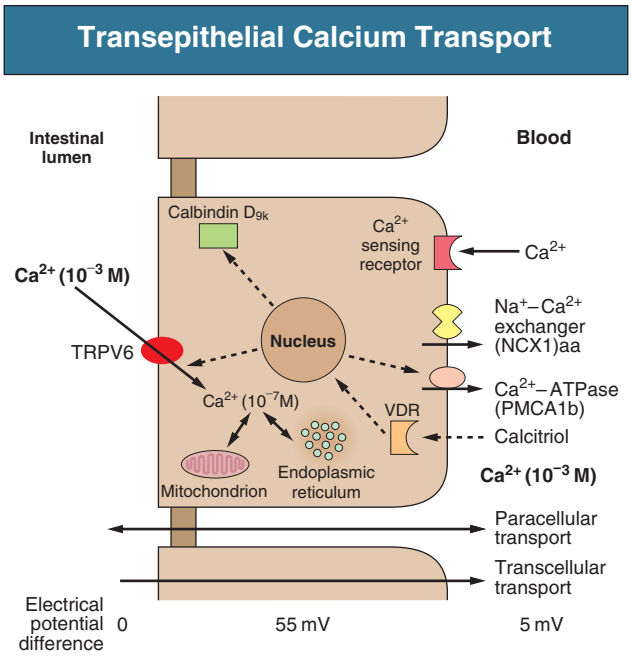


Figure 10-4 Transepithelial calcium transport in small intestine. Calcium penetrates into the enterocyte channels via a transient receptor potential calcium channel *(TRPV6)* through the brush border membrane along a favorable electrochemical gradient. Under physiologic conditions, the cation is pumped out of the cell at the basolateral side against a steep electrochemical gradient by the adenosine triphosphate–consuming pump Ca^{2+}-ATPase. When there is a major elevation of intracytoplasmic Ca^{2+}, the cation leaves the cell using the Na^{+}-Ca^{2+} exchanger. Passive Ca^{2+} influx as well as efflux is sensitive to calcitriol, which binds the vitamin D receptor *(VDR)*.

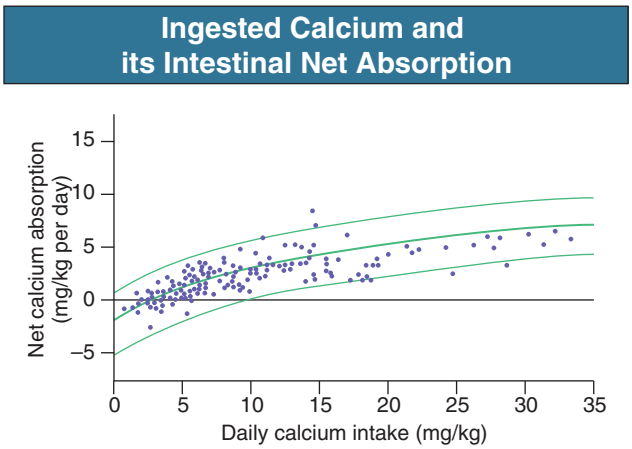
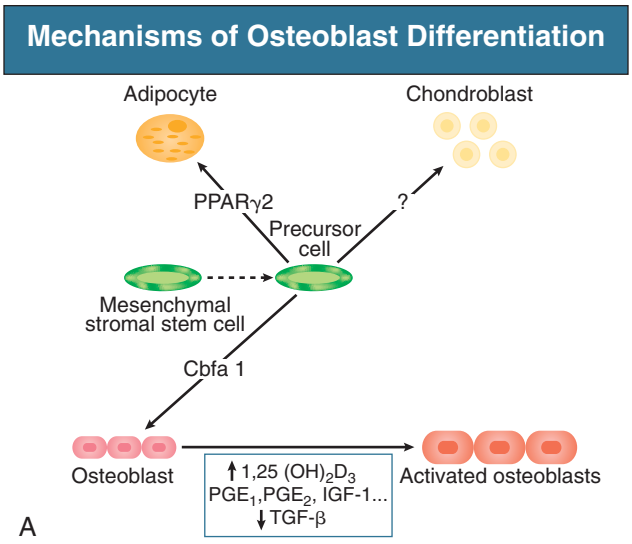


Figure 10-5 Calcium ingestion and absorption. Relationship between ingested calcium and its absorption in the intestinal tract (net) in healthy young adults. *(From reference 4.)*

occurs via the transcellular route through the calcium transient receptor potential channel V5 (TRPV5) located in the apical membrane and coupled with a specific basolateral calcium-ATPase (PMCa1b) and a Na^{+}-Ca^{2+} exchanger (NCX1). Both PTH and calcitriol regulate distal tubular Ca^{2+} transport. The expression and role of CaR_G in tubular segments other than TAL has recently been questioned.[9]

Numerous factors control the glomerular filtration and tubular Ca^{2+} reabsorption.[2,10,11] Elevated renal blood flow and glomerular filtration pressure (during ECF volume expansion) lead to an increase in filtered load, as do changes in the ultrafiltration coefficient K_f and



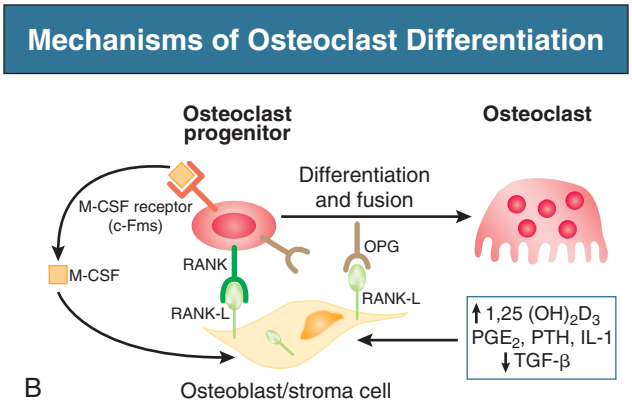


Figure 10-6 Mechanisms of osteoblast differentiation. A, Major growth factors and hormones controlling in the differentiation from the mesenchymal precursor cell to the osteoblast. **B,** The major growth factors, cytokines, and hormones controlling osteoblast and osteoclast activity. *IGF,* Insulin-like growth factor; *IL,* interleukin; *M-CSF,* macrophage colony-stimulating factor; *OPG,* osteoprotegerin; *PGE_2,* prostaglandin E_2; *PPAR,* peroxisome proliferator–activated receptor; *PTH,* parathyroid hormone; *RANK-L,* receptor activator of nuclear factor-κβ ligand; *TGF,* transforming growth factor.

an increase in glomerular surface. True hypercalcemia also increases ultrafilterable calcium; whereas true hypocalcemia decreases it. PTH decreases glomerular K_f and thus reduces the ultrafiltered calcium load; PTH increases Ca^{2+} reabsorption in the distal nephron. However, PTH and PTH-related peptide (PTHrp) also induce hypercalcemia, and, because of the increase in serum calcium, the excretion of filtered calcium is elevated overall. Both extracellular Ca^{2+} and intracellular Ca^{2+} reduce tubular calcium reabsorption by activating CaR_G, and the effect of extracellular Ca^{2+} is enhanced by the calcimimetics (discussed later). Respiratory acidosis leads to hypercalciuria through an increase in plasma Ca^{2+}, whereas metabolic acidosis leads to hypercalciuria through Ca^{2+} release from bone and an inhibitory effect on tubular Ca^{2+} reabsorption. Conversely, alkali ingestion reduces renal excretion of calcium. The enhancing effect of phosphate depletion on urinary calcium elimination can partly occur through changes in PTH and calcitriol secretion. Dietary factors modify urinary excretion of calcium mostly by their effects on intestinal Ca^{2+} absorption. Several classes of diuretics act directly on the tubules. Loop diuretics and mannitol favor hypercalciuria, with a major impact on TAL, whereas the thiazide diuretics and amiloride induce hypocalciuria.

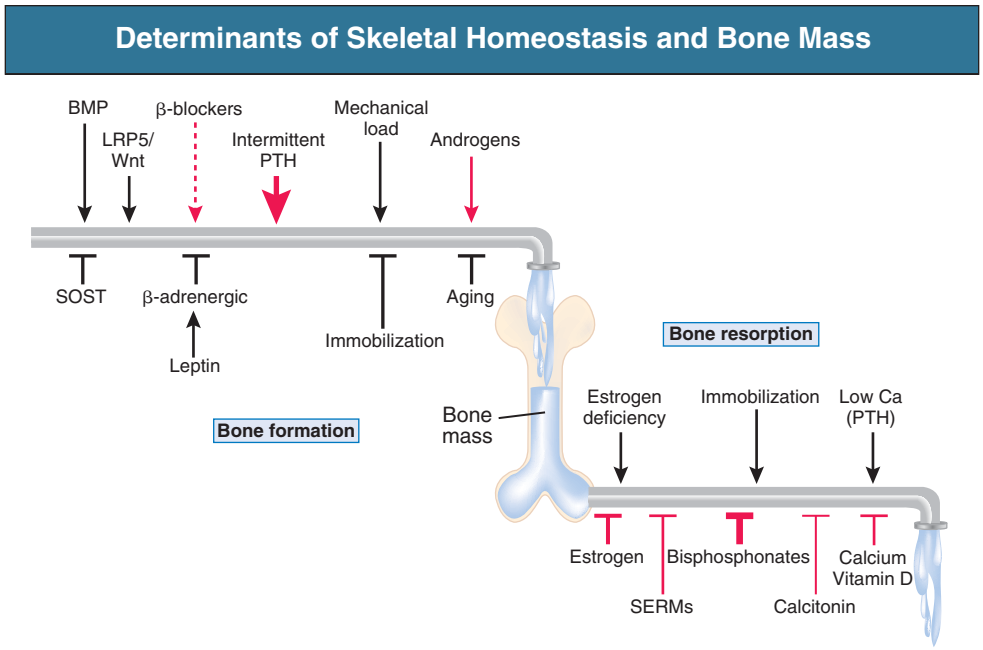


Figure 10-7 Determinants of skeletal homeostasis and bone mass. Physiologic *(black)* and pharmacologic *(red)* stimulators and inhibitors of bone formation and resorption are listed with the relative impact (represented by thickness of *arrows*). *BMP,* Bone morphogenetic protein; *LRP5,* low-density lipoprotein receptor–related protein 5; *PTH,* parathyroid protein; *SERMs,* selective estrogen receptor modulators; *SOST,* sclerostin. *(From reference 6.)*

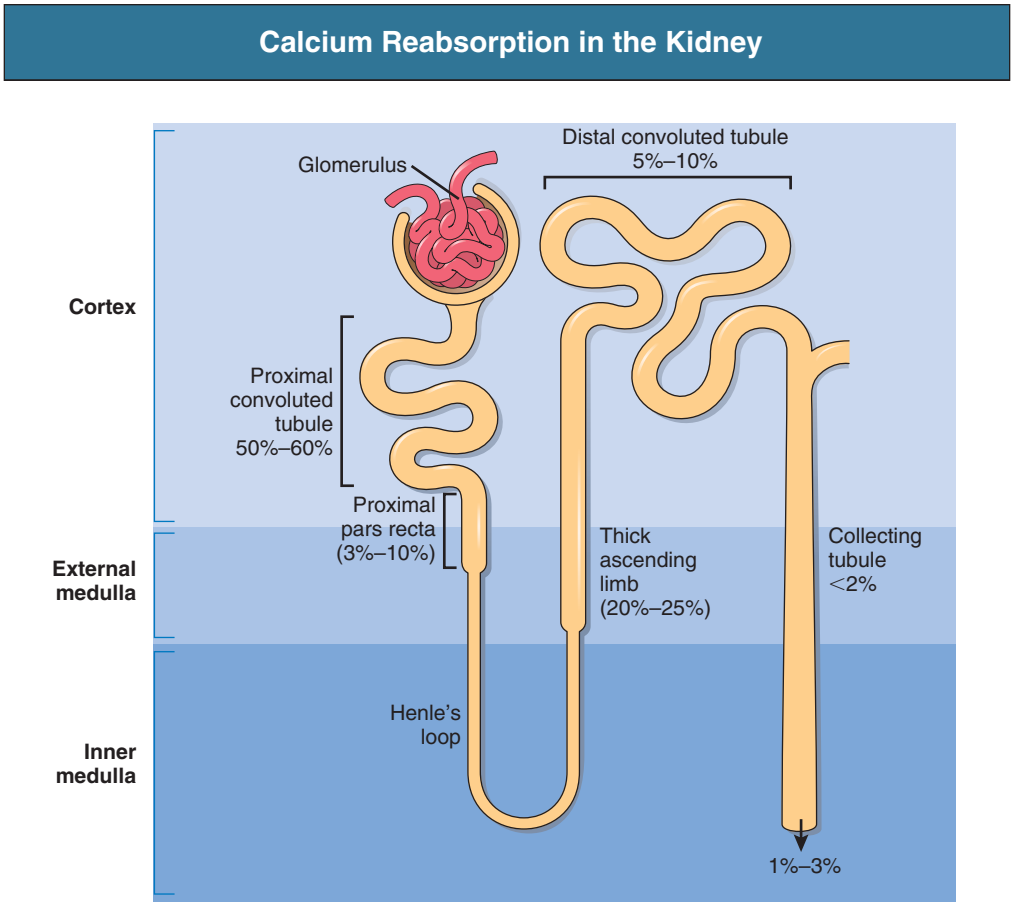


Figure 10-8 Sites of calcium reabsorption. Percentage of Ca^{2+} absorbed in various segments of the renal tubule after glomerular ultrafiltration. *(Redrawn from reference 8.)*

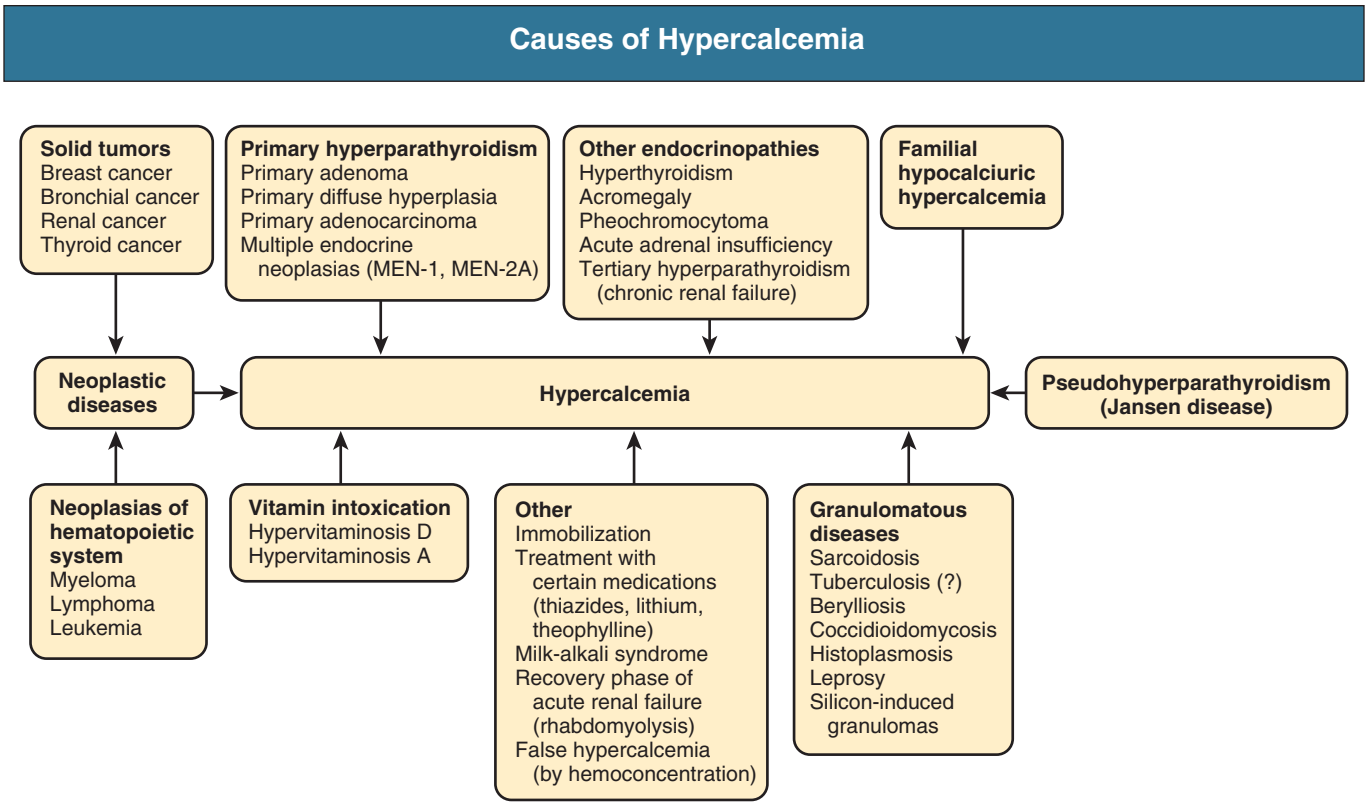


Figure 10-9 Causes of hypercalcemia. Neoplastic diseases and primary hyperparathyroidism are the most common causes of hypercalcemia. *(From reference 8.)*

HYPERCALCEMIA

Increased total plasma calcium concentration (plasma [Ca^{2+}]) can result from an increase in plasma proteins (false hypercalcemia) or from an increase in plasma ionized Ca^{2+} (true hypercalcemia). Only increased Ca^{2+} leads to clinically relevant hypercalcemia. When only the value for the total plasma [Ca^{2+}] is available rather than the free level ions, as generally occurs in clinical practice, plasma [Ca^{2+}] can be estimated by taking into account plasma albumin; an increase in albumin of 1.0 g/dl reflects a concomitant increase of 0.20 to 0.25 mmol/l (0.8 to 1.0 mg/dl) plasma calcium. However, simple correction of total calcium for serum albumin may not be valid in patients with CKD. A study of 691 individuals with CKD stages 3 to 5 showed that the albumin-corrected total serum [Ca^{2+}] correlated poorly with the ionized [Ca^{2+}].[11a] Moreover, the two most common assays used to measure serum albumin yield discordant results in uremic patients, the bromcresol purple method providing lower albumin values than the bromcresol green method.

The Ca^{2+}-sensing receptor has been identified in numerous tissues, and its function and role in various disease states are well defined.[12] Mutations of the gene for CaR_G result in various clinical syndromes characterized by hypercalcemia or hypocalcemia (see later discussion). Other Ca^{2+} receptors subsequently cloned include GPRC6A, which is expressed in osteoblasts and is clearly distinct from CaR_G.[13] Although its functional properties have been characterized, however, the role of GPRC6A in regulation of osteoblast function and in human disease is still unknown.

Causes of Hypercalcemia

True hypercalcemia results from an increase in intestinal Ca^{2+} absorption, a stimulation of bone resorption, or a decrease in urinary Ca^{2+} excretion. Enhanced bone resorption is the predominant mechanism in most cases of hypercalcemia (Fig. 10-9).

Malignant Neoplasias

The main cause of hypercalcemia is excessive bone resorption induced by neoplastic processes, usually solid tumors. Tumors of the breast, lung, and kidney are the most common, followed by hematopoietic neoplasias, particularly myeloma. Most hypercalcemic tumors act on the skeleton either by direct invasion (metastases) or by producing factors that stimulate osteoclastic activity, including most frequently PTHrp, as well as other factors activating osteoclasts, transforming growth factors (TGFs), prostaglandin E (PGE), and rarely calcitriol and tumor necrosis factor α (TNF-α), and even more rarely PTH, as produced by parathyroid cancer.

Only 8 of the 13 first amino acids of PTHrp are identical with those of the N-terminal fragment of PTH, but the effects of both hormones on target cells are mostly the same. In addition to their common receptor, the PTH/PTHrp receptor, at least one other receptor exists, the PTH_2 receptor, which recognizes only PTH, with similar or identical signal transduction systems. In pathologic conditions, most of the PTHrp in the body is synthesized by solid tumors. PTHrp stimulates osteoclastic activity and thus liberates excess quantities of calcium from the skeleton.

Osteoclast-activating factors secreted by myeloma plasmocytes and the lymphoblasts of malignant lymphomas include interleukins (IL-1α, IL-1β, IL-6) and TNF-α, which stimulate osteoclast activity. Other osteoclast-activating factors include PGE_1 and PGE_2, which can be secreted in large amounts by some tumors, especially renal masses. Some lymphoid tumors synthesize excess quantities of calcitriol. This capacity has been described in Hodgkin disease, T cell lymphoma, and leiomyoblastoma.

Primary Hyperparathyroidism

The second most common cause of hypercalcemia is primary hyperparathyroidism. Early diagnosis is achieved through the widespread use of routine plasma calcium determination. In more than 80% of patients, the disease is caused by adenoma of a single parathyroid gland; 10% to 15% have diffuse hyperplasia of all glands and less than 5%, a parathyroid cancer. Primary hyperparathyroidism can be inherited either as diffuse hyperplasia of the parathyroid glands alone or as a component in multiple glandular hereditary endocrine disorders. Patients with multiple endocrine neoplasia type 1 (MEN-1) have various combinations of parathyroid, anterior pituitary, enteropancreatic, and other endocrine tumors, resulting in hypersecretion of prolactin and gastrin in addition to parathormone. MEN-1 is caused by inactivating germ-line mutations of a tumor suppressor gene *(MEN-1)* that is inherited as an autosomal dominant trait. In MEN-2A, the thyroid medulla and the adrenal medulla are involved with the parathyroid, resulting in hypersecretion of calcitonin and catecholamines. MEN-2A is caused by activating mutations of the *RET* proto-oncogene. It is also inherited as an autosomal dominant trait. Not all patients with mildly elevated plasma PTH levels develop hypercalcemia. The development of the latter may depend on a concomitant elevation of plasma calcitriol.

Jansen Disease

Jansen disease is a rare hereditary form of short-limbed dwarfism characterized by severe hypercalcemia, hypophosphatemia, and metaphyseal chondrodysplasia. It is the result of activating mutations of the gene coding for the PTH/PTHrp receptor, a particular form of pseudohyperparathyroidism.

Familial Hypocalciuric Hypercalcemia

Familial hypocalciuric hypercalcemia (FHH) is a rare hereditary disease caused by inactivating mutations in the gene for CaR_G with autosomal dominant transmission.[14] The key clinical finding in FHH is an inappropriately low urinary calcium excretion in the setting of high-normal serum calcium. Other features include hypophosphatemia, hyperchloremia, and hypermagnesemia. Plasma PTH concentration is normal or moderately elevated, and the fractional excretion of calcium is lower than that observed in hyperparathyroidism. The fractional excretion of calcium is best assessed by calculating the calcium-to-creatinine clearance ratio from a 24-hour urine collection, as follows:

$$\text{Calcium-creatinine clearance ratio} = \frac{(\text{24-hour urine calcium}) \times (\text{Serum creatinine})}{(\text{24-hour urine creatinine}) \times (\text{Serum calcium})}$$

In FHH, the urine calcium–creatinine clearance ratio (calculated using milligrams) is usually less than 0.01. The urine Ca–creatinine concentration ratio is most often less than 0.07 mg/mg (0.2 mmol/mmol). In patients with FHH, hypercalcemia never leads to severe clinical signs, except in the neonatal period, when malignant hypercalcemia can be observed in the patient with severe hyperparathyroidism.

Other Endocrine Causes

Other endocrine disorders associated with moderate hypercalcemia include hyperthyroidism, acromegaly, and pheochromocytoma. In addition, acute adrenal insufficiency should also be considered in the differential diagnosis, although in these patients, hypercalcemia is usually false and results from hemoconcentration. Hypercalcemia can also occur in severe forms of the secondary hyperparathyroidism of CKD, which have also been called "tertiary hyperparathyroidism." However, this is relatively uncommon to date because low circulating calcitriol concentrations in CKD patients limit GI calcium absorption, and overfunctioning parathyroid glands can be controlled more easily.

Other Causes

Several other disorders sometimes induce hypercalcemia. Among the granulomatoses, sarcoidosis results in increased plasma Ca^{2+}, particularly in patients exposed to sunlight. The cause is uncontrolled production of calcitriol by macrophages, a result of 1α-hydroxylase in the macrophages within the granulomas. Tuberculosis, leprosy, berylliosis, and many other granulomatous diseases are occasionally (but rarely compared with sarcoidosis) the origin of hypercalcemia, probably through the same mechanism.

Hypercalcemia may also result from prolonged bed rest, especially in patients with preexisting high bone turnover rates, such as children, adolescents, and patients with Paget disease. Recovery from acute renal failure secondary to rhabdomyolysis-induced renal failure has been associated with hypercalcemia in 25% of cases and likely results from mobilization of soft tissue calcium deposits and through increases in PTH and calcitriol. Other causes include intoxication by vitamin D or its derivatives, vitamin A overload, and thiazide diuretics. Large doses of calcium (5 to 10 g/day), especially when ingested with alkali (antacids), can also lead to hypercalcemia and nephrocalcinosis (milk-alkali syndrome).

Clinical Manifestations

The severity of clinical symptoms and signs caused by hypercalcemia depends on not only the degree but also the velocity of its development. Severe hypercalcemia can be accompanied by few manifestations in some patients because of its slow, progressive development, whereas much less severe hypercalcemia can lead to major disorders if it develops rapidly.

In general, the first symptoms are increasing fatigue, muscle weakness, inability to concentrate, nervousness, increased sleepiness, and depression. Subsequently, GI signs may occur, such as constipation, nausea and vomiting, and rarely peptic ulcer disease or pancreatitis. Renal-related signs include polyuria (secondary to nephrogenic diabetes insipidus), urinary tract stones and their complications, and occasionally tubulointerstitial disease with medullary and to a lesser extent cortical deposition of calcium (nephrocalcinosis). Neuropsychiatric manifestations include headache, loss of memory, somnolence, stupor, and rarely coma. Ocular symptoms include conjunctivitis from crystal deposition and rarely band keratopathy. Osteoarticular pain in primary hyperparathyroidism has become rare in Western countries because of earlier diagnosis of hypercalcemia. High blood pressure can be induced by hypercalcemia, but it is more frequently a chance association. Soft tissue calcifications can occur with longstanding hypercalcemia. The electrocardiogram (ECG) may show shortening of the QT interval and coving of the ST wave. Hypercalcemia may also increase cardiac contractility and can amplify digitalis toxicity.

Diagnosis

When the history and clinical examination are not helpful, primary hyperparathyroidism should be investigated first. Although this is only the second most frequent cause, its laboratory diagnosis is at present easier than that of tumoral involvement. The initial step should be to measure plasma PTH and total or ionized $[Ca^{2+}]$, as available. When the PTH value is high-normal or high in the presence of high-normal or high $[Ca^{2+}]$, the diagnosis of primary hyperparathyroidism is likely (although FHH is not excluded). Other

helpful laboratory tests may include phosphate, creatinine, total alkaline phosphatases, and urinary calcium and creatinine. Note that prolonged hypercalcemia is often associated with (reversible) increased serum creatinine. Cervical ultrasound and sestamibi isotope scanning may be performed to locate a parathyroid adenoma, although some surgeons still consider these examinations unnecessary before an initial neck exploration. However, imaging is indispensable in patients with recurrent hyperparathyroidism and having unilateral neck surgery under local anesthesia. If the plasma PTH level is low-normal or low, the possibility of a neoplastic disorder should be seriously considered. A low serum anion gap may be caused by multiple myeloma, because occasionally the monoclonal IgG is positively charged. In addition to the usual examinations, such as serum protein electrophoresis, measurement of the plasma PTHrp level can now be done in specialized laboratories. Exogenous vitamin D overload is associated with increased serum 25-hydroxyvitamin D levels, and granulomatous diseases such as sarcoidosis are associated with elevated calcitriol levels and with increased serum angiotensin-converting enzyme (ACE) activity.

Treatment

Treatment of the patient with hypercalcemia is aimed at the underlying cause. However, severe and symptomatic hypercalcemia requires rapid correction, whatever the cause. Initially, the patient must be rapidly rehydrated with isotonic saline to correct the often marked volume depletion, to reduce proximal tubule calcium reabsorption and enhance calcium excretion. Only when euvolemia is established should loop diuretics be used (e.g., IV furosemide, 100 to 200 mg every other hour) to facilitate urinary excretion of calcium; however, intravenous saline should be continued to prevent hypovolemia. Oral intake and IV administration of fluids and electrolytes should be carefully monitored, and urinary and gastric excretions measured if excessive, especially potassium, magnesium, and phosphate. Acid-base balance should also be carefully monitored. Severe cardiac failure and CKD are contraindications to massive ECF volume expansion along with diuretics.

Bisphosphonates are the treatment of first choice, especially in patients with hypercalcemia associated with cancer.[15] These agents inhibit bone resorption as well as calcitriol synthesis. Bisphosphonates can be administered orally (PO) in less severe disease or intravenously (IV) in severe hypercalcemia. Common bisphosphonates include clodronate (1600 to 3200 mg/day PO), pamidronate (15 to 90 mg IV over 1 to 3 days, once a month), and alendronate (10 mg/day PO). IV doses should be infused in 500 ml of isotonic saline or dextrose over at least 2 hours and up to 24 hours. Although package warnings state that bisphosphonates should be used with caution in patients with CKD, virtually no safety data support such warnings. Bisphosphonates have been safely used in CKD patients for the correction of hypercalcemia. A reasonable strategy is first to attempt correcting acute kidney injury before administering a bisphosphonate, and to avoid repetitive dosing; a single 60-mg dose of pamidronate can maintain normal [Ca^{2+}] for weeks. Calcitonin acts within hours, especially after IV administration. Human, porcine, or salmon calcitonin can be given. However, calcitonin often has no effect, or only a short-term effect, because of the rapid development of tachyphylaxis.

Mithramycin is a cytostatic drug with remarkable power to inhibit bone resorption. Administration of a single IV dose is generally followed by a rapid decline in plasma calcium within a few hours, and this effect lasts several days. However, mithramycin is reserved for malignant hypercalcemia, and its cytotoxic effect and side effects (thrombocytopenia, liver function abnormalities) preclude prolonged administration. The maximal daily dose of mithramycin is 25 μg/kg.

Corticosteroids such as prednisone (or prednisolone), 0.5 to 1.0 mg/kg daily, are mainly indicated in hypervitaminosis D of endogenous origin, as in patients with sarcoidosis or tuberculosis, to decrease macrophage synthesis of calcitriol. Ketoconazole, an antifungal agent that can inhibit renal and extrarenal calcitriol synthesis, has also been proposed in hypervitaminosis D. Corticosteroids can also be used in patients with hypercalcemia associated with some hematopoietic tumors (e.g., myeloma, lymphoma) and even for some solid tumors such as breast cancer.

In rare cases of malignant hypercalcemia, treatment with prostaglandin antagonists such as indomethacin or aspirin can be successful. Hyperkalemia and impaired renal function may occur with indomethacin. Hypercalcemia caused by thyrotoxicosis can rapidly resolve with IV administration of propranolol or less rapidly with oral administration.

In moderate and nonsymptomatic hypercalcemia of primary hyperparathyroidism, treatment with estrogens has been tried, at least in female patients. In patients with primary hyperparathyroidism, cinacalcet, the first of a newer therapeutic class of CaR_G agonists, the *calcimimetics,* can achieve normalization of serum Ca^{2+} in most cases, together with a reduction in serum PTH.[16] However, surgical removal of benign parathyroid adenomas remains the first option in patients with no overt contraindications because this allows definitive cure in most patients; surgery is also less expensive than life-long cinacalcet therapy. In dialysis patients with secondary (and many cases of so-called tertiary) uremic hyperparathyroidism, long-term administration of cinacalcet is superior to standard therapy in controlling serum PTH, calcium, and phosphate, and in avoiding surgical parathyroidectomy[17] (see Chapter 85). Surgical parathyroidectomy remains an alternative solution in dialysis patients who are unresponsive to medical treatment. Of note, cinacalcet may also be effective in patients with parathyroid carcinoma.

HYPOCALCEMIA

As with hypercalcemia, hypocalcemia can be secondary either to reduced plasma albumin (false hypocalcemia) or to a change in ionized [Ca^{2+}] (true hypocalcemia). False hypocalcemia can be excluded by directly measuring plasma [Ca^{2+}], by determining plasma total protein or albumin levels, by the clinical context, or by other laboratory results (Figure 10-10). Acute hypocalcemia is often observed during acute hyperventilation and the respiratory alkalosis that follows, regardless of the cause of hyperventilation. Hyperventilation can result from cardiopulmonary or cerebral diseases. After excluding false hypocalcemia linked to hypoalbuminemia, hypocalcemia can be divided into that associated with elevated and that associated with low plasma phosphate concentration.

Hypocalcemia Associated with Hyperphosphatemia

Chronic kidney disease leads to diminished calcitriol production and subsequently a low-normal serum [Ca^{2+}]. In parallel, declining glomerular ultrafiltration of phosphate leads to a progressive rise in serum phosphate levels once the glomerular filtration rate (GFR) falls below about 35 ml/min/1.73 m^2. Acute kidney injury (AKI) may also cause hypocalcemia and hyperphosphatemia through these mechanisms in combination with hypocalcemia of critical illness. This finding may be particularly pronounced in AKI caused by rhabdomyolysis or pancreatitis.

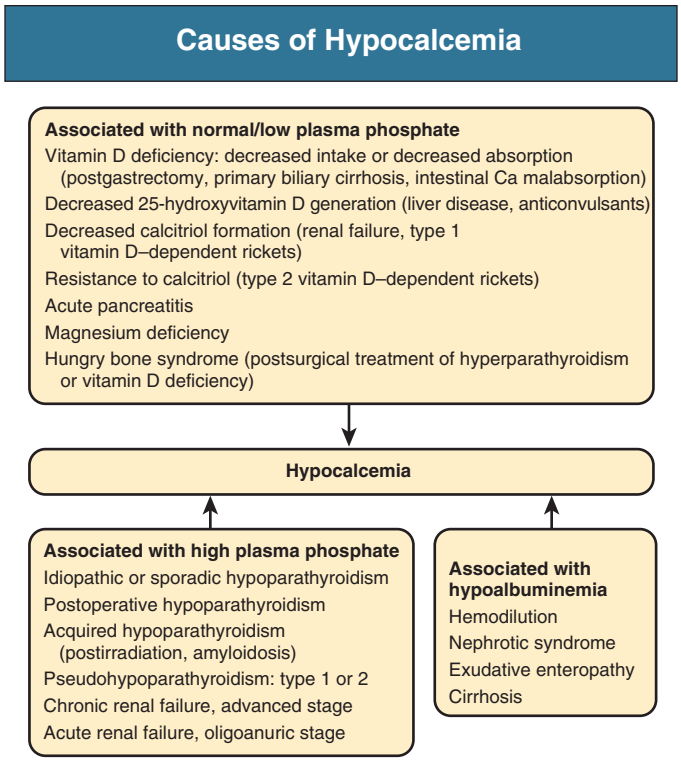


Figure 10-10 Causes of hypocalcemia.

Hypoparathyroidism may be caused by surgical removal of the parathyroid glands (post thyroidectomy or parathyroidectomy), radiation, autoimmune destruction of parathyroid tissue, or infiltrative diseases. Sporadic cases of hypoparathyroidism are occasionally seen in patients with pernicious anemia or adrenal insufficiency. Pseudohypoparathyroidism (Albright hereditary osteodystrophy) is characterized by a particular phenotype including short neck, round face, and short metacarpals, with end-organ resistance to PTH.

In addition, massive phosphate administration, such as that used in bowel preparations, can also lead to hypocalcemia with hyperphosphatemia, often with AKI.[18]

Hypocalcemia Associated with Hypophosphatemia

Hypocalcemia with hypophosphatemia may occur in vitamin D–deficient states. This may result from insufficient sunlight exposure, dietary deficiency of vitamin D, decreased absorption after gastrointestinal surgery, intestinal malabsorption syndromes (steatorrhea), or hepatobiliary disease (primary biliary cirrhosis). Hyperuricemia or gout may also be associated with low 1,25-dihydroxyvitamin D levels. Hypocalcemia may also be caused by magnesium deficiency, often in conjunction with hypokalemia, which may be caused by inappropriate kaliuresis or diarrhea. The mechanism for hypocalcemia in this setting appears to be decreased PTH release and end-organ resistance. AKI in the polyuric phase, especially following rhabdomyolysis, may also be associated with hypocalcemia and hypophosphatemia.

Clinical Manifestations

As with hypercalcemia, the symptoms of hypocalcemia depend on rate of development and severity. The most common manifestations, in addition to fatigue and muscular weakness, are increased irritability, loss of memory, a state of confusion, hallucination, paranoia, and depression. The best known clinical signs are Chvostek sign (tapping of facial nerve branches leading to twitching of facial muscle) and Trousseau sign (carpal spasm in response to forearm ischemia caused by inflation of a sphygmomanometer cuff). Patients with acute hypocalcemia may have paresthesias of the lips and the extremities, muscle cramps, and occasionally frank tetany, laryngeal stridor, or convulsions. Chronic hypocalcemia may be associated with cataracts, brittle nails with transverse grooves, dry skin, and decreased or even absent axillary and pubic hair, especially in idiopathic hypoparathyroidism, which is often of autoimmune origin.

Laboratory and Radiographic Signs

Plasma phosphate is elevated in hypoparathyroidism, pseudohypoparathyroidism, and advanced CKD, whereas it is decreased in steatorrhea, vitamin D deficiency, acute pancreatitis, and the polyuric phase during recovery from AKI. Plasma PTH is reduced in hypoparathyroidism and also during chronic magnesium deficiency, whereas it is normal or increased in pseudohypoparathyroidism and in CKD. Urinary calcium excretion is increased only in patients with hypoparathyroidism receiving calcium or vitamin D derivatives, in whom it may lead to nephrocalcinosis; excretion is low in all other patients with hypocalcemia. *Fractional* urinary calcium excretion, however, is high in hypoparathyroidism, in the polyuric phase during recovery from AKI, and in severe CKD; it is low in all other hypocalcemic patients. Urinary phosphate excretion is low in hypoparathyroidism, pseudohypoparathyroidism, and magnesium deficiency; it is high in vitamin D deficiency, steatorrhea, CKD, and during phosphate administration. Determination of serum 25-hydroxyvitamin D and calcitriol levels may also be useful.

On the ECG the corrected QT interval is frequently prolonged, and arrhythmias may occur. The electroencephalogram (EEG) shows nonspecific signs such as an increase in slow, high-voltage waves. Intracranial calcifications, notably of the basal ganglia, are observed radiographically in 20% of patients with idiopathic hypoparathyroidism, but much less frequently in patients with postsurgical hypoparathyroidism or pseudohypoparathyroidism.

Treatment

Therapy for the patient with hypocalcemia is directed toward the underlying cause. Severe and symptomatic (tetany) hypocalcemia requires rapid treatment. Acute respiratory alkalosis, if present, should be corrected if possible. When the cause is functional, simple CO_2 retention, as by breathing into a paper bag, may suffice. In other patients, and to obtain a prolonged effect, IV infusion of calcium salts is most often required. In the patient with seizures or tetany, calcium gluconate should be administered as an IV bolus (e.g., 10 ml 10% w/v [2.2 mmol of calcium], diluted in 50 ml of 5% dextrose in water [D5W] or isotonic saline), followed by 12 to 24 g over 24 hours (in D5W or isotonic saline). Calcium gluconate is preferred to calcium chloride, which can lead to extensive skin necrosis in accidental extravasation.

Treatment of chronic hypocalcemia includes oral administration of calcium salts, thiazide diuretics, or vitamin D. Several oral presentations of calcium are available, each with their advantages and disadvantages. It should be remembered that the amount of elemental calcium of the various salts differs greatly. For example, the calcium content is 40% in carbonate, 36% in chloride, 12% in lactate, and only 8% in gluconate salts. The daily amount prescribed can be 2 to 4 g elemental Ca. Concurrent magnesium deficiency (serum [Mg^{2+}]

<0.75 mmol/l) should be treated either with oral magnesium oxide (250 to 500 mg every 6 days) or with magnesium sulfate: intramuscular (IM, 4 to 8 mmol/day) or IV (e.g., 12 ml 50% magnesium sulfate in 1000 ml D5W over 3 to 4 hours).

Treatment of hypocalcemia secondary to hypoparathyroidism is difficult as urinary calcium excretion increases markedly with calcium supplementation and can lead to nephrocalcinosis and loss of renal function. To reduce urinary calcium concentration, thiazide diuretics can be used in association with restricted salt intake and high fluid intake.

Therapy with active forms of vitamin D—calcitriol or its analogue 1α-hydroxycholecalciferol (alfacalcidol), 0.25 to 1.0 μg/day—is the treatment of choice for idiopathic or acquired hypoparathyroidism, because these compounds are better tolerated than massive doses of calcium salts. Administration of vitamin D derivatives generally leads to hypercalciuria and rarely to nephrocalcinosis. The patient requires regular monitoring to avoid hypercalcemia.

PHOSPHATE HOMEOSTASIS

Distribution of Phosphate in the Organism

Phosphate plays a crucial role in cell structure, signaling, and metabolism. Phosphate is found in the organism both as mineral phosphate and organic phosphate (phosphoric esters). As with calcium, the vast majority of phosphate in the body resides in bone, teeth, and inside cells, with less than 1% circulating in the serum. The serum phosphorus concentration is maintained within a narrow range under the direction of hormonal regulators FGF23, PTH, and calcitriol. Phosphate circulates as HPO_4^{2-} and $H_2PO_4^-$, in a 4:1 ratio at normal pH. Normal serum phosphate levels of 2.8 to 4.5 mg/dl (0.9 to 1.5 mmol/l) fluctuate in a circadian rhythm, with levels approximately 0.6 mg/dl higher in the afternoon, compared to an 11 AM nadir. Figure 10-11 shows the distribution of phosphate in the ECF and ICF compartments.

Figure 10-12 shows the balance of ingestion, body distribution, and excretion of phosphate in a healthy human. A young adult requires approximately 0.5 mmol/kg of phosphate daily. These needs are much greater in the child during growth. Phosphate is widely found in milk products, meat, eggs, and cereals and is used extensively as food additives. Bone permanently exchanges phosphate with the surrounding milieu. Entry and exit of phosphate amount to approximately 100 mmol daily (slowly exchangeable phosphate), for a total skeleton content of about 20,000 mmol. The net balance is positive during growth, zero in the young adult, and negative in the elderly adult.

Phosphate enters cells by active transport through a variety of sodium-phosphate (Na-Pi) cotransporters. In the small intestine, phosphate is absorbed through the type 2b Na-Pi cotransporter (NPT2b).The major hormonal regulator of NPT2b is calcitriol, which increases phosphate transport into the body. In contrast, the lipid-lowering agent niacin inhibits NPT2b activity, thereby decreasing phosphate uptake. In CKD patients, niacin treatment lowers serum phosphate by approximately 0.4 mg/dl. A genome-wide association study of more than 16,000 normal adults found that a common genetic variant in NPT2a was associated with serum phosphate concentrations.[19] In the proximal tubule of the kidney, most of the filtered phosphate load is reabsorbed through type 2a and type 2c Na-Pi cotransporters (NPT2a, NPT2c). The phosphaturic hormones FGF-23 and PTH are the principal factors that downregulate NPT2a, increasing phosphate excretion in the urine. Now recognized as a central hormone in phosphate homeostasis, FGF-23 is made by osteocytes but possesses weak inherent binding properties, requiring a cofactor, klotho, for optimal binding and function within the kidney.[20] Disruption of klotho or FGF-23 genes in animal models leads to a similar hyperphosphatemic phenotype. In addition to promoting phosphate excretion, FGF-23 potently suppresses calcitriol by inhibiting CYP27B1 and stimulating CYP24A1. Other hormones that may influence phosphate transport within the kidney include growth hormone, insulin-like growth factor 1 (IGF-1), insulin, thyroid hormone, secreted frizzled-related protein 4 (sFRP-4), and FGF-7.

Phosphate transport across the intestinal wall occurs via both the transepithelial and the paracellular routes (Fig. 10-13). Absorption is a linear, nonsaturable function of phosphate intake (Fig. 10-14). Absorption amounts to 60% to 75% of total phosphate intake (15 to 50 mmol/day). Calcitriol, which stimulates the NP2b cotransporter,

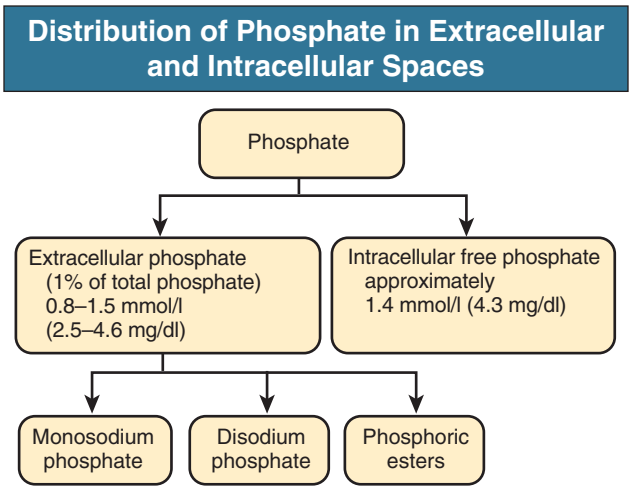


Figure 10-11 Phosphate distribution in extracellular and intracellular spaces.

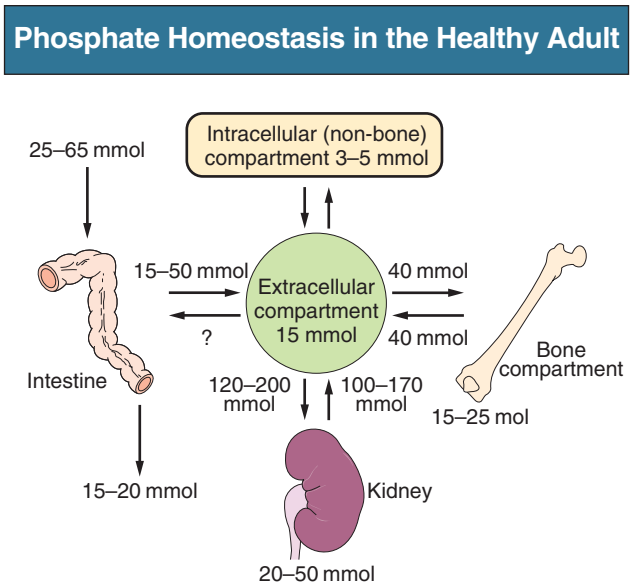


Figure 10-12 Phosphate homeostasis in healthy young adults. At net zero balance, identical net intestinal uptake (absorption minus secretion) and urinary loss occur. After its passage into the extracellular fluid, phosphate enters the intracellular space, is deposited in bone or soft tissue, or is eliminated via the kidneys. Entry and exit fluxes between the extracellular and intracellular spaces (skeletal and nonskeletal compartments) are also the same under steady-state conditions.

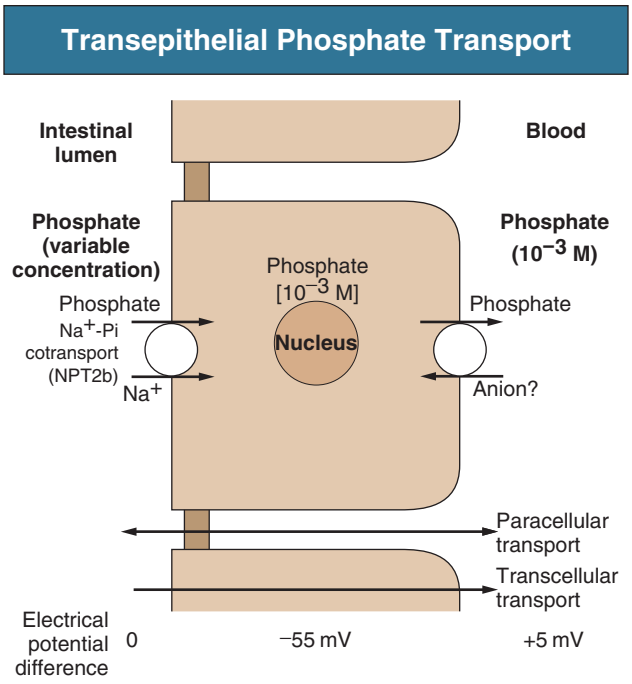


Figure 10-13 Transepithelial phosphate transport in the small intestine. Phosphate enters the enterocyte (influx) through the brush border membrane using the Na^+/Pi cotransport system, with a stoichiometry of 2 : 1, operating against an electrochemical gradient. Phosphate exit at the basolateral side possibly occurs by passive diffusion or more probably by anion exchange.

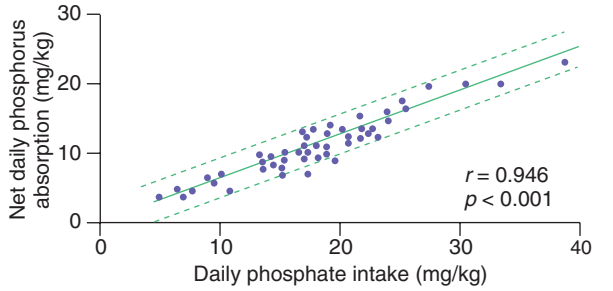


Figure 10-14 Phosphate ingestion and absorption. Relationship between ingested phosphate and phosphorus absorbed in the digestive tract (net absorption) in healthy young adults. *(From reference 4.)*

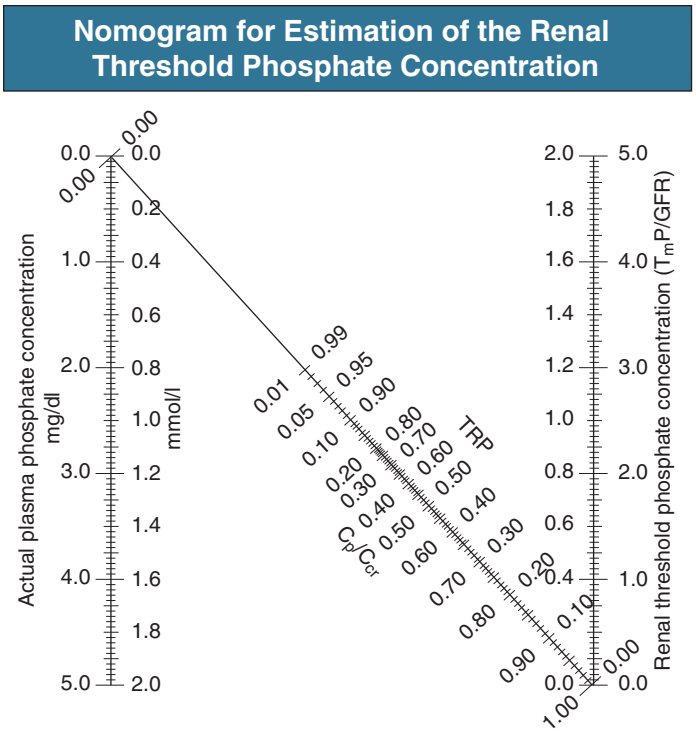


Figure 10-15 Nomogram for estimation of renal threshold phosphate concentration. A straight line through the appropriate values of phosphate concentration and TRP (amount of phosphate reabsorbed, or C_P/C_{cr}, where C is clearance for phosphate or creatinine) passes through the corresponding value of T_mP/GFR. *(From reference 23.)*

is the major hormonal determinant of intestinal phosphate absorption. Cations, such as calcium, magnesium, or aluminum, bind to phosphate in the GI tract, limiting its absorption. In both animals and humans, ingestion of a high-phosphate meal results in the rapid excretion of phosphate in the urine, without detectable changes in serum phosphate levels.

The kidneys play a central role in controlling extracellular phosphate homeostasis.[21,22] Phosphate is minimally protein bound, freely filtered at the glomerulus, and reabsorbed primarily in the proximal tubule. To maintain steady-state homeostasis, the daily amount of phosphate excreted in urine must equal that absorbed in the intestine. Normally, the kidneys excrete 5% to 20% of the filtered phosphate load to maintain phosphate balance. In CKD, however, fewer functioning nephrons necessitate the excretion of a higher proportion of the filtered phosphate load per nephron to maintain phosphate homeostasis. For this reason, the fractional excretion of phosphate may exceed 50% in late stages of CKD.

The amount of phosphate reabsorbed can be expressed in relation to the amount filtered as the urinary fractional excretion of phosphate (FE_{Po4}), as follows:

$$FE_{Po4} = (U_{Po4} \times S_{cr})/(S_{Po4} \times U_{cr})$$

where U_{Po4}, S_{Po4}, U_{cr}, and S_{cr} are urinary and serum phosphate and creatinine concentrations, respectively. Ideally FE_{Po4} should be calculated from 24-hour urine samples to incorporate dietary phosphate consumption and circadian changes in serum phosphate throughout the day. In practice, FE_{Po4} is typically calculated using spot urine samples, the validity and precision of which are unknown (Fig. 10-15).[23]

HYPERPHOSPHATEMIA

Causes of Hyperphosphatemia

The most common cause of increased serum phosphate levels is reduced urinary excretion caused by acute and chronic kidney diseases.[24] Although seen particularly in patients with disturbed urinary phosphate excretion, hyperphosphatemia can also be caused by increased exogenous or endogenous phosphate supply (Fig. 10-16).

Acute Kidney Injury

The kidneys are the major route for phosphate excretion. An acute reduction in GFR leads directly to a rise in the serum phosphate concentration, often in parallel with serum creatinine.

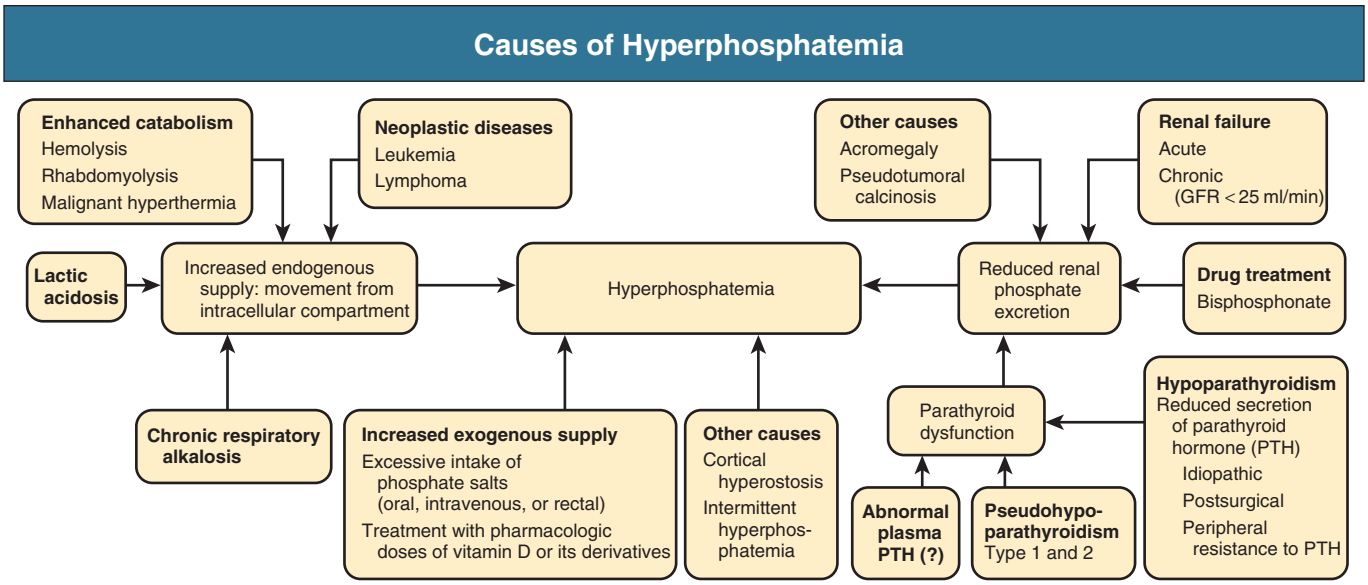


Figure 10-16 Causes of hyperphosphatemia.

Chronic Kidney Disease

Over time, the organism is able to respond to a loss of filtering nephrons by increasing the proportionate phosphate excretion in remaining nephrons to preserve serum phosphate concentrations. As kidney function slowly declines during CKD, levels of phosphaturic hormones FGF-23 and PTH rise to enhance the fractional excretion of phosphate in surviving nephrons and preserve phosphate homeostasis. This system is able to maintain phosphate balance until about 75% of normal kidney function has been lost. Once GFR falls below about 35 ml/min/1.73 m^2, inadequate nephron mass results in a steady rise in serum phosphate. Similar to acidosis and anemia, the presence of hyperphosphatemia in CKD patients generally suggests more advanced disease.

The price paid for preservation of serum phosphate in CKD is high circulating levels of FGF-23 and PTH. FGF-23 potently suppresses calcitriol, inhibiting intestinal phosphate absorption through NPT2b and further defending against phosphate excess. However, suppression of calcitriol may have an adverse impact on cardiovascular and kidney health because of biologic activities of calcitriol in downregulating renin expression, reducing inflammatory cytokines, and moderating ventricular hypertrophy. FGF-23 excess may have direct cardiovascular toxicity through stimulation of cardiac hypertrophy, as seen in animal models. A randomized controlled trial of phosphate binders in 148 nondialysis CKD patients recently assessed the hormonal impact of phosphate excess.[25] Compared with placebo, intensive therapy with phosphate binders over a median 8 months of follow-up prevented increased PTH, lowered serum phosphate by 0.3 mg/dl, and reduced mean 24-hour urine phosphate by 22%, but did not significantly lower FGF-23 levels.

Lytic States

Exaggerated phosphate loss by tissues is seen in states of extreme cell lysis, particularly rhabdomyolysis (crush injury), and in patients with malignancies, especially lymphoma and leukemia, and with their treatment. The hyperphosphatemia of rhabdomyolysis is typically accompanied by hypocalcemia, myoglobinuria, and AKI. Severe hypercatabolic states during severe infection or in diabetic ketoacidosis can also cause hyperphosphatemia through increased cellular release of phosphate, usually accompanied by an acute reduction in GFR.

Treatment-Induced Hyperphosphatemia

A massive supply of phosphate, as may accumulate with phosphate-based laxatives or enemas, can lead to hyperphosphatemia. Oral sodium phosphate solutions used to prepare for colonoscopy contain massive quantities of phosphate and can cause precipitation of calcium phosphate crystals within the renal tubules and AKI. Recovery from this condition is slow and often incomplete, with some cases resulting in permanent dialysis. For these reasons, patients with CKD should receive bowel preparations other than those based on sodium-phosphate salts. Bisphosphonates, in particular etidronate in Paget disease, can increase serum phosphate levels, possibly through increased liberation of tissue phosphate or an increase in renal tubular reabsorption.

Hypoparathyroidism

Parathormone (PTH) is a major phosphaturic hormone. In states of reduced PTH secretion (idiopathic or postsurgical hypoparathyroidism) or resistance to its peripheral action (pseudohypoparathyroidism), tubular excretion of phosphate is diminished. The resulting increase in plasma phosphate leads to an increase in the ultrafiltered load. This results in the regulation of plasma phosphate at a new steady-state level.

Chronic Hypocalcemia

Hyperphosphatemia may be observed in association with chronic hypocalcemia with normal or high plasma PTH levels. In the absence of characteristic abnormalities of pseudohypoparathyroidism, the existence of an abnormal form of plasma PTH has been suggested, perhaps caused by abnormal conversion of the prohormone to its secreted form.

Acromegaly

In acromegaly, hyperphosphatemia results from an increase in tubular reabsorption of phosphate caused by stimulation by growth hormone and IGF-1.

Familial Tumoral Calcinosis

This rare, autosomal recessive disorder seen primarily in people of Middle Eastern or African ancestry is caused by an inactivating mutation in *GALNT3, FGF23,* or klotho gene. The glycosyltransferase encoded by *GALNT3* is necessary for FGF-23 activity thus resulting in a shared phenotype.[26] The lack of functional FGF-23 results in an exaggerated tubular phosphate reabsorption and uninhibited vitamin D activation, leading to hyperphosphatemia and hypercalcemia, high circulating levels of calcitriol, and metastatic soft tissue calcifications. The most common finding is densely calcified masses surrounding major joints that recur after removal. Circulating PTH is not decreased.

Respiratory Alkalosis with Prolonged Hyperventilation

Respiratory alkalosis resulting from prolonged hyperventilation is characterized by resistance to the renal action of PTH, hyperphosphatemia, and hypocalcemia. There may also be functional pseudohypoparathyroidism because renal phosphate clearance is diminished, whereas plasma PTH is normal, despite hypocalcemia. There is no decrease in urinary calcium excretion.

Clinical Manifestations

The major clinical implication of hyperphosphatemia is deposition of phosphate and calcium in soft tissues. Chronic hyperphosphatemia is suspected to play a causal role in the pathogenesis of vascular calcification, particularly in CKD (see Chapter 82). In extreme cases, hyperphosphatemia can induce tumor-like soft tissue calcium phosphate deposits (Figure 10-17) or extensive vascular calcification within the arteries of the skin (calciphylaxis or calcific uremic arteriolopathy; see Chapter 88). Hyperphosphatemia also blocks the conversion of 25-hydroxyvitamin D to calcitriol, leading to concomitant hypocalcemia and the stimulation of PTH.

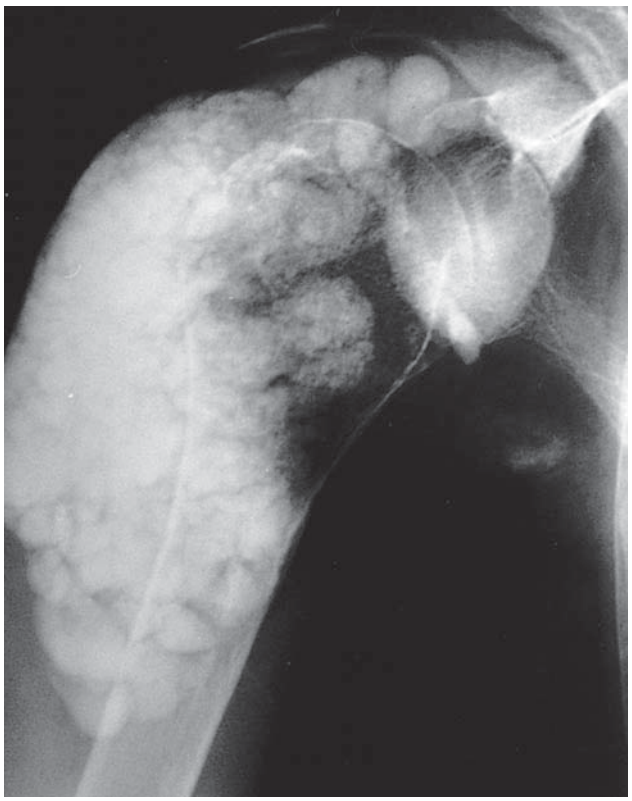


Figure 10-17 Tumor-like extraskeletal calcification in the shoulder.

Treatment

Treatment of acute hyperphosphatemia is usually targeted at improving phosphate excretion by IV fluids or by renal replacement therapy in patients with severe AKI. IV dextrose and insulin can also shift phosphate into cells, similar to its use in treating hyperkalemia.

Treatment of chronic hyperphosphatemia in CKD and dialysis patients remains a major component of CKD clinical care. Higher serum phosphate concentrations are *associated* with vascular calcification, cardiovascular events, and mortality in CKD.[27] However, no available treatment for hyperphosphatemia has proven clinical benefit, defined by placebo-controlled trials of hard outcomes. In chronic dialysis patients, dietary phosphate restriction and phosphate binders lower the serum phosphate concentration. Choices for phosphate binders include calcium acetate, calcium carbonate, sevelamer, lanthanum carbonate, and magnesium containing salts which must be taken multiple times per day with meals to complex with phosphate in the GI tract and limit absorption (see Chapter 85). Niacin is an intriguing possible alternative to phosphate binding agents due to its ease of administration (once daily) and novel mechanism of action (inhibition of NPT2b in small intestine, blocking phosphate absorption).[28]

HYPOPHOSPHATEMIA

Decreased plasma phosphate levels may reflect phosphate deficiency. This can theoretically be observed during a prolonged decrease in phosphate intake. However, several defense mechanisms counter a decrease in plasma phosphate resulting from low intake (Fig. 10-18). Moderately reduced plasma phosphate levels may also accompany maldistribution between the ICF and ECF compartments during acute respiratory alkalosis.

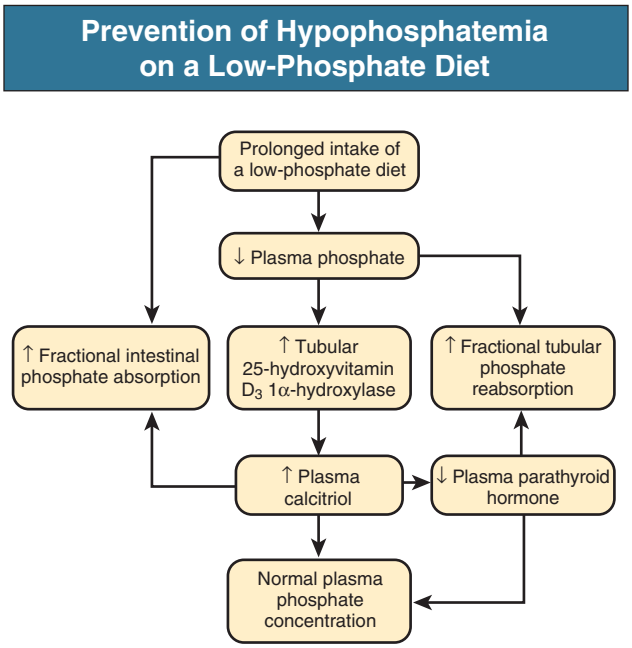


Figure 10-18 Prevention of hypophosphatemia. Compensatory mechanisms during prolonged intake of a phosphate-poor diet help to prevent hypophosphatemia.

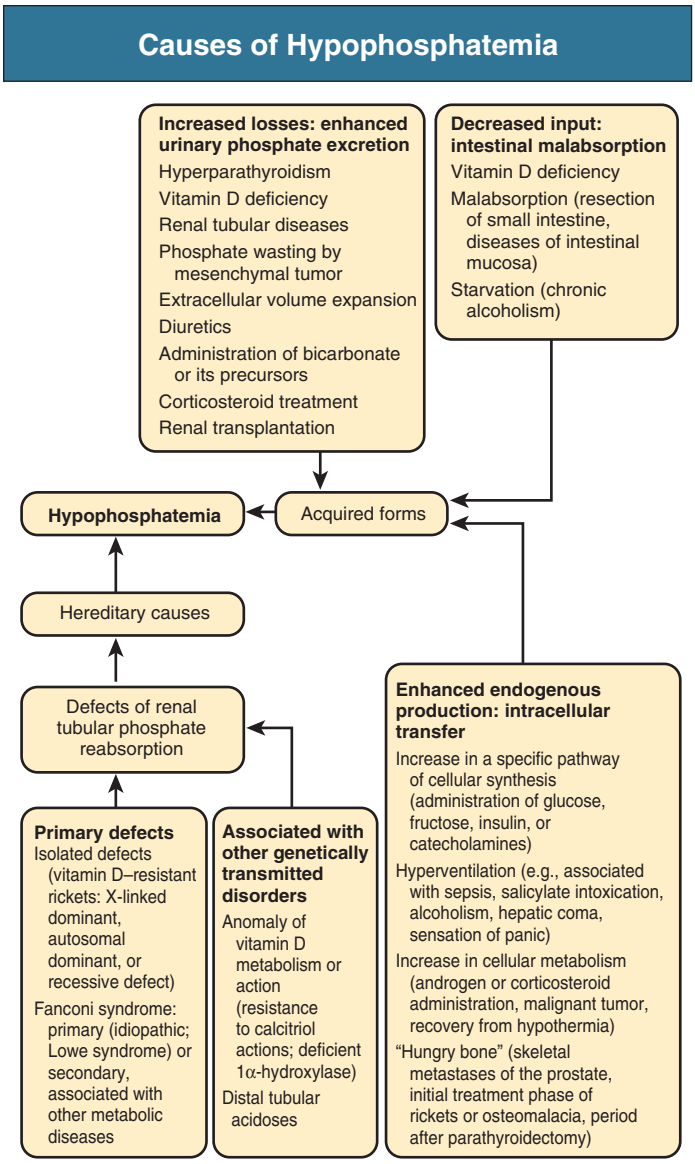


Figure 10-19 Causes of hypophosphatemia.

Causes of Hypophosphatemia

Moderate hypophosphatemia can be caused by genetic diseases or by acquired conditions (Fig. 10-19). The main acquired condition is malnutrition because of low food intake or anorexia during severe disease or alcoholism. Another cause is a shift of phosphate into cells, which can occur through various mechanisms, but especially with insulin administration. Although there are many genetic diseases and syndromes, overall these are rare. Severe forms of hypophosphatemia are all acquired conditions.

Inherited Forms of Hypophosphatemia

Inherited diseases associated with chronic hypophosphatemia are generally diagnosed in childhood.[29] Persistently low plasma phosphate usually leads to rickets or osteomalacia. Inherited hypophosphatemia results from primary defects, which are isolated or associated with tubular disorders (Fanconi syndrome) or defects secondary to another genetically transmitted disease, mainly metabolic disorders or disturbances in vitamin D activity.

Autosomal Dominant Hypophosphatemic Rickets Children with this phosphate wasting disorder present with skeletal defects, including bowing of the long bones and widening of costochondral joints. Autosomal dominant hypophosphatemic rickets is linked to mutations in *FGF23,* in which an aberrant form of the molecule is resistant to proteolytic cleavage.[30] Excess FGF-23 causes phosphate wasting by downregulating NPT2a in the proximal renal tubule.

X-Linked Hypophosphatemic Rickets This rare phosphate wasting syndrome is characterized by skeletal deformities, short stature, and osteomalacia. X-linked hypophosphatemic rickets has been associated with various mutations in the *PHEX* gene (phosphate-regulating endopeptidase on X chromosome). *PHEX* likely plays a role in the proteolysis of FGF-23.[31] *PHEX* mutations result in high circulating FGF-23 concentrations, renal phosphate wasting, and hypophosphatemia. Plasma calcium, calcitriol, and PTH levels are normal, and alkaline phosphatase level is elevated.

Autosomal Recessive Hypophosphatemic Rickets This inherited rickets disorder is caused by mutations in dentin matrix protein 1 gene *(DMP1),* which is believed to suppress FGF-23 secretion by bone.

Fanconi Syndrome and Proximal Renal Tubular Acidosis Fanconi syndrome is characterized by a complex transport defect of the proximal tubule that results in decreased reabsorption of glucose, amino acids, bicarbonate, and phosphate (see Chapter 50). Because 70% of the filtered phosphate load is typically reabsorbed in the proximal tubule, Fanconi syndrome can lead to phosphate wasting and hypophosphatemia. Causes of Fanconi syndrome can be classified as primary (e.g., idiopathic, Lowe syndrome, Dent disease) or associated with other metabolic diseases (e.g., cystinosis, Wilson disease). In Dent disease and Lowe syndrome, a defective recycling of megalin to the apical cell surface of the proximal tubule has implicated a role in abnormal tubular endocytic function.[32]

Fanconi syndrome with phosphate wasting can also occur as an acquired disorder in adults. Common causes are multiple myeloma and specific medications, including tenofovir, ifosfamide, and carbonic anhydrase inhibitors.

In addition to a tubular defect causing phosphate wasting, the activity of renal 1α-25-OH–vitamin D hydroxylase may be insufficient, resulting in decreased circulating calcitriol levels and bone disease such as rickets and osteomalacia. Functional disorders associated with the Fanconi syndrome, such as polyuria and ECF volume contraction, lead to hyperaldosteronism with hypokalemia and eventually to renal failure.

Vitamin D–Dependent Rickets Several rare inherited diseases are associated with hypophosphatemia and include vitamin D–dependent rickets type 1, caused by a defect of renal 1α-25-OH–vitamin D hydroxylase, and type 2, caused by peripheral resistance to the action of calcitriol. Clinical signs are similar to those of vitamin D–deficient rickets, but alopecia also occurs in 50% of patients. In type 1, calcitriol levels are low, whereas in type 2 there is normal circulating 1α-25-hydroxyvitamin D and high calcitriol. Treatment with low doses of calcitriol is sufficient to treat type 1, whereas extremely high doses of calcitriol or alfacalcidol are required for type 2 vitamin D–dependent rickets.

Distal Renal Tubular Acidosis (Type 1) Distal renal tubular acidosis (type 1 RTA) is associated with hypercalciuria and sometimes nephrocalcinosis. Chronic acidosis enhances the reabsorption of citrate in the proximal tubule, preventing it from forming soluble calcium-citrate complexes in the urine (see Chapter 12). Chronic acidosis also causes increased calcium and phosphate release from bone. Hypophosphatemia is inconstant, possibly resulting only with concomitant vitamin D deficiency.

Acquired Forms of Hypophosphatemia

The number of acquired diseases that can be associated with hypophosphatemia is even greater than inherited diseases and includes

hyperparathyroidism and vitamin D deficiency (Fig. 10-19). True phosphate deficiency associated with total body depletion must be distinguished from enhanced influx of phosphate from the extracellular to the intracellular space or increased skeletal mineralization.

Alcoholism Alcoholism is the most common cause of severe hypophosphatemia in Western countries. The multiple causes include prolonged poor food intake, excessive phosphate loss in urine secondary to hypomagnesemia, and phosphate transfer from the ECF to ICF compartment caused by hyperventilation or glucose infusion in patients with postalcoholic cirrhosis or in acute abstinence.

Hyperparathyroidism Parathormone enhances urinary phosphate excretion by downregulating the NPT2a cotransporter. Patients with primary hyperparathyroidism typically present with mild hypercalcemia and hypophosphatemia.

Post-Transplant Hypophosphatemia Renal phosphate wasting is exceedingly common in both cadaveric and living-related renal transplant recipients. At some point in their post-transplant course, most renal transplant patients develop hypophosphatemia which may be prolonged. Proposed explanations include residual hyperparathyroidism from CKD, but the best evidence implicates persistently high circulating levels of FGF-23 as the key factor responsible for post-transplant urinary phosphate wasting.

Acute Respiratory Alkalosis In intense and short-term hyperventilation, plasma phosphate can decrease to values as low as 0.1 mmol/l (0.3 mg/dl). Such a decrease is never observed in acute metabolic alkalosis. Hypophosphatemia following acute and intense hyperventilation is probably the result of muscle sequestration of extracellular phosphate. However, it must be remembered that prolonged chronic hyperventilation leads to hyperphosphatemia (see previous discussion).

Diabetic Ketoacidosis During decompensated diabetes associated with acidosis provoked by accumulation of ketone bodies, glycosuria, and polyuria, plasma phosphate can be normal or high, even in the presence of hyperphosphaturia. Correction of this complication by administering insulin and refilling the ECF compartment leads to massive transfer of phosphate into the intracellular compartment, hypophosphatemia, and subsequently less urinary loss of phosphate. In general, plasma phosphate does not decrease to less than 0.3 mmol/l (0.9 mg/dl), except when there is preexisting phosphate deficiency.

Total Parenteral Nutrition Hyperalimentation can also be associated with severe hypophosphatemia through the insulin-mediated shift of phosphate into cells, particularly if phosphate is omitted from the parenteral nutrition solution. Severe hypophosphatemia can also occur with acute feeding after starvation.

Oncogenic Hypophosphatemic Osteomalacia Hypophosphatemia associated with tumor-induced osteomalacia results from renal phosphate wasting in patients with mesenchymal tumors (hemangiopericytoma, fibroma, angiosarcoma). The mechanism of hypophosphatemia is tumor secretion of phosphatonins (FGF-23, sFRP-4, MEPE, FGF-7).[33] The condition resolves after tumor resection.

Drug-Induced Hypophosphatemia Imatinib mesylate, a tyrosine kinase inhibitor, has been reported to cause hypophosphatemia and elevated PTH levels. The mechanism of action is not yet clear.

Clinical Manifestations

Clinical manifestations depend more on the rate of onset of hypophosphatemia than on its severity or the total body phosphate deficit. In practice, it is not clinically evident when serum phosphate is greater than 0.65 mmol/l (2.0 mg/dl). Manifestations include metabolic encephalopathy, red and white blood cell dysfunction, sometimes hemolysis, and thrombocytopenia. Reduced muscle strength (e.g., diaphragmatic strength) and decreased myocardial contractility, with occasional rhabdomyolysis and cardiomyopathy, respectively, may occur.

Treatment

In general, phosphate deficiency is not an emergency. First, the mechanism involved should be defined to determine the most appropriate treatment. When phosphate deficiency is diagnosed, oral treatment by milk products or phosphate salts should always be tried first whenever possible, except in the presence of nephrocalcinosis or nephrolithiasis with urinary phosphate wasting. In severe symptomatic deficiency, phosphate can also be infused intravenously, in divided doses over 24 hours. In patients undergoing parenteral nutrition, 10 to 25 mmol potassium phosphate should be given for each 1000 kcal, taking care to avoid hyperphosphatemia because of the risk of inducing soft tissue calcifications. Dipyridamole reduces the urinary excretion of phosphate in patients with a low renal phosphate threshold.

MAGNESIUM HOMEOSTASIS AND DISORDERS OF MAGNESIUM METABOLISM

Distribution of Magnesium in the Organism

Magnesium (Mg^{2+}) is the second most abundant cation in the ICF in living organisms and the fourth most abundant cation in the body. Mg^{2+} is involved in the majority of metabolic processes. In addition, it plays a part in DNA and protein synthesis. Magnesium is involved in the regulation of mitochondrial function, in inflammatory processes and immune defense, allergy, growth, and stress, and the control of neuronal activity, cardiac excitability, neuromuscular transmission, vasomotor tone, and blood pressure. Figure 10-20 shows the distribution of Mg^{2+} within the intracellular and extracellular spaces. Figure 10-21 shows the balance of ingestion, body distribution, and excretion of Mg^{2+} in healthy humans. Cell influx and efflux are linked to carbohydrate-dependent active transport systems; stimulation of β-adrenoceptors favors Mg^{2+} exit, whereas insulin, calcitriol, and vitamin B_6 favor Mg^{2+} entry into cells.

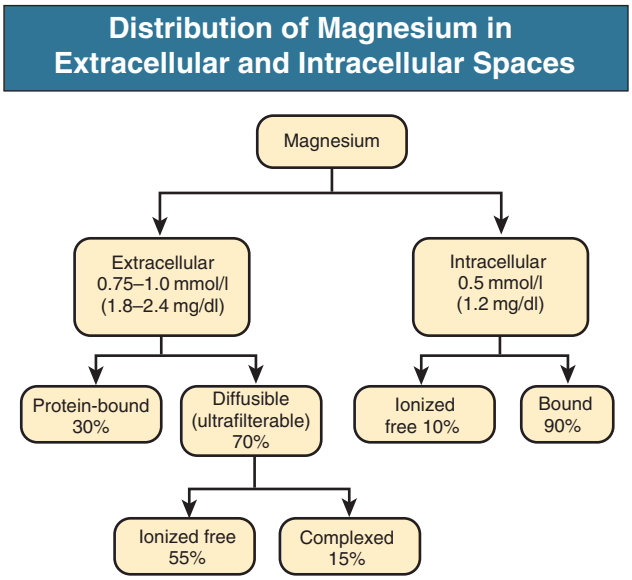


Figure 10-20 Magnesium distribution in extracellular and intracellular spaces.

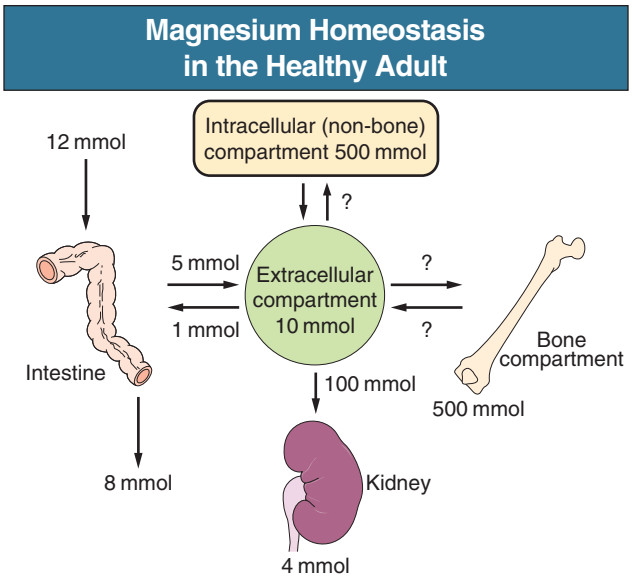


Figure 10-21 Magnesium homeostasis in healthy young adults. Net zero balance results from net intestinal uptake (absorption minus secretion) equaling urinary loss. After its passage into the extracellular fluid, Mg^{2+} enters the intracellular space, is deposited in bone or soft tissue, or is eliminated via the kidneys. Entry and exit fluxes between the extracellular and intracellular spaces (skeletal and nonskeletal compartments) are also of identical magnitude; however, precise values of exchange are still debated.

Intestinal and Renal Handling of Magnesium

The intestinal absorption of dietary Mg^{2+} occurs by both saturable and passive transport processes, the major part being absorbed in the distal small intestine and the colon. Paracellular Mg^{2+} absorption is responsible for 80% to 90% of intestinal Mg^{2+} uptake. It seems restricted primarily to areas that lack tightening claudins. Transcellular Mg^{2+} transport is mediated by transient receptor potential channel melastatin member 6 (TRPM6) and TRPM7 Mg^{2+} channels.[5] Mg^{2+} absorption can vary by as much as 25% to 60%, mainly depending on magnesium intake, with a mean absorption of approximately 30%. When magnesium intake is low, intestinal transport can rise up to 80%.[34]

Various factors modify intestinal Mg^{2+} absorption. In addition to high magnesium intake, high dietary phosphate intake is inhibitory, as is high phytate consumption. The effect of dietary calcium is complex, and calcitriol has an enhancing effect. Growth hormone slightly increases Mg^{2+} absorption, whereas aldosterone and calcitonin appear to reduce it. Vitamin B_6 has been reported to enhance absorption.

Magnesium is mainly eliminated by the kidney. Losses through intestinal secretion and sweat are negligible under normal conditions. With an ultrafilterable plasma magnesium concentration of 0.5 to 0.7 mmol/l (80% of total plasma magnesium), the filtered load of magnesium amounts to approximately 104 mmol (or 2500 mg) daily. The urine output represents approximately 5% of the filtered load (4 to 5 mmol, or 100 mg daily). The major portion of filtered magnesium is reabsorbed by the renal tubules: 25% in proximal tubule, 65% in TAL, and 5% in distal tubule (Fig. 10-22).[35]

Transport of Mg^{2+} in the TAL is primarily passive via the paracellular route. However, two conditions are necessary for normal Mg^{2+} reabsorption: (1) generation of an electrical, lumen-positive gradient induced by NaCl reabsorption that creates the driving force required for the reabsorption of divalent cations and (2) expression of claudins 16 and 19, which form a cation-selective tight junction, facilitating paracellular Mg^{2+} transport. Different anomalies associated with either NaCl reabsorption or with claudin-16/19 expression result in hypermagnesuria, such as Bartter syndrome, which is defined by genetic defects related to NaCl transport in the TAL.[36]

In the distal nephron (i.e., distal convoluted tubule and connecting tubule), Mg^{2+} is reabsorbed via the transcellular route against an uphill electrochemical gradient. The molecular identity of the gatekeeper channel that controls Mg^{2+} entry into the tubular epithelium across the brush border membrane is TRPM6.[5] Its activity is regulated by epidermal growth factor (EGF) and estrogen, but not by calcitriol or PTH.

Tubular Mg^{2+} transport is modulated by serum Mg^{2+} and Ca^{2+} and ECF volume. An increase in plasma Mg^{2+} or Ca^{2+} concentration results in impaired magnesium transport. ECF volume expansion produces a decrease in proximal tubular Mg^{2+} reabsorption, in parallel with that of Na^+ and Ca^{2+}. Dietary phosphate restriction results in marked hypercalciuria and hypermagnesuria and thus leads to overt hypomagnesemia. PTH, vasopressin, calcitonin, and glucagon increase tubular Mg^{2+} reabsorption, probably by the paracellular pathway, whereas acetylcholine, bradykinin, and atrial natriuretic peptide stimulate urinary Mg^{2+} excretion.

A number of drugs have also been shown to increase renal Mg^{2+} excretion, including the loop diuretics (furosemide, ethacrynic acid), distal diuretics (thiazides), and osmotic diuretics (mannitol, urea). Thiazide diuretics increase sodium delivery to the cortical collecting duct, dissipating the favorable electrochemical gradient for magnesium entry at this site. Thiazides also reduce TRPM6 expression in the distal convoluted tubule. Furthermore, renal Mg^{2+} wasting syndromes have been observed in patients treated with antibiotics such as gentamicin, antineoplastic agents such as cisplatin, and the calcineurin inhibitors cyclosporine and tacrolimus. The precise mechanisms of action of most of these agents are not well understood.

HYPERMAGNESEMIA

Elevated plasma Mg^{2+} is seen in patients with AKI and CKD, during the administration of pharmacologic doses of magnesium, in some infants born to mothers who received magnesium for eclampsia, and with the use of oral laxatives or rectal enemas containing magnesium (Fig. 10-23). Mild hypermagnesemia may also be present in patients with adrenal insufficiency, acromegaly, or FHH.

Clinical Manifestations

Symptoms and signs are the result of the pharmacologic effects of increased $[Mg^{2+}]$ on the nervous and cardiovascular systems. At $[Mg^{2+}]$ up to 1.5 mmol/l (3.6 mg/dl), hypermagnesemia is asymptomatic. Deep tendon reflexes are usually lost when plasma $[Mg^{2+}]$ is greater than 3 mmol/l (7.2 mg/dl). Respiratory paralysis, hypotension, abnormal cardiac conduction, and loss of consciousness may occur as plasma levels of magnesium approach 5 mmol/l (12 mg/dl).

Treatment

Treatment consists of cessation of magnesium administration and IV infusion of calcium salts, which is thought to counteract Mg blockade of calcium channels at the neuromuscular junction. For the management of symptomatic hypermagnesemia, calcium gluconate may be given, 1 g in 10 ml IV over 5 to 10 minutes (each gram calcium gluconate is approximately 90 mg elemental calcium).

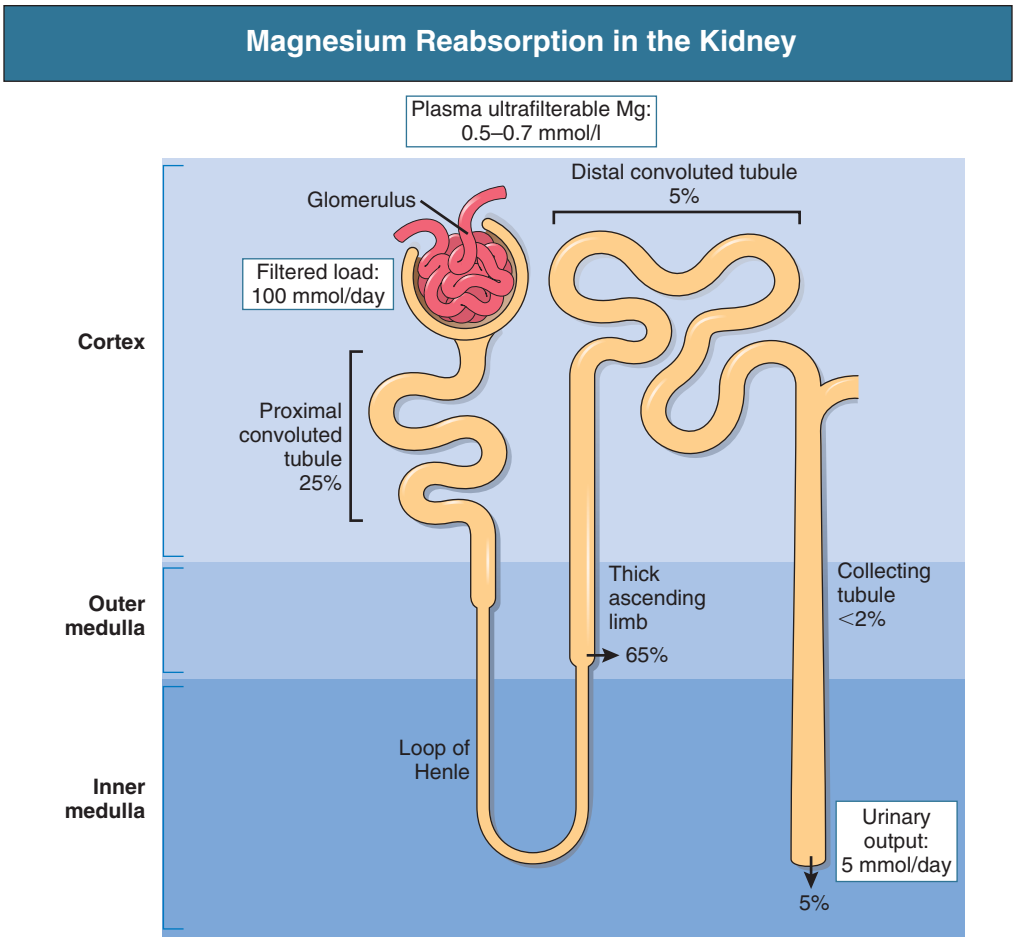


Figure 10-22 Sites of magnesium reabsorption in various segments. Percentage absorbed in various segments of the renal tubule from the glomerular ultrafiltrate. *(Redrawn from reference 35.)*

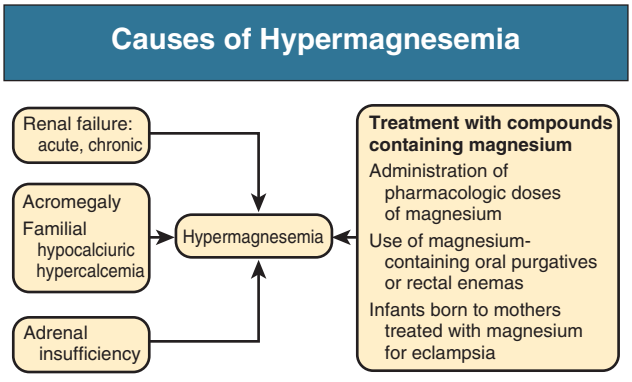


Figure 10-23 Causes of hypermagnesemia.

HYPOMAGNESEMIA AND MAGNESIUM DEFICIENCY

Magnesium deficiency is defined as a decrease in total body magnesium content. Poor dietary intake of magnesium is usually not associated with marked magnesium deficiency because of the ability of the intestine to increase Mg^{2+} absorption and the kidney to conserve Mg^{2+}. However, prolonged and severe dietary magnesium restriction of less than 0.5 mmol/day can produce symptomatic magnesium deficiency. Severe hypomagnesemia is usually associated with magnesium deficiency. About 10% of patients admitted to a large U.S. city hospital were hypomagnesemic. The incidence may be as high as 65% in medical intensive care units.

Underlying causes are usually GI diseases, in particular malabsorption syndromes such as nontropical sprue (celiac disease) and massive resection of the small intestine. Hypomagnesemia can also be induced by prolonged tube feeding without magnesium supplements and excessive use of non-magnesium-containing laxatives (Fig. 10-24).

Hypomagnesemia occurs in 25% to 35% of patients with acute pancreatitis, is frequently observed in chronic alcoholism, and can also occur in poorly controlled diabetes mellitus. Hypomagnesemia may be observed in patients with hypercalcemic disorders and primary aldosteronism, and magnesium deficiency can contribute to the metabolic syndrome.[37]

Excessive urinary loss of magnesium leads to hypomagnesemia and magnesium deficiency, even with normal dietary intake. It may result from the overzealous use of diuretics, and therefore it is important to monitor plasma Mg^{2+} levels in patients with congestive heart failure who are treated with diuretic agents. Other drugs that may cause hypomagnesemia, as previously described, include gentamicin, cisplatin, cyclosporine, and tacrolimus.

Several familial diseases are associated with hypermagnesuria, with or without hypomagnesemia. These are caused by inactivating mutations of genes whose abnormal products are responsible for

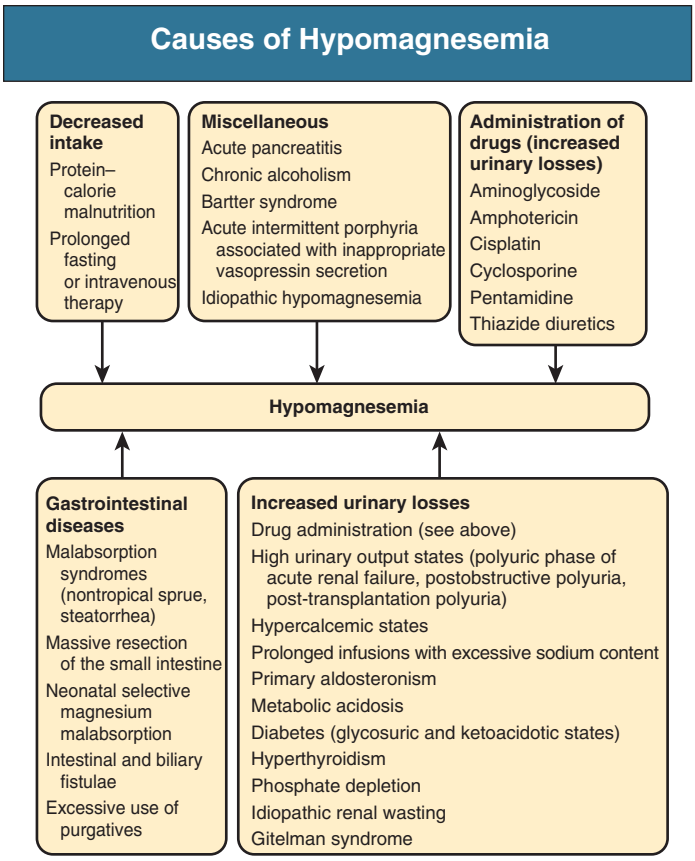


Figure 10-24 Causes of hypomagnesemia.

disturbed Mg^{2+} reabsorption in the TAL or distal nephron. Inactivating mutations of the genes of the Na^+-K^+-$2Cl^-$ cotransporter, rectifying K^+ channel (ROMK), or basolateral Cl^- channel in Bartter syndrome are responsible for the abolition of the driving force for Mg^{2+} reabsorption. This results in hypermagnesuria, which, however, is not always associated with hypomagnesemia. Inactivating mutations of the CaR_G gene, whose protein product is a key regulator of NaCl reabsorption in the TAL through extracellular $[Ca^{2+}]$, lead to hypermagnesuria and hypomagnesemia. Mutation of the claudin-16 gene reportedly induces recessive diseases characterized by hypomagnesemia, hypermagnesuria, hypercalciuria, and nephrocalcinosis. Mutations in the TRPM6 gene induce profound hypomagnesemia from impaired intestinal Mg^{2+} absorption and renal Mg^{2+} wasting, with secondary hypocalcemia.[38]

In the distal convoluted tubule, inactivating mutations of the thiazide-sensitive, electroneutral NaCl cotransporter gene (NCCT) in Gitelman syndrome are also responsible for selective renal magnesium wasting and hypomagnesemia.

Hypomagnesemia associated with inappropriate magnesuria has been reported in an autosomal-dominant, isolated familial hypomagnesemia syndrome, apparently caused by misrouting of the Na^+, K^+-ATPase γ subunit.

Clinical Manifestations

Specific clinical manifestations of hypomagnesemia may be difficult to appreciate because of concomitant hypocalcemia and hypokalemia. The main clinical manifestations of moderate to severe magnesium depletion include general weakness and neuromuscular hyperexcitability with hyperreflexia, carpopedal spasm, seizure, tremor, and rarely tetany. Cardiac findings include a prolonged QT interval and ST depression. There is a predisposition to ventricular arrhythmias and potentiation of digoxin toxicity. The role of magnesium deficiency in the clinical development of seizures and cardiac arrhythmias is demonstrated by the treatment of these conditions with magnesium. In mothers with pregnancy-related hypertension, IV magnesium was more effective than phenytoin for preventing eclamptic seizures. In patients with acute myocardial infarction and hypomagnesemia, magnesium repletion reduced the frequency of cardiac arrhythmias.

Magnesium deficiency can also be associated with hypocalcemia (decreased PTH release and end-organ responsiveness) and hypokalemia (urinary loss). In addition, intracellular K^+ is frequently decreased. Magnesium deficit constitutes a cardiovascular risk factor and also a risk factor in pregnancy for the mother and the fetus.

The diagnosis of moderate degrees of magnesium deficiency is not easy because clinical manifestations may be absent and serum Mg^{2+} levels may not reflect the state of body magnesium. Severe magnesium deficits, however, are associated with hypomagnesemia.

Treatment

Magnesium deficiency is managed with the administration of magnesium salts. Magnesium sulfate is generally used for parenteral therapy, 1500 to 3000 mg (150 to 300 mg elemental Mg) daily. A variety of magnesium salts are available for oral administration, including oxide, hydroxide, sulfate, lactate, chloride, carbonate, and pidolate. Oral magnesium salts often are not well tolerated, at least at high dosage. All may induce gastrointestinal intolerance, in particular diarrhea.

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CHAPTER 11

Normal Acid-Base Balance

Biff F. Palmer

DEFINITION

The acid-base status of the body is carefully regulated to maintain the arterial pH between 7.35 and 7.45 and the intracellular pH between 7.0 and 7.3. This regulation occurs in the setting of continuous production of acidic metabolites and is accomplished by intracellular and extracellular buffering processes in conjunction with respiratory and renal regulatory mechanisms. This chapter reviews the normal physiology of acid-base homeostasis.

NET ACID PRODUCTION

Both acid and alkali are generated from the diet. Lipid and carbohydrate metabolism results in production of carbon dioxide (CO_2), a volatile acid, at the rate of approximately 15,000 mmol/day. Protein metabolism yields amino acids, which can be metabolized to form nonvolatile acid and alkali. Amino acids such as lysine and arginine yield acid on metabolism, whereas the amino acids glutamate and aspartate as well as organic anions such as acetate and citrate generate alkali. Sulfur-containing amino acids (methionine, cysteine) are metabolized to sulfuric acid (H_2SO_4), and organophosphates are metabolized to phosphoric acid (H_3PO_4). In general, animal foods are high in proteins and organophosphates, thereby providing a net acid diet; plant foods are higher in organic anions and provide a net alkaline load. In addition to acid and alkali generated from the diet, there is a small daily production of organic acids, including acetic acid, lactic acid, and pyruvic acid. Also, a small amount of acid is generated by the excretion of alkali into the stool. Under normal circumstances, daily net nonvolatile acid production is approximately 1 millimole (mmol) of hydrogen ions (H^+) per kilogram (kg) of body weight (Fig. 11-1).

BUFFER SYSTEMS IN REGULATION OF pH

Intracellular and extracellular buffer systems minimize the change in pH during the addition of acid or base equivalents but do not remove acid or alkali from the body. The most important buffer system is that of the bicarbonate ion and carbon dioxide (HCO_3^--CO_2). In this system, carbon dioxide concentration, [CO_2], is maintained at a constant level set by respiratory control. Addition of acid (HA) leads to conversion of HCO_3^- to CO_2 according to the reaction HA + $NaHCO_3$ → NaA + H_2O + CO_2. HCO_3^- is consumed, but [CO_2] does not change because this is maintained by respiration. The net result is that the acid load has been buffered and pH changes are minimal.

Whereas the HCO_3^--CO_2 buffer system is the most important of the buffers in extracellular fluid (ECF), other buffers such as plasma proteins and phosphate ions also participate in the maintenance of a stable pH. During metabolic acidosis, the skeleton becomes a major buffer source as acid-induced dissolution of bone apatite releases alkaline Ca^{2+} salts and HCO_3^- into the ECF. With chronic metabolic acidosis, this can result in osteomalacia and osteoporosis. The calcium released can result in hypercalciuria and an increased likelihood of renal stones. Within the intracellular fluid (ICF) compartment, pH is maintained by intracellular buffers such as hemoglobin, cellular proteins, organophosphate complexes, and HCO_3^- as well as by the H^+-HCO_3^- mechanisms that transport acid and alkali in and out of the cell.

RESPIRATORY SYSTEM IN REGULATION OF pH

Removal of acid or alkali from the body is accomplished by the lungs and kidneys. The lungs regulate the CO_2 tension (P_{CO_2}), and the kidneys regulate the serum bicarbonate concentration, [HCO_3^-]. Although the HCO_3^--CO_2 buffer system is not the only buffer system, all extracellular buffer systems are in equilibrium. Because serum [HCO_3^-] is much greater than that of other buffers, changes in the HCO_3^--CO_2 buffer pair can easily titrate other buffer systems and thus set pH. The following Henderson-Hasselbalch equation explains how the lungs and kidneys function in concert:

$$pH = 6.1 + \log\left[\frac{HCO_3^-}{(0.03 \times Pa_{CO_2})}\right]$$

As can be seen, pH is determined by the ratio of HCO_3^- to CO_2. Conditions associated with similar fractional changes in [HCO_3^-] and [CO_2], such as when both are halved, will not change blood pH.

The lungs defend pH by altering alveolar ventilation, which alters the CO_2 excretion rate and thereby controls the arterial CO_2 tension (Pa_{CO_2}) of body fluids. Systemic acidosis stimulates the respiratory center, resulting in increased respiratory drive that lowers the Pa_{CO_2}. As a result, the fall in blood pH is less than would have occurred in the absence of respiratory compensation. If the fractional change in P_{CO_2} were similar to that in serum [HCO_3^-], blood pH would not change. However, respiratory compensation rarely normalizes blood pH, and thus the fractional change in P_{CO_2} is less than the change in serum [HCO_3^-]. Quantitatively, the normal respiratory response in metabolic acidosis is a 1.2 mm Hg decrease in Pa_{CO_2} for every 1 mmol/l decrease in HCO_3^-; the increase in Pa_{CO_2} in response to metabolic alkalosis averages 0.7 mm Hg for every 1 mmol/l increase in HCO_3^- above baseline.[1]

RENAL REGULATION OF pH

Buffer systems and respiratory excretion of CO_2 help maintain normal acid-base balance, but the kidneys provide a critical role in acid-base homeostasis. The kidneys normally generate sufficient net

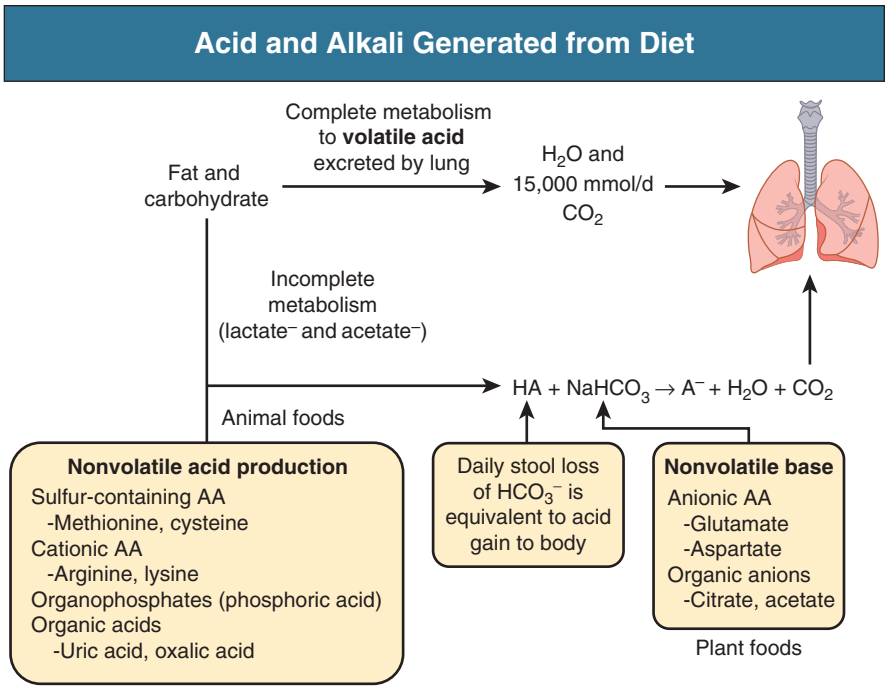

Figure 11-1 Acid and alkali generated from the diet. A nonvolatile acid is an acid produced from sources other than CO_2 and is not excreted by the lungs. Nonvolatile acids are produced from incomplete metabolism of carbohydrates, fats, and proteins and from metabolism of animal foods. Plant foods tend to produce an alkali load. *AA,* Amino acids.

acid excretion (NAE) to balance nonvolatile acid produced from normal metabolism. NAE has three components, titratable acids, ammonium (NH_4^+), and bicarbonate, and is calculated by the following formula:

$$NAE = U_{Am}V + U_{TA}V - U_{HCO_3^-}V$$

where $U_{Am}V$ is the rate of NH_4^+ excretion, $U_{TA}V$ is the rate of titratable acid excretion, and $U_{HCO_3^-}V$ is the rate of HCO_3^- excretion. Under basal conditions, approximately 40% of NAE is in the form of titratable acids and 60% is in the form of ammonia (NH_3); urinary bicarbonate concentrations and excretion are essentially zero under normal conditions. When acid production increases, the increase in acid excretion is almost entirely caused by an increase in excretion of NH_4^+.

RENAL TRANSPORT MECHANISMS OF HYDROGEN AND BICARBONATE IONS

Glomerulus

The glomerulus is not normally considered as participating in acid-base regulation. However, the glomerulus filters an amount of HCO_3^- equivalent to serum [HCO_3^-] multiplied by the glomerular filtration rate (GFR). Under normal circumstances, the filtered load of HCO_3^- averages approximately 4000 mmol/day. Normal acid-base homeostasis requires both the reabsorption of this filtered bicarbonate and the generation of "new" bicarbonate; the latter replenishes bicarbonate and other alkaline buffers consumed in the process of titrating endogenous acid production. From the standpoint of prevention of or correction of acidosis, GFR is not regulated by alterations in acid or base and therefore does not contribute to acid-base homeostasis.

Proximal Tubule

The proximal tubule reabsorbs approximately 80% of the filtered load of HCO_3^-. In addition, by titration of luminal pH from 7.4 down to approximately 6.7, the majority of phosphate, the major form of titratable acid, is titrated to its acid form. Lastly, ammonia synthesis occurs in the proximal tubule.

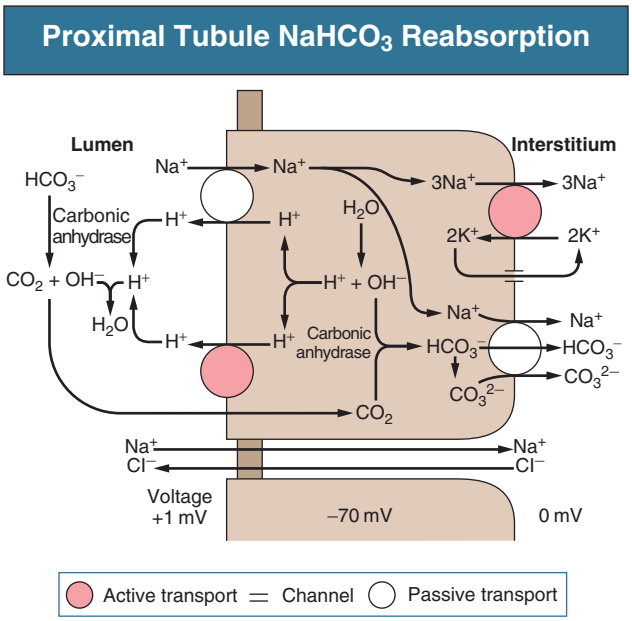

Figure 11-2 Proximal tubule sodium bicarbonate ($NaHCO_3$) reabsorption. The secretion of H^+ into the proximal tubule lumen involves a Na^+-H^+ antiporter and an H^+-ATPase. Apical membrane H^+ secretion generates OH^-, which reacts with CO_2 to form HCO_3^- and CO_3^{2-}, and these exit with a Na^+ on the basolateral membrane Na^+-HCO_3^--CO_3^{2-} cotransporter. The Na^+ absorbed by the Na^+-H^+ antiporter exits the cell on the basolateral membrane Na^+,K^+-ATPase and the Na^+-HCO_3^--CO_3^{2-} cotransporter. The K^+ that enters the cell on the Na^+,K^+-ATPase exits on a basolateral membrane K^+ channel. Carbonic anhydrase catalyzes the conversion of HCO_3^- to CO_2 and OH^- in the lumen and the reverse reaction in the cell. Electrogenic H^+ secretion generates a small, lumen-positive voltage that generates a current flow across the paracellular pathway.

Figure 11-2 shows the acid-base transport mechanisms of the proximal tubule cell. HCO_3^- absorption from the tubular lumen is mediated by H^+ secretion across the membrane.[2] This H^+ secretion

is active in that the electrochemical gradient favors H^+ movement from lumen to cell. Two mechanisms mediate active apical H^+ secretion. Approximately two thirds occurs through the apical membrane Na^+-H^+ antiporter NHE3.[3] This protein uses the inward Na^+ gradient to drive H^+ secretion. The Na^+-H^+ exchanger has a 1 : 1 stoichiometry and is electroneutral. In parallel with the Na^+-H^+ antiporter, there is an apical membrane H^+-ATPase that mediates approximately one third of basal proximal tubular HCO_3^- absorption.

Both these H^+ transporters generate base in the cell, which must exit across the basolateral membrane to effect transepithelial transport. This primarily occurs through a basolateral Na^+-HCO_3^--CO_3^{2-} cotransporter. Because this protein transports the equivalent of two net negative charges, the negative cell voltage generated by the basolateral Na^+,K^+-ATPase provides a strong favorable driving force for base efflux. The Na^+ that is carried on this transporter is moved out of the cell energy free in that ATP is not required. The Na^+-$3HCO_3^-$ cotransporter NBC1, encoded by the gene *SLC4A4,* mediates the majority of proximal tubule basolateral base exit.[4]

Carbonic anhydrase II is present in the proximal tubular cell cytoplasm, and carbonic anhydrase IV is on the apical and basolateral membranes. Carbonic anhydrase (carbonate dehydratase) has a number of functions in the proximal tubule. Apical membrane carbonic anhydrase allows secreted H^+ ions to react with luminal HCO_3^-, forming H_2CO_3, which rapidly dissociates to $CO_2 + H_2O$. This CO_2 diffuses across the apical plasma membrane into the cell. There the process is reversed, with use of cytoplasmic carbonic anhydrase, generating intracellular H^+ and HCO_3^-. This H^+ "replenishes" the H^+ secreted across the apical membrane, resulting in net movement of the HCO_3^- from the luminal solution to the cell cytoplasm. The intracellular HCO_3^- is then secreted across the basolateral plasma membrane, as described previously.

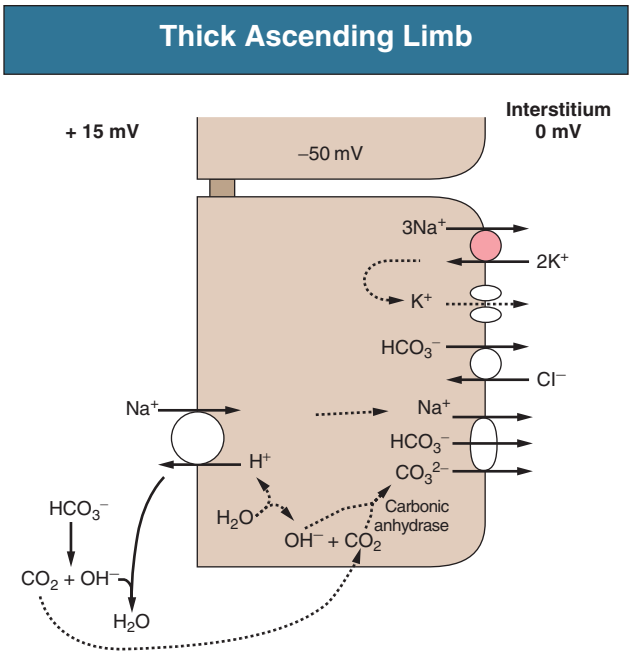

Figure 11-3 Hydrogen (H^+) and bicarbonate (HCO_3^-) ion transport in thick ascending limb. Apical H^+ secretion is mediated by a Na^+-H^+ antiporter. The low intracellular Na^+ concentration, maintained by the basolateral Na^+,K^+-ATPase, provides the primary driving force for the antiporter. Both Cl^--HCO_3^- exchange and Na^+-HCO_3^--CO_3^{2-} cotransport mediate base exit across the basolateral membrane.

Thick Ascending Limb of Henle Loop

Tubular fluid arriving at the early distal tubule has a pH and serum [HCO_3^-] similar to that in the late proximal tubule. Because there is significant water extraction in the loop of Henle, maintenance of a constant serum HCO_3^- concentration requires reabsorption of HCO_3^-. The majority of this HCO_3^- absorption occurs in the thick ascending limb (TAL) through mechanisms similar to those present in the proximal tubule (Fig. 11-3). The majority of apical membrane H^+ secretion is mediated by the Na^+-H^+ antiporter NHE3. As in the proximal tubule, the low intracellular Na^+ concentration maintained by the basolateral Na^+,K^+-ATPase provides the primary driving force for the antiporter. Base efflux across the basolateral membrane is mediated by a Cl^--HCO_3^- exchanger and a Na^+-HCO_3^--CO_3^{2-} cotransporter. These cells also possess an H^+-ATPase. The contribution of this pump to overall acidification in this segment is not clear.

Thick Distal Nephron

Approximately 80% of the filtered HCO_3^- is reabsorbed in the proximal tubule; most but not all of the remainder is absorbed in the TAL. One function of the distal nephron is to reabsorb the remaining 5% of filtered HCO_3^-. In addition, the distal nephron must secrete a quantity of H^+ equal to that generated systemically by metabolism to maintain acid-base balance.

The distal nephron is subdivided into several distinct portions that differ in their anatomy and acid secretory properties. Most of these segments transport H^+ and HCO_3^- into the luminal fluid, but the main segments appear to be in the collecting duct.[5] The segments of the collecting duct include the cortical collecting duct (CCD), the outer medullary collecting duct, and the inner medullary collecting duct. There are two distinct cell types in the CCD that can be distinguished histologically: the *principal* cell and the *intercalated* (IC) cell. The principal cell reabsorbs Na^+ and secretes K^+ and is discussed later. Depending on chronic acid-base status, the CCD is capable of either H^+ or HCO_3^- secretion. These functions are mediated by two types of IC cells: the acid-secreting α-intercalated cell and the base-secreting β-intercalated cell. Both IC cell types are rich in carbonic anhydrase II.

Reabsorption of HCO_3^- in the distal nephron is mediated by apical H^+ secretion by the α-intercalated cell. Two transporters secrete H^+: a vacuolar H^+-ATPase and an H^+,K^+-ATPase (Fig. 11-4). The vacuolar H^+-ATPase is an electrogenic pump related to the H^+ pump present within lysosomes, the Golgi apparatus, and endosomes. The H^+,K^+-ATPase uses the energy derived from adenosine triphosphate hydrolysis to secrete H^+ into the lumen and to reabsorb K^+ in an electroneutral fashion. The activity of the H^+,K^+-ATPase increases in K^+ depletion and thus provides a mechanism by which K^+ depletion enhances both collecting duct H^+ secretion and K^+ absorption.

Active H^+ secretion by the apical membrane generates intracellular base that must exit the basolateral membrane. A basolateral Cl^--HCO_3^- exchanger is the mechanism by which this base exit occurs. The Cl^- that enters the cell in exchange for HCO_3^- exits the cell through a basolateral membrane Cl^- conductance channel (Fig. 11-4).

The HCO_3^--secreting β-intercalated cell is a mirror image of the α-intercalated cell (Fig. 11-5). It possesses an H^+-ATPase on the basolateral membrane, which mediates active H^+ extrusion. Alkali that is generated within the cell then exits on an apical membrane Cl^--HCO_3^- exchanger. This Cl^--HCO_3^- exchanger is distinct from the basolateral Cl^--HCO_3^- exchanger present in the α-intercalated cell and functions as an anion exchanger or Cl^- channel in the luminal

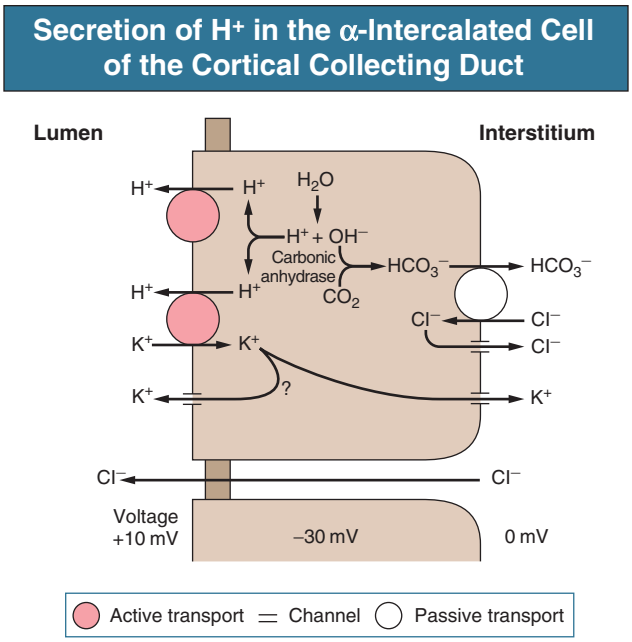

Figure 11-4 H^+ secretion in cortical collecting duct α-intercalated cell. Secretion of hydrogen ions into the lumen by an H^+-ATPase and an H^+,K^+-ATPase. Apical membrane H^+ secretion generates OH^-, which reacts with CO_2 to form HCO_3^-. This bicarbonate exits across the basolateral membrane on a Cl^--HCO3$^-$ exchanger, a member of the anion exchanger 1 (AE1) family and a truncated form of the red blood cell AE1 Cl^--HCO_3^- exchanger. The Cl^- that enters the cell on the exchanger recycles across a basolateral membrane Cl^- channel. The K^+ that enters the cell on the H^+,K^+-ATPase appears to be able either to recycle across the apical membrane or to exit across the basolateral membrane, depending on the potassium balance of the individual. Carbonic anhydrase catalyzes the conversion of CO_2 and OH^- to HCO_3^- in the cell. Electrogenic H^+ secretion generates a lumen-positive voltage that generates a current flow across the paracellular pathway.

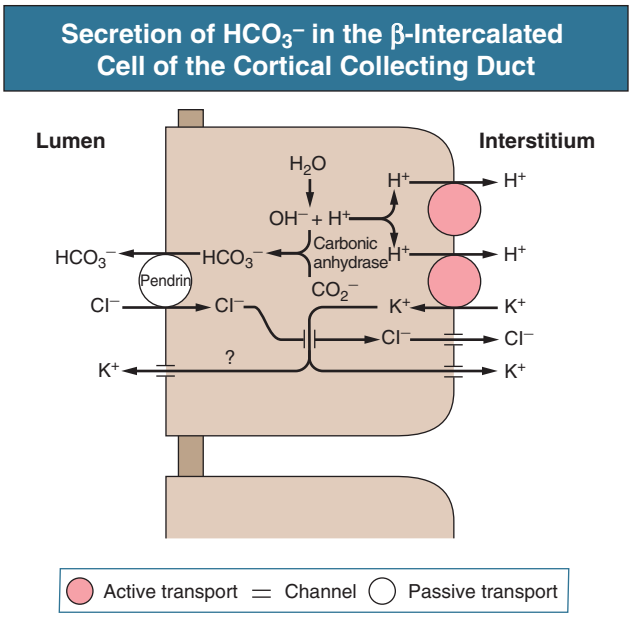

Figure 11-5 Bicarbonate secretion by cortical collecting duct β-intercalated cell. H^+ is secreted into the interstitium by an H^+-ATPase. The OH^- generated by basolateral membrane H^+ secretion reacts with CO_2 to form HCO_3^-, which exits across the apical membrane on a Cl^--HCO_3^- exchanger. The Cl^- that enters the cell on the exchanger exits across a basolateral membrane Cl^- channel. Carbonic anhydrase catalyzes the conversion of CO_2 and OH^- to HCO_3^- in the cell.

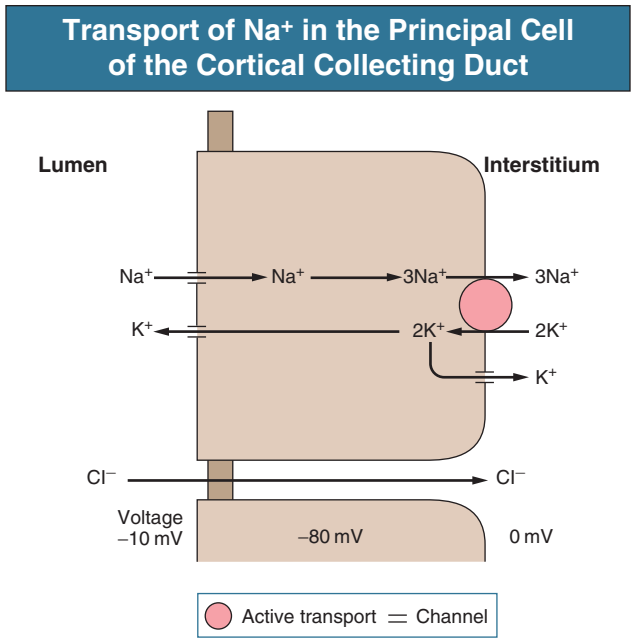

Figure 11-6 Sodium transport in cortical collecting duct principal cell. Electrogenic Na^+ absorption is mediated by an Na^+ channel. The Na^+ enters the cell across the apical membrane channel and exits the cell on the basolateral membrane Na^+,K^+-ATPase. The K^+ that enters the cell on the basolateral Na^+,K^+-ATPase can be secreted into the luminal fluid by an apical membrane K^+ channel. Electrogenic Na^+ absorption establishes a lumen-negative voltage that drives a paracellular current.

membrane of epithelial cells.[6] The SLC26A4 protein (pendrin) is a family member that mediates apical Cl^--HCO_3^- exchange in the β-intercalated cell of the kidney.

The other cortical collecting tubule cell type is the principal cell, which also regulates acid-base transport, although indirectly. Principal cells mediate electrogenic Na^+ reabsorption that results in a net negative luminal charge (Fig. 11-6). The greater this negative charge, the lesser is the electrochemical gradient for electrogenic proton secretion, and therefore the greater the rate of net proton secretion. Thus, factors that stimulate Na^+ reabsorption indirectly regulate the H^+ secretory rate.

The medullary collecting duct possesses mechanisms only for H^+ secretion. This H^+ secretion is mediated by α-intercalated cells but also by cells that appear morphologically distinct from IC cells but are functionally similar.

Net Acid Excretion

For the kidney to generate NAE, it must both reabsorb filtered HCO_3^- and excrete titratable acids and ammonia. Several weak acids, such as phosphate, creatinine, and uric acid, are filtered at the glomerulus and can buffer secreted protons. Of these, phosphate is the most important because of its favorable pK_a of 6.80 and its relatively high rate of urinary excretion (~25 to 30 mmol/day). However, the capacity of phosphate to buffer protons is maximized at a urine pH of 5.8, and acid-base disturbances do not, in general, induce substantial changes in urinary phosphate excretion. Other titratable acids, such as creatinine and uric acid, are limited by their lower excretion rate, which is not dramatically changed in response to acid-base disturbances. Titratable acid excretion is a minor component of the increase in NAE in response to metabolic acidosis (Fig. 11-7).

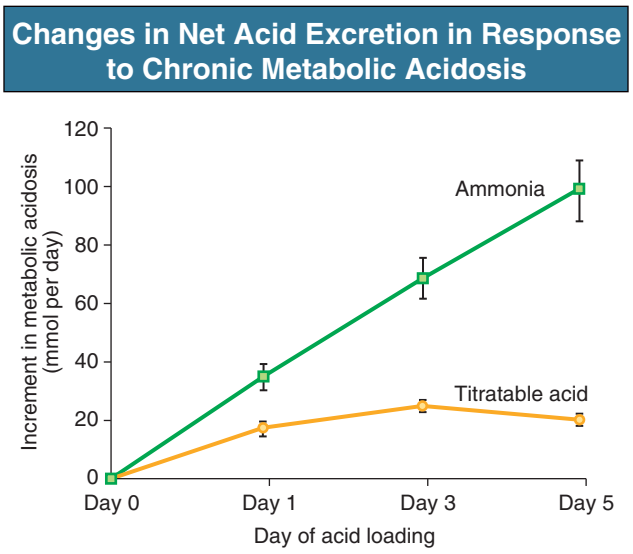

Figure 11-7 Changes in net acid excretion. Chronic metabolic acidosis increases net acid excretion dramatically during several days; shown quantitatively are the increases in the two major components of net acid excretion, titratable acids and ammonia. Titratable acid excretion increases slightly and predominantly in the first 24 to 48 hours. In contrast, urinary ammonia excretion progressively increases over 7 days and is responsible for most of the increase in net acid excretion in chronic metabolic acidosis. *(Plotted data redrawn from original data in reference 10.)*

Ammonia Metabolism

Quantitatively, the most important component of NAE is the NH_3/NH_4^+ system.[7] Unlike for titratable acids, the rate of ammonia (NH_3) production and excretion varies according to physiologic needs. Under normal circumstances, ammonia excretion accounts for approximately 60% of total NAE, and in chronic metabolic acidosis, almost the entire increase in NAE is caused by increased NH_3 metabolism. Ammonia metabolism involves an interplay among the proximal tubule, TAL, and collecting duct.

The proximal tubule is responsible for both ammonia production and luminal secretion. Ammonia is synthesized in the proximal tubule predominantly from glutamine metabolism through enzymatic processes in which phosphoenolpyruvate carboxykinase and phosphate-dependent glutaminase are the rate-limiting steps. This results in production of two ammonium (NH_4^+) and two HCO_3^- ions from each glutamine ion. Ammonia is then preferentially secreted into the lumen. The primary mechanism for this luminal secretion appears to be NH_4^+ transport by the apical Na^+-H^+ antiporter NHE3 (Fig. 11-8).

Metabolic acidosis increases the mobilization of glutamine from skeletal muscle and intestinal cells. Glutamine is preferentially taken up by the proximal tubular cell through the Na^+- and H^+-dependent glutamine transporter SNAT3. This transporter is a member of the *SCL38* gene family of Na^+-coupled neutral amino acid transporters. SNAT3 expression increases several-fold in metabolic acidosis, and

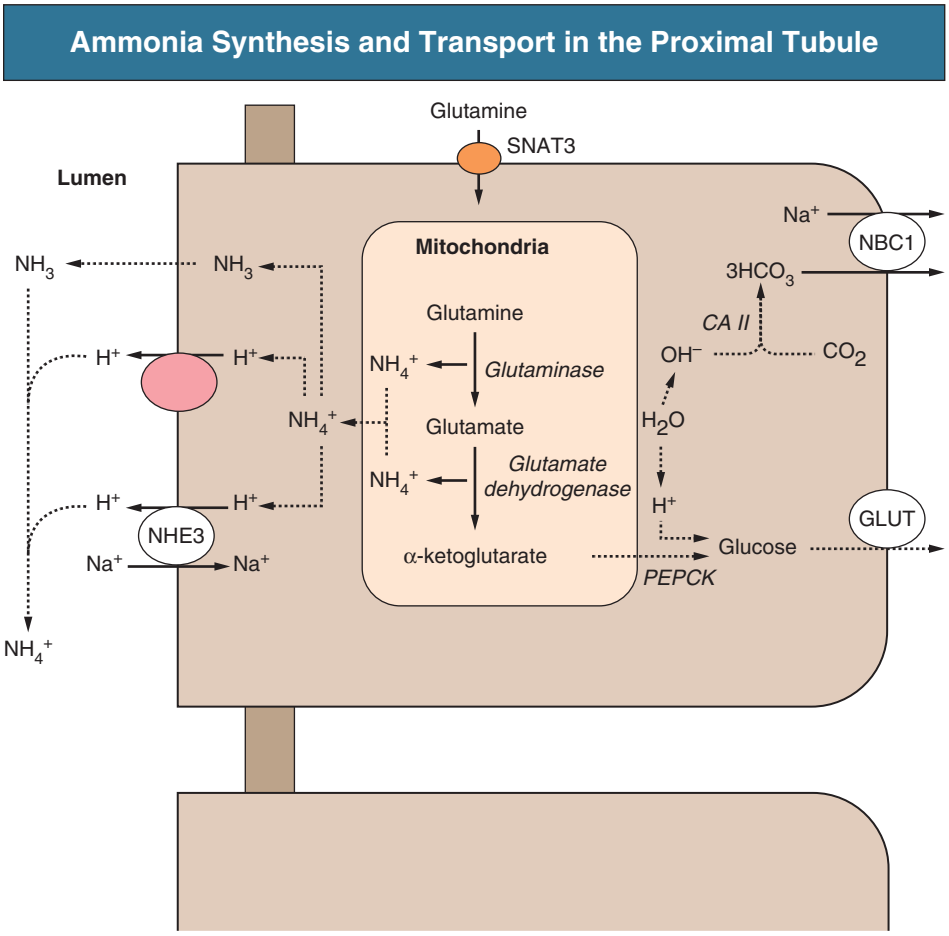

Figure 11-8 Ammonia synthesis and transport in proximal tubule. Metabolic acidosis and hypokalemia stimulate proximal ammonia synthesis by stimulating the uptake of glutamine through SNAT3.The generation of ammonia is the result of glutamine metabolism by enzymes closely linked to gluconeogenesis.

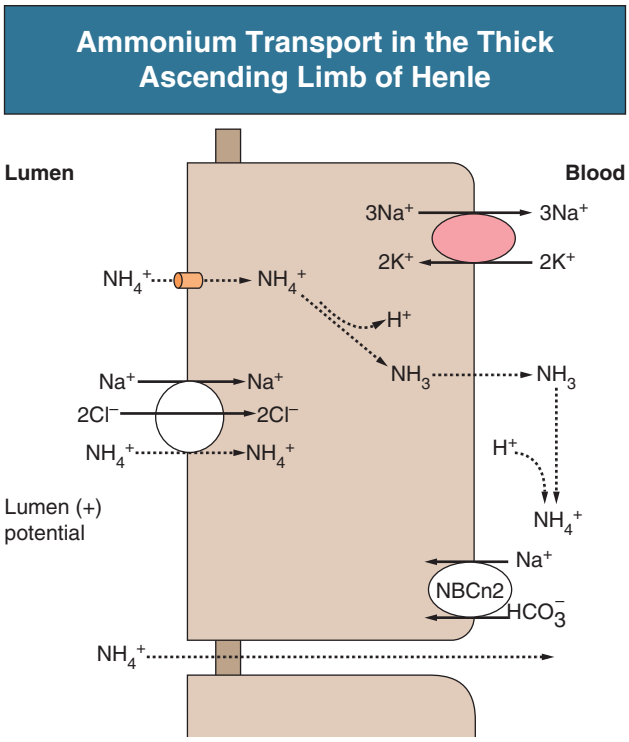

Figure 11-9 Ammonia transport in thick ascending limb of Henle loop. In addition to reabsorption through the paracellular pathway driven by the lumen-positive potential, ammonium can substitute for K^+ on the Na^+-K^+-$2Cl^-$ transporter and the apical membrane K^+ channel (ROMK). The basolateral Na^+-HCO_3^- cotransporter (NBCn2) is thought to play a housekeeping role to maintain cell pH given the large transcellular ammonium flux.

it is preferentially expressed on the cell's basolateral surface, where it is poised for glutamine uptake.[8] The increase in plasma cortisol that typically accompanies metabolic acidosis plays a role in this transporter's upregulation.[9] Metabolic acidosis also causes increased expression and activity of phosphate-activated glutaminase and glutamate dehydrogenase.

Most of the ammonia that leaves the proximal tubule does not return to the distal tubule. Thus, there is transport of ammonia out of the loop of Henle. This ammonia transport appears to occur predominantly in the TAL and is mediated by at least three mechanisms (Fig. 11-9). First, the lumen-positive voltage provides a driving force for passive paracellular NH_4^+ transport out of the TAL. Second, NH_4^+ can be transported out of the lumen by the furosemide-sensitive Na^+-K^+-$2Cl^-$ transporter. Third, NH_4^+ can leave the lumen across the apical membrane K^+ channel of the TAL cell. How NH_4^+ would then leave the cell across the basolateral membrane is largely unknown.

In addition, ammonia is secreted by the collecting duct. Although the traditional thought was that NH_3/NH_4^+ then enters the collecting duct by nonionic diffusion driven by the acid luminal pH, increasing evidence suggests that the nonerythroid glycoproteins Rhbg and Rhcg may be involved in collecting duct ammonia secretion.[11,12]

On the basis of the preceding discussion, ammonia excretion can be regulated by three mechanisms. First, ammonia synthesis in the proximal tubule can be regulated. Chronic acidosis and hypokalemia increase ammonia synthesis, whereas hyperkalemia suppresses ammonia synthesis. Second, ammonia delivery from the proximal tubule to the medullary interstitium can be regulated. In particular, chronic metabolic acidosis increases expression of both NHE3 and the loop of Henle Na^+-K^+-$2Cl^-$ cotransporter. Hyperkalemia can inhibit NH_4^+ reabsorption from the TAL. This may explain the low urinary $[NH_4^+]$ found in hyperkalemic distal renal tubular acidosis (in addition to decreased NH_3 synthesis by hyperkalemia). Also, any interstitial renal disease that destroys renal medullary anatomy may decrease medullary interstitial $[NH_3/NH_4^+]$. Third, mechanisms that regulate collecting duct H^+ secretion or ammonia transporter expression can regulate ammonia entry into the collecting duct and ammonia excretion. Importantly, the primary mechanisms require synthesis of new proteins to increase both ammonia production and transport. Accordingly, changes in ammonia excretion may be delayed, and the maximal renal response to chronic metabolic acidosis requires 4 to 7 days.

REGULATION OF RENAL ACIDIFICATION

The regulation of acid-base balance requires an integrated system that precisely regulates proximal tubular H^+-HCO_3^- transport, distal nephron H^+-HCO_3^- transport, and ammonia synthesis and transport.

Blood pH

The regulation of acid-base balance requires that net H^+ excretion increase in states of acidosis and decrease in states of alkalosis. This form of regulation involves both acute and chronic mechanisms. In the proximal tubule, acute decreases in blood pH increase the rate of HCO_3^- absorption, and acute increases in blood pH inhibit HCO_3^- absorption. These alterations in the rate of HCO_3^- absorption occur whether the change in pH is the result of changes in P_{CO_2} or serum $[HCO_3^-]$. Similarly, in the collecting duct, acute changes in peritubular serum $[HCO_3^-]$ and pH regulate the rate of H^+ secretion.

In addition to acute regulation, mechanisms exist for chronic regulation. Chronic acidosis or alkalosis leads to parallel changes in the activities of the proximal tubule apical membrane Na^+-H^+ antiporter and basolateral membrane Na^+-HCO_3^--CO_3^{2-} cotransporter. Metabolic acidosis acutely increases the kinetic activity of NHE3 through direct pH effects and by phosphorylation; chronic acidosis increases the number of NHE3 transporters.[13,14] In addition, chronic acidosis increases proximal tubular ammonia synthesis by increasing the activities of the enzymes involved in ammonia metabolism.

The CCD is also modified by chronic acid-base changes. Long-term increases in dietary acid lead to an increase in H^+ secretion, whereas long-term increases in dietary alkali lead to an increased capacity for HCO_3^- secretion.[15] This effect is mediated by changes in the relative number of α- and β-intercalated cells. For example, during metabolic acidosis, the number of α-intercalated cells increases while the number of β-intercalated cells decreases, without a change in the total number of IC cells. Recent evidence suggests that the extracellular protein hensin may be involved in the switch between the predominant IC cell types.[16]

Mineralocorticoids, Distal Sodium Delivery, and Extracellular Fluid Volume

Mineralocorticoid hormones are key regulators of distal nephron and collecting duct H^+ secretion. Two mechanisms appear to be involved. First, mineralocorticoid hormone stimulates Na^+ absorption in principal cells of the CCD (see Fig. 11-6). This leads to a more lumen-negative voltage that then stimulates H^+ secretion. This mechanism is indirect in that it requires the presence of Na^+ and of Na^+ transport. The second mechanism is the direct activation of H^+ secretion by mineralocorticoids. This effect is chronic, requiring long

exposure, and involves parallel increases in apical membrane H^+-ATPase and basolateral membrane Cl^--HCO_3^- exchanger activity.

Plasma Volume

Changes in plasma volume have important effects on acid-base homeostasis. This effect appears to be related to a number of factors. First, volume contraction is associated with a decreased GFR, which lowers the filtered load of HCO_3^- and decreases the load placed on the tubules, to maintain NAE. Volume contraction also acutely decreases the paracellular permeability of the proximal tubule. This will decrease HCO_3^- backleak around cells, thereby increasing net bicarbonate reabsorption by the proximal tubule. Third, chronic volume contraction is associated with an adaptive increase in the activity of the proximal tubule apical membrane Na^+-H^+ antiporter NHE3. Because this transporter contributes to both $NaHCO_3$ and NaCl absorption, both these capacities will be increased with chronic volume contraction. Further, volume contraction limits distal delivery of chloride. In the presence of chronic metabolic alkalosis, the CCD is poised for HCO_3^- secretion. However, collecting duct HCO_3^- secretion requires luminal Cl^- and is inhibited by Cl^- deficiency.

Potassium

Potassium deficiency is associated with an increase in renal NAE. This effect is multifactorial. First, chronic K^+ deficiency increases the proximal tubule apical membrane Na^+-H^+ antiporter and basolateral membrane Na^+-HCO_3^--CO_3^{2-} cotransporter activities. This effect is similar to that seen with chronic acidosis and may be caused by intracellular acidosis. Chronic K^+ deficiency also increases proximal tubular ammonia production. Last, chronic K^+ deficiency leads to an increase in collecting duct H^+ secretion. This appears to be related to increased activity of the apical membrane H^+,K^+-ATPase. Such an effect increases the rate of H^+ secretion and the rate of K^+ reabsorption in the collecting duct. In addition, ammonia, whose production is stimulated by hypokalemia, has direct effects that stimulate collecting duct H^+ secretion. Counterbalancing these effects is that K^+ deficiency decreases aldosterone secretion, which can inhibit distal acidification. Thus, in normal individuals, the net effect of K^+ deficiency is typically a minor change in acid-base balance. However, in patients with nonsuppressible mineralocorticoid secretion (e.g., hyperaldosteronism, Cushing syndrome), K^+ deficiency can greatly stimulate renal acidification and cause profound metabolic alkalosis.

Hyperkalemia appears to have opposite effects on renal acidification. The most notable effect of hyperkalemia is inhibition of ammonia synthesis in the proximal tubule and ammonia absorption in Henle loop, resulting in inappropriately low levels of urinary ammonia excretion. This contributes to the metabolic acidosis seen in patients with hyperkalemic distal (type 4) renal tubular acidosis.

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CHAPTER 12

Metabolic Acidosis

Biff F. Palmer

DEFINITION

Metabolic acidosis is defined as a low arterial blood pH in conjunction with a reduced serum bicarbonate concentration, [HCO_3^-]. Respiratory compensation results in a decrease in arterial carbon dioxide tension ($Paco_2$). A low serum [HCO_3^-] alone is not diagnostic of metabolic acidosis because it also results from the renal compensation to chronic respiratory alkalosis. Measurement of the arterial pH differentiates between these two possibilities. Box 12-1 shows the expected compensatory responses for metabolic and respiratory acid-base disorders.[1]

After the diagnosis of metabolic acidosis is confirmed, the first step in the examination of the patient is to calculate the serum anion gap. The *anion gap* equals the difference between the plasma concentrations of the major cation, sodium ([Na^+]), and the major measured anions, chloride and bicarbonate ([Cl^-] and [HCO_3^-]), and is given by the following formula:

$$\text{Anion gap} = [Na^+] - ([Cl^-] + [HCO_3^-])$$

In healthy individuals, the normal value of the anion gap is approximately 12 ± 2 mmol/l. Because many of the unmeasured anions consist of albumin, the normal anion gap is decreased by approximately 4 mmol/l for each 1 g/dl decrease in the serum albumin concentration below normal. The total number of cations must equal the total number of anions, so a decrease in the serum HCO_3^- concentration must be offset by an increase in the concentration of other anions. If the anion accompanying excess H^+ is Cl^-, the decrease in serum [HCO_3^-] is matched by an equal increase in serum [Cl^-]. This acidosis is classified as a "normal anion gap" or a "non–anion gap" or a hyperchloremic metabolic acidosis. By contrast, if excess H^+ is accompanied by an anion other than Cl^-, the decreased [HCO_3^-] is balanced by an increase in the concentration of the unmeasured anion. [Cl^-] remains the same. In this setting, the acidosis is said to be a "high anion gap" or "anion gap" metabolic acidosis.

The normal value for the anion gap has tended to fall over time because of changes in how serum Na^+ and Cl^- are measured.[2] Flame photometry for Na^+ measurement and a colorimetric assay for Cl^- have been replaced by the use of ion-selective electrodes, with which the serum Na^+ values have largely remained the same, whereas the serum Cl^- values have tended to be higher. As a result, the normal value for the anion gap has decreased to as low as 6 mmol/l in some reports. Recognizing this change, some laboratories have adjusted the calibration set point for Cl^- to return the normal value for the anion gap to the 12 ± 2 mmol/l range. The clinician needs to be aware that the average anion gap and range of normal values will vary in different facilities.

Figure 12-1 provides a recommended approach to a patient with metabolic acidosis and lists the common causes of metabolic acidosis according to the anion gap.

NON–ANION GAP (NORMAL ANION GAP) METABOLIC ACIDOSIS

A non–anion gap metabolic acidosis can result from either renal or extrarenal causes. Renal causes of metabolic acidosis occur when renal bicarbonate generation, which results from net acid excretion, does not balance the loss of bicarbonate and other alkali buffers consumed in the buffering of normal endogenous acid production. This failure of net acid excretion is termed *renal tubular acidosis* (RTA). Extrarenal causes occur when exogenous acid loads, endogenous acid production, or endogenous bicarbonate losses are elevated and exceed renal net acid excretion. The most common extrarenal cause of non–anion gap metabolic acidosis is chronic diarrhea.

Renal and extrarenal causes of metabolic acidosis can be distinguished by measuring urinary ammonia excretion.[3] The primary response of the kidney to metabolic acidosis is to increase urinary ammonia excretion, each millimole of urinary ammonia excreted resulting in the generation of 1 mmol of "new" bicarbonate. Thus, renal causes of metabolic acidosis are characterized by low urinary ammonia excretion rates. In contrast, in extrarenal metabolic acidosis, urinary ammonia excretion is elevated. Because most laboratories do not measure urinary ammonia, one can indirectly assess ammonia excretion by measuring the *urinary anion gap* (UAG):

$$\text{UAG} = (U_{Na^+} + U_{K^+}) - U_{Cl^-}$$

The UAG is normally a positive value, ranging from +30 to +50 mmol/l. A negative value for the UAG suggests increased renal excretion of an unmeasured cation (i.e., cation other than Na^+ or K^+). One such cation is NH_4^+. With chronic metabolic acidosis due to extrarenal causes, urinary ammonia concentrations, in the form of NH_4Cl, can reach 200 to 300 mmol/l. As a result, the measured cation concentration will be less than the measured anion concentration, which includes the increased urinary Cl^-, and the UAG will be less than zero and frequently less than −20 mmol/l.

The UAG only indirectly reflects the urinary ammonia concentration and, if other unmeasured ions are excreted, can give misleading results. Examples include diabetic ketoacidosis, associated with substantial urinary excretion of sodium keto acid salts, and toluene exposure (discussed later), associated with increased urinary excretion of sodium hippurate and sodium benzoate. In these settings, the UAG value may remain positive despite an appropriate increase in urinary ammonia excretion because of the increased urinary excretion of Na^+ acid-anion salts. In most patients, these conditions are associated with an elevated–anion gap metabolic acidosis, not a non–anion gap metabolic acidosis, and thus are easily distinguishable from diarrhea-induced metabolic acidosis.

Urine pH, in contrast to the UAG, does not reliably differentiate acidosis of renal origin from that of extrarenal origin. For example, an acid urine pH does not necessarily indicate an appropriate

Compensation in Acid-Base Disorders

Acute respiratory acidosis
For every 10 mm Hg rise in P_{CO_2}, HCO_3^- increases by 1 mmol/l

Chronic respiratory acidosis
For every 10 mm Hg rise in P_{CO_2}, HCO_3^- increases by 3.5 mmol/l

Acute respiratory alkalosis
For every 10 mm Hg fall in P_{CO_2}, HCO_3^- decreases by 2 mmol/l

Chronic respiratory alkalosis
For every 10 mm Hg decrease in P_{CO_2}, HCO_3^- decreases by 5 mmol/l

Metabolic acidosis
1.2 mm Hg decrease in P_{CO_2} for each 1 mmol/l fall in HCO_3^-
$P_{CO_2} = HCO_3^- + 15$
P_{CO_2} = last digits of pH

Metabolic alkalosis
P_{CO_2} increases by 0.7 for each mmol/l HCO_3^-

Box 12-1 Expected compensatory responses to acid-base disorders. *P_{CO_2}*, Carbon dioxide tension; *HCO_3^-*, bicarbonate ions.

increase in net acid excretion. If renal ammonia metabolism is inhibited, as occurs with chronic hyperkalemia, there is decreased ammonia available in the distal nephron to serve as a buffer, and small amounts of distal H^+ secretion can lead to a significant urine acidification. In this setting, the urine pH is acid, but net acid excretion is low because of the low ammonia excretion. Similarly, alkaline urine does not necessarily imply a renal acidification defect. In conditions in which ammonia metabolism is stimulated, distal H^+ secretion can be massive and yet the urine remains relatively alkaline because of the buffering effects of ammonia.

Metabolic Acidosis of Renal Origin

An overall approach to patient assessment for workup of metabolic acidosis of renal origin is shown in Figure 12-2.

Proximal Renal Tubular Acidosis (Type 2)

Normally, 80% to 90% of the filtered load of HCO_3^- is reabsorbed in the proximal tubule. In proximal (type 2) RTA, the proximal tubule has a decreased capacity to reabsorb filtered bicarbonate. When serum bicarbonate concentration is normal or nearly normal, the amount of bicarbonate filtered by the glomerulus exceeds proximal tubule bicarbonate reabsorptive capacity. When this happens, there is increased bicarbonate delivery to the loop of Henle and distal nephron that exceeds their capacity to reabsorb bicarbonate. As a result, some filtered bicarbonate appears in the urine. The net effect is that serum [HCO_3^-] decreases. Eventually, the filtered bicarbonate load decreases to the point at which the proximal tubule is able to reabsorb sufficient filtered bicarbonate that the bicarbonate load to Henle loop and the distal nephron is within their reabsorptive capacity. When this occurs, no further bicarbonate is lost in the urine, net acid excretion normalizes, and a new steady-state serum [HCO_3^-] develops, although at a lower-than-normal level.

Hypokalemia is present in proximal RTA. Renal $NaHCO_3$ losses lead to intravascular volume depletion, which in turn activates the renin-angiotensin-aldosterone system. Distal Na^+ delivery is increased as a result of the impaired proximal reabsorption of $NaHCO_3$. Because of the associated hyperaldosteronism and increased distal nephron Na^+ reabsorption, there is increased K^+ secretion. The net result is renal potassium wasting and the development of hypokalemia. In the steady state, when virtually all the filtered HCO_3^- is reabsorbed in the proximal and distal nephron, renal potassium wasting is less, and the degree of hypokalemia tends to be mild.

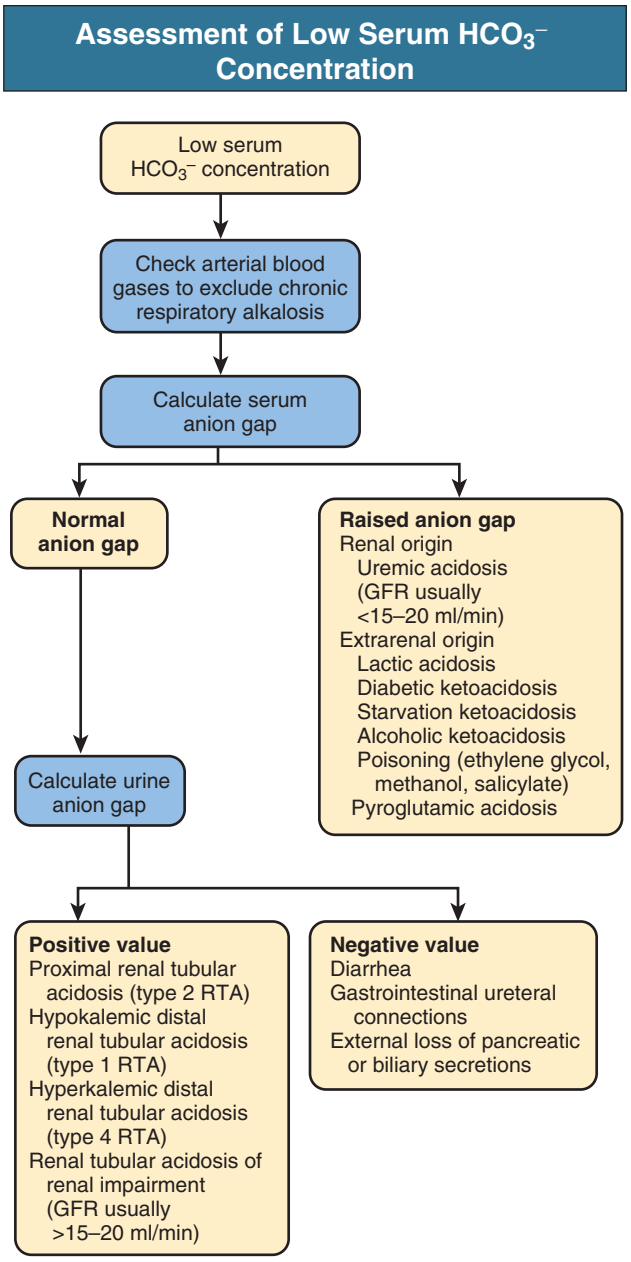

Figure 12-1 Approach to the patient with low serum HCO_3^- concentration.

Proximal RTA may occur as an isolated defect in acidification, but type 2 typically occurs in the setting of widespread proximal tubule dysfunction (Fanconi syndrome). In addition to decreased HCO_3^- reabsorption, patients with Fanconi syndrome have impaired reabsorption of glucose, phosphate, uric acid, amino acids, and low-molecular-weight proteins. Various inherited and acquired disorders have been associated with the development of Fanconi syndrome and proximal RTA (Box 12-2). The most common inherited cause in children is cystinosis (see Chapter 50). Most adults with Fanconi syndrome have an acquired condition that is related to an underlying dysproteinemic condition, such as multiple myeloma.

Skeletal abnormalities are common in these patients. Osteomalacia can develop from chronic hypophosphatemia caused by

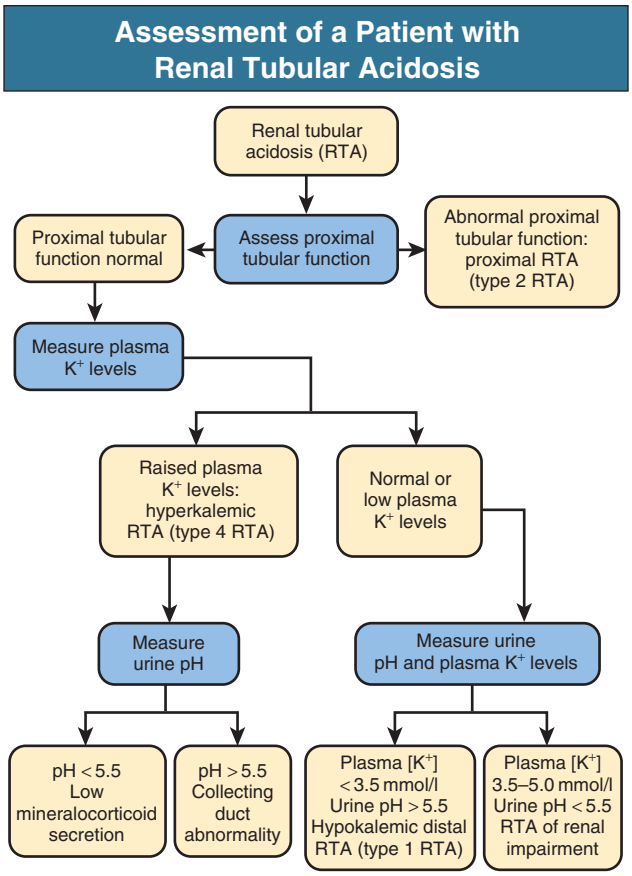

Figure 12-2 **Approach to the patient with renal tubular acidosis.**

renal phosphate wasting if Fanconi syndrome is present. These patients may also have a deficiency in the active form of vitamin D because of an inability to convert 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D in the proximal tubule.

In contrast to distal RTA, proximal RTA is not associated with nephrolithiasis or nephrocalcinosis. One exception is the use of topiramate,[4,5] an antiepileptic drug that is increasingly used to treat a variety of neurologic and metabolic disorders. The drug exerts an inhibitory effect on renal carbonic anhydrase activity, resulting in a proximal acidification defect similar to that observed with acetazolamide. Topiramate also is associated with hypocitraturia, hypercalciuria, and elevated urine pH, leading to an increased risk of kidney stone disease.

Proximal RTA should be suspected in a patient with a normal anion gap acidosis and hypokalemia who has an intact ability to acidify the urine to below 5.5 while in a steady state.[6] Proximal tubular dysfunction, such as euglycemic glycosuria, hypophosphatemia, hypouricemia, and mild proteinuria, helps support this diagnosis. The UAG is greater than zero, indicating the lack of increase in net acid excretion.

Treatment of proximal RTA is difficult. Administration of alkali increases serum [HCO_3^-], which increases urinary bicarbonate losses and thereby minimizes subsequent increases in the serum [HCO_3^-]. Moreover, the increased distal sodium load, in combination with increased circulating plasma aldosterone, results in increased renal potassium wasting and worsening hypokalemia. As a result, substantial amounts of alkali, often in the form of a potassium salt, such as potassium citrate, are required to prevent worsening hypokalemia. Children with proximal RTA should be aggressively treated to normalize their serum [HCO_3^-] to minimize growth retardation. These children may require large amounts of alkali therapy, typically 5 to 15 mmol/kg/day.

Adults with proximal RTA are frequently not treated as aggressively as children are because of the lack of systemic metabolic abnormalities or bone disease. Many clinicians administer alkali therapy if serum [HCO_3^-] is less than 18 mmol/l to prevent severe acidosis. Whether more aggressive therapy to normalize serum [HCO_3^-] is beneficial remains unknown. However, the large amounts

Causes of Type 2 Renal Tubular Acidosis

Not Associated with Fanconi Syndrome

Sporadic

Familial

Disorder of Carbonic Anhydrase

Drugs: acetazolamide, sulfanilamide, topiramate

Carbonic anhydrase II deficiency

Associated with Fanconi Syndrome

Selective (no systemic disease present)

Sporadic

Familial

Autosomal recessive proximal RTA with ocular abnormalities: Na^+-HCO_3^- cotransporter (NBCe1) defect

Autosomal recessive proximal RTA with osteopetrosis and cerebral calcification: carbonic anhydrase II defect

Generalized (systemic disorder present)

Genetic disorders

- Cystinosis
- Wilson disease
- Hereditary fructose intolerance
- Lowe syndrome
- Metachromatic leukodystrophy

Dysproteinemic States

Myeloma kidney

Light-chain deposition disease

Hyperparathyroidism

Primary

Secondary

Drugs and Toxins

Outdated tetracycline

Ifosfamide

Gentamicin

Streptozocin

Lead

Cadmium

Mercury

Tubulointerstitial Disease

Post-transplantation rejection

Balkan nephropathy

Medullary cystic disease

Others

Bone fibroma

Osteopetrosis

Paroxysmal nocturnal hemoglobinuria

Box 12-2 **Causes of proximal (type 2) renal tubular acidosis (RTA).**

of alkali required, about 700 to 1000 mmol/day for a 70-kg individual, make this approach problematic.

Hypokalemic Distal Renal Tubular Acidosis (Type 1)

In contrast to proximal RTA, patients with distal RTA are unable to acidify their urine, either under basal conditions or in response to metabolic acidosis.[7,8] Type 1 RTA results from a reduction in net H^+ secretion in the distal nephron, which leads to continued urinary bicarbonate losses and prevents urinary acidification, thereby minimizing titratable acid excretion and urinary ammonia excretion. As a result, these patients are unable to match net acid excretion to endogenous acid production, and acid accumulation ensues. The subsequent metabolic acidosis stimulates reabsorption of bone matrix to release the calcium alkali salts present in bone. During prolonged periods, this can result in progressive osteopenia in adults and in osteomalacia in children.

Distal RTA can be caused by either impaired H^+ secretion (secretory defect) or an abnormally permeable distal tubule, resulting in increased backleak of normally secreted H^+ (gradient defect); it may be genetic or acquired. Certain medications, especially amphotericin, result in increased backleak of protons across the apical plasma membrane, leading to a gradient defect form of distal RTA.

For patients with a secretory defect, the inability to acidify the urine below pH 5.5 results from abnormalities in any of the proteins involved in collecting duct H^+ secretion. Some patients may have an isolated defect in the H^+,K^+-ATPase that impairs H^+ secretion and K^+ reabsorption.[9] A defect confined to the vacuolar H^+-ATPase also results in renal potassium wasting.[10] The development of systemic acidosis tends to diminish net proximal fluid reabsorption with an increase in distal delivery, resulting in volume contraction and activation of the renin-aldosterone system (RAS). Increased distal Na^+ delivery coupled to increased circulating levels of aldosterone then leads to increased renal K^+ secretion. Defects in the basolateral anion exchanger (AE1) can also cause distal RTA. In this case, the lack of basolateral HCO_3^- exit leads to intracellular alkalinization, which inhibits apical proton secretion.

Patients with distal RTA have low ammonia secretion rates. The decreased secretion is caused by the failure to trap ammonia in the tubular lumen of the collecting duct as a result of the inability to lower luminal fluid pH. In addition, there is often impaired medullary transfer of ammonia because of interstitial disease. Interstitial disease is frequently present in such patients through an associated underlying disease or as a result of nephrocalcinosis or hypokalemia-induced interstitial fibrosis.

In contrast to proximal RTA, nephrolithiasis and nephrocalcinosis are common.[11] Urinary Ca^{2+} excretion is high secondary to acidosis-induced bone mineral dissolution. Luminal alkalinization also inhibits calcium reabsorption, resulting in further increases in urinary calcium excretion.[12] Calcium phosphate solubility is also greatly lowered at alkaline pH, and calcium phosphate stone formation is accelerated. Stone formation is further enhanced as a result of low urinary citrate excretion. Citrate is metabolized to HCO_3^-, and its renal reabsorption is stimulated by metabolic acidosis, thereby minimizing the severity of metabolic acidosis. Urinary citrate also chelates urinary calcium, decreasing ionized calcium concentrations. Accordingly, the decreased citrate excretion that occurs in chronic metabolic acidosis due to distal RTA further contributes to both nephrolithiasis and nephrocalcinosis.

Distal RTA may be a primary disorder, either idiopathic or inherited, but it most often occurs in association with a systemic disease, one of the most common of which is Sjögren syndrome (Box 12-3). Hypergammaglobulinemic states as well as drugs and toxins may also cause this disorder.

Causes of Type 1 Renal Tubular Acidosis

Primary
Idiopathic
Familial

Secondary
Autoimmune Disorders
Hypergammaglobulinemia
Sjögren syndrome
Primary biliary cirrhosis
Systemic lupus erythematosus

Genetic Diseases
Autosomal dominant RTA: anion exchanger 1 defect
Autosomal recessive RTA: H^+-ATPase A4 subunit
Autosomal recessive with progressive nerve deafness: H^+-ATPase B1 subunit

Drugs and Toxins
Amphotericin B
Toluene

Disorders with Nephrocalcinosis
Hyperparathyroidism
Vitamin D intoxication
Idiopathic hypercalciuria

Tubulointerstitial Disease
Obstructive uropathy
Renal transplantation

Box 12-3 Causes of hypokalemic distal (type 1) renal tubular acidosis (RTA).

A common cause of acquired distal RTA is glue sniffing. Inhalation of toluene from the fumes of model glue, spray paint, and paint thinners can give rise to hypokalemic normal gap acidosis through multiple mechanisms. First, toluene inhibits collecting duct proton secretion. Second, metabolism of toluene produces the organic acids hippuric and benzoic acid. These are buffered by sodium bicarbonate, resulting in metabolic acidosis and the production of sodium hippurate and sodium benzoate. If plasma volume is normal, these salts are rapidly excreted in the urine, and a non–anion gap metabolic acidosis develops. If plasma volume is decreased, urinary excretion is limited, these salts accumulate, and an anion gap metabolic acidosis develops.

Distal RTA should be considered in all patients with a non–anion gap metabolic acidosis and hypokalemia who have an inability to lower the urine pH maximally. A urine pH above 5.5 in the patient with systemic acidosis suggests distal RTA, and a UAG value greater than zero is confirmatory. Depending on the duration of the distal RTA, the metabolic acidosis can be mild or very severe, with a serum [HCO_3^-] as low as 10 mmol/l. Urinary potassium losses lead to the development of hypokalemia. Severe hypokalemia (<2.5 mmol/l) may result in musculoskeletal weakness and nephrogenic diabetes insipidus. The latter occurs because hypokalemia decreases aquaporin 2 (AQP2) expression in the collecting duct, thereby minimizing the ability to concentrate urine. An abdominal ultrasound scan may reveal nephrocalcinosis.

In patients with minimal disturbances in blood pH and plasma [HCO_3^-], a test of urinary acidification is required. Traditionally, such a test involved oral NH_4Cl administration to induce metabolic acidosis with assessment of the renal response by serial measurement

of urine pH. Many patients poorly tolerate NH_4Cl ingestion because of gastric irritation, nausea, and vomiting. An alternative way to test the capacity for distal acidification is to administer furosemide and the mineralocorticoid fludrocortisone simultaneously.[13] The combination of both increased distal Na^+ delivery and mineralocorticoid effect will stimulate distal H^+ secretion by both an increase in the luminal electronegativity and a direct stimulatory effect on H^+ secretion. Normal individuals will lower urine pH to values below 5.5 with either maneuver.

Correction of the metabolic acidosis in distal RTA can be achieved by administration of alkali in an amount only slightly greater than daily acid production, usually 1 to 2 mmol/kg/day. In patients with severe K^+ deficits, correction of the acidosis with HCO_3^-, particularly if it is done with sodium alkali salts such as $NaHCO_3$, can lower serum potassium concentration to dangerous levels. In this setting, potassium replacement should begin before the acidosis is corrected. In general, a combination of sodium alkali and potassium alkali is required for long-term treatment of distal RTA. For the patient with recurrent renal stone disease caused by distal RTA, treatment of the acidosis increases urinary citrate excretion, which slows the rate of further stone formation and may even lead to stone dissolution.

Hyperkalemic Distal Renal Tubular Acidosis (Type 4)

Type 4 RTA is characterized by distal nephron dysfunction, resulting in impaired renal excretion of both H^+ and K^+ and causing a hyperchloremic normal gap acidosis and hyperkalemia.[14] The syndrome occurs most frequently with mild to moderate impairment in renal function; however, the magnitude of hyperkalemia and acidosis is disproportionately severe for the observed glomerular filtration rate (GFR). Whereas hypokalemic distal (type 1) RTA is also a disorder of distal nephron acidification, type 4 is distinguished from type 1 RTA on the basis of several important characteristics (Table 12-1). Type 4 RTA is also a much more common form of RTA, particularly in adults.

Hyperkalemic distal RTA results from deficient circulating aldosterone or abnormal cortical collecting duct (CCD) function, or it can be related to hyperkalemia. In either case, a defect in distal H^+ secretion develops. Impaired Na^+ reabsorption by the principal cell leads to a decrease in the luminal electronegativity of the CCD, which impairs distal acidification as a result of the decrease in driving force for H^+ secretion into the tubular lumen. The H^+ secretion is further impaired in this segment as well as in the medullary collecting duct as a result of either the loss of the direct stimulatory effect of aldosterone on H^+ secretion or an abnormality in the H^+-secreting cell.

A consequence of the decrease in luminal electronegativity in the CCD is impaired renal K^+ excretion. In addition, a primary abnormality in CCD transport can also impair K^+ secretion. The development of hyperkalemia adds to the defect in distal acidification by decreasing the amount of ammonia available to act as a urinary buffer. Some studies suggest that hyperkalemia itself, through its effects on ammonia metabolism, is the primary mechanism by which the metabolic acidosis develops in type 4 RTA.

The etiology of type 4 RTA includes disorders associated with decreased circulating levels of aldosterone and conditions associated with impaired CCD function. The most common disease associated with type 4 RTA in adults is diabetes mellitus. In these patients, primary NaCl retention leads to volume expansion and suppression and atrophy of the renin-secreting juxtaglomerular apparatus. Several common drugs, such as nonsteroidal anti-inflammatory agents (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, and high doses of heparin, as used for systemic anticoagulation, can lead to decreased mineralocorticoid synthesis. Impaired function of the CCD can be a feature of structural damage to the kidney, as in interstitial renal diseases such as sickle cell nephropathy, urinary tract obstruction, and lupus. CCD function also may be impaired from use of drugs such as amiloride, triamterene, and spironolactone.[15]

Type 4 RTA should be suspected in a patient with a normal gap metabolic acidosis associated with hyperkalemia. The typical patient is in the fifth to seventh decade of life with a longstanding history of diabetes mellitus with a moderate reduction in the GFR. Plasma $[HCO_3^-]$ is usually 18 to 22 mmol/l and serum $[K^+]$ between 5.5 and 6.5 mmol/l. Most patients are asymptomatic; however, the hyperkalemia may occasionally be severe enough to cause muscle weakness or cardiac arrhythmias. The UAG value is slightly positive, indicating minimal ammonia excretion in the urine. When the disorder is caused by a defect in mineralocorticoid activity, patients typically have urine pH below 5.5, reflecting a more severe defect in ammonia availability than in H^+ secretion (Fig. 12-3). In patients with structural damage to the collecting duct, the urine pH may be alkaline, reflecting both impaired H^+ secretion and decreased urinary ammonia excretion.

Treatment of patients with type 4 RTA is directed at both the hyperkalemia and the metabolic acidosis. In many patients, lowering serum $[K^+]$ will simultaneously correct the acidosis.[16] Correction of the hyperkalemia allows renal ammonia production to increase, thereby increasing the buffer supply for distal acidification. The first consideration in the treatment of patients is to discontinue any nonessential medication that might interfere in either the synthesis or activity of aldosterone or the ability of the kidneys to excrete potassium (Box 12-4). ACE inhibitors and angiotensin receptor blockers (ARBs) should usually be continued because of the beneficial effects on cardiovascular disease and their renoprotective benefits in patients with chronic kidney disease (CKD). In patients with aldosterone deficiency who are neither hypertensive nor fluid overloaded, administration of a synthetic mineralocorticoid such as fludrocortisone (0.1 mg/day) can be effective. In patients with hypertension or volume overload, particularly in association with CKD, administration of either a thiazide or a loop diuretic is frequently effective. Loop diuretics are required in patients with an estimated GFR below 30 ml/min. Loop and thiazide diuretics increase distal Na^+ delivery and thus stimulate K^+ and H^+ secretion in the collecting duct. Alkali therapy (e.g., $NaHCO_3$) can also be used to treat the acidosis and

Factors Differentiating Types 1, 2, and 4 Renal Tubular Acidosis

Factor	Type 1	Type 2	Type 4
Serum K^+	Low	Low	High
Renal function	Normal or near normal	Normal or near normal	Stage 3, 4, or 5 chronic kidney disease
Urine pH during acidosis	High	Low	Low or high
Serum HCO_3^- (mmol/l)	10–20	16–18	16–22
Urine P_{CO_2} (mm Hg)	<40	<40	>70
Urine citrate	Low	High	Low
Fanconi syndrome	No	May be present	No

Table 12-1 Differentiation of RTA types. Factors distinguishing hypokalemic distal (type 1), proximal (type 2), and hyperkalemic distal (type 4) renal tubular acidosis.

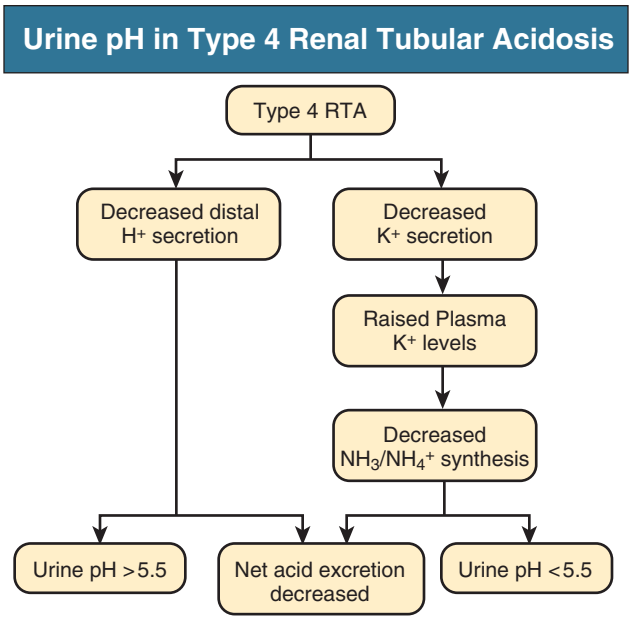

Figure 12-3 Urine pH in hyperkalemic distal (type 4) renal tubular acidosis. Net acid excretion is always decreased; however, the urine pH can be variable. In structural disease of the kidney, the predominant defect is usually decreased distal H^+ secretion, and the urine pH is above 5.5. In disorders associated with decreased mineralocorticoid activity, urine pH is usually below 5.5.

Causes of Type 4 Renal Tubular Acidosis

Mineralocorticoid Deficiency

Low Renin, Low Aldosterone

Diabetes mellitus

Drugs

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Cyclosporine, tacrolimus
- β-Blockers

High Renin, Low Aldosterone

Adrenal destruction

Congenital enzyme defects

Drugs

- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin II receptor blockers (ARBs)
- Heparin
- Ketoconazole

Abnormal Cortical Collecting Duct

Absent or defective mineralocorticoid receptor

Drugs

- Spironolactone, eplerenone
- Triamterene
- Amiloride
- Trimethoprim
- Pentamidine

Chronic tubulointerstitial disease

Box 12-4 Causes of hyperkalemic distal (type 4) renal tubular acidosis.

hyperkalemia, but the patient must be closely monitored to avoid volume overload and worsening hypertension.

Renal Tubular Acidosis in Chronic Kidney Disease

Metabolic acidosis in advanced CKD is caused by failure of the tubular acidification process to excrete the normal daily acid load. As functional renal mass is reduced by disease, there is an adaptive increase in ammonia production and H^+ secretion by the remaining nephrons. Despite increased production of ammonia from each remaining nephron, overall production may be decreased secondary to the decrease in total renal mass. In addition, less ammonia is delivered to the medullary interstitium secondary to a disrupted medullary anatomy.[17] The ability to lower the urinary pH remains intact, reflecting the fact that the impairment in distal nephron H^+ secretion is less than that in ammonia secretion. Quantitatively, however, the total amount of H^+ secretion is small, and the acidic urine pH is the consequence of very little buffer in the urine. The lack of ammonia in the urine is reflected by a positive value for the UAG. Differentiation of RTA from type 4 RTA can be difficult as it is based on the clinician's determination of whether the severity of metabolic acidosis is out of proportion to the degree of renal dysfunction.

Patients with CKD may develop a hyperchloremic normal gap metabolic acidosis associated with normokalemia or mild hyperkalemia as GFR decreases to less than 30 ml/min. With more advanced CKD (GFR <15 ml/min), the acidosis may change to an anion gap metabolic acidosis, reflecting a progressive inability to excrete phosphate, sulfate, and various organic acids. At this stage, the acidosis is commonly referred to as "uremic acidosis."

Correction of the metabolic acidosis in patients with CKD is achieved by treatment with $NaHCO_3$, 0.5 to 1.5 mmol/kg/day, beginning when the HCO_3^- level is less than 22 mmol/l. In some patients, non–sodium citrate formulations can be used. Loop diuretics are often used in conjunction with alkali therapy to prevent volume overload. If the acidosis becomes refractory to medical therapy, dialysis needs to be initiated. Recent evidence suggests that metabolic acidosis in the patient with CKD needs to be aggressively treated because chronic acidosis is associated with metabolic bone disease and may lead to an accelerated catabolic state in patients with CKD.[18,19]

Metabolic Acidosis of Extrarenal Origin

Diarrhea

Intestinal secretions from sites distal to the stomach are rich in HCO_3^-. Accelerated loss of this HCO_3^--rich solution can result in metabolic acidosis. The resultant volume loss signals the kidney to increase NaCl reabsorption; this combined with the intestinal $NaHCO_3$ losses generates a normal anion gap metabolic acidosis. The renal response is to increase net acid excretion by increasing urinary excretion of ammonia.[20] Hypokalemia, as a result of gastrointestinal losses, and the low serum pH both stimulate the synthesis of ammonia in the proximal tubule. The increase in availability of ammonia to act as a urinary buffer allows a maximal increase in H^+ secretion by the distal nephron.

The increase in urinary ammonia excretion associated with an extrarenal normal anion gap acidosis results in a negative UAG value. Urine pH can be misleading and in chronic diarrhea may be above 6.0 because of substantial increases in renal ammonia metabolism that result in increased urine pH from the buffering ability of the ammonia. Although the clinical history should distinguish between these two possibilities, in a patient with surreptitious laxative abuse, this may not be helpful because diarrhea may not be

reported. Colonoscopy may be required to demonstrate characteristic findings of laxative abuse (e.g., melanosis coli) if this diagnosis is being considered.

Treatment of diarrhea-associated metabolic acidosis is based on treatment of the underlying diarrhea. If this is not possible, alkali treatment, possibly including potassium alkali to treat hypokalemia and metabolic acidosis simultaneously, is indicated.

Ileal Conduits

Surgical diversion of the ureter into an ileal pouch is used in the treatment of the patient with neurogenic bladder or after cystectomy. The procedure may be associated rarely with development of a hyperchloremic normal anion gap metabolic acidosis. Acidosis in part is caused by reabsorption of urinary NH_4Cl by the intestine. The ammonia is transported through the portal circulation to the liver or is metabolized to urea to prevent hyperammonemic encephalopathy. This metabolic process consumes equimolar amounts of bicarbonate and therefore can result in the development of metabolic acidosis. Metabolic acidosis may also develop because urinary Cl^- can be exchanged for HCO_3^- through activation of a Cl^--HCO_3^- exchanger on the intestinal lumen. In some patients, a renal defect in acidification can develop and exacerbate the degree of acidosis. Such a defect may result from tubular damage caused by pyelonephritis or high colonic pressures, secondarily causing urinary obstruction.

The severity of acidosis relates to the length of time the urine is in contact with the bowel and the total surface area of bowel exposed to urine. In patients with a ureterosigmoid anastomosis, these factors are increased and the acidosis tends to be more common and more severe than in patients with an ileal conduit. The ileal conduit was designed to minimize the time and area of contact between urine and intestinal surface. Patients with surgical diversion of the ureter who develop metabolic acidosis should be examined for an ileal loop obstruction because this would lead to an increase in contact time between the urine and intestinal surface.

ANION GAP METABOLIC ACIDOSIS

Lactic Acidosis

Lactic acid is the end product in the anaerobic metabolism of glucose and is generated by the reversible reduction of pyruvic acid by lactic acid dehydrogenase and NADH (reduced nicotinamide adenine dinucleotide), as shown in the following formula:

$$\text{Pyruvate} + \text{NADH} + H^+ \leftrightarrow \text{Lactate} + NAD^+$$

Under normal conditions, the reaction is shifted toward the right, and the normal lactate to pyruvate ratio is approximately 10:1. The reactants in this pathway are interrelated, as shown in the following equation:

$$\text{Lactate} = K[(\text{pyruvate})(\text{NADH})(H^+)]/(NAD^+)$$

where K is the equilibrium constant.

On the basis of this relationship, it is evident that lactate can increase for three reasons.[21] First, lactate can increase because of increased pyruvate production alone. In this situation, the normal 10:1 lactate-pyruvate ratio will be maintained. An isolated increase in pyruvate production can be seen in the setting of intravenous (IV) glucose infusions, IV administration of epinephrine, and respiratory alkalosis. Lactate levels in these conditions are minimally elevated, rarely exceeding 5 mmol/l. Second, lactate can increase as a result of an increased NADH-NAD^+ ratio. Under these conditions, the lactate-pyruvate ratio can increase to very high values. Third, lactate can increase with a combination of increased pyruvate production and increased NADH/NAD^+. This is common in severe lactic acidosis.

Lactic acidosis occurs whenever there is an imbalance between the production and the use of lactic acid. The net result is an accumulation of serum lactate and development of metabolic acidosis. The accumulation of the non–chloride anion lactate accounts for the increase in anion gap. Severe exercise and grand mal seizures are examples of lactic acidosis developing as a result of increased production. The short-lived nature of the acidosis in these conditions suggests that a concomitant defect in lactic acid use is present in most conditions of sustained and severe lactic acidosis.

Some of the disorders associated with the development of lactic acidosis are listed in Box 12-5. Type A lactic acidosis is characterized by underperfusion of tissue or acute hypoxia, such as hypotension, sepsis, acute tissue hypoperfusion, cardiopulmonary failure, severe anemia, hemorrhage, and carbon monoxide poisoning. Type B lactic acidosis occurs in the absence of overt hypoperfusion or hypoxia, such as with congenital defects in glucose or lactate metabolism, diabetes mellitus, liver disease, effects of drugs and toxins, and neoplastic diseases.[22-27] In clinical practice, many patients will often exhibit features of type A and type B lactic acidosis simultaneously.

Therapy is aimed at correction of the underlying disorder. Restoration of tissue perfusion and oxygenation is attempted if these are compromised. The role of alkali in the treatment of patients with lactic acidosis is controversial; some experimental models and clinical observations suggest that administration of HCO_3^- may depress cardiac function and exacerbate the acidemia. In addition, such therapy may be complicated by volume overload, hypernatremia, and rebound alkalosis after the acidosis has resolved. In general, HCO_3^- should be given when the systemic pH decreases to below 7.1, because hemodynamic instability becomes much more likely with severe acidemia. In such patients, alkali therapy should be directed at increasing the pH above 7.1; attempts to normalize the

Causes of Lactic Acidosis

Type A (Tissue Underperfusion or Hypoxia)
- Cardiogenic shock
- Septic shock
- Hemorrhagic shock
- Acute hypoxia
- Carbon monoxide poisoning
- Anemia

Type B (Absence of Hypotension and Hypoxia)
- Hereditary enzyme deficiency (glucose 6-phosphatase)
- Drugs or toxins
  - Phenformin, metformin
  - Cyanide
  - Salicylate, ethylene glycol, methanol
  - Propylene glycol[25]
  - Linezolid[22]
  - Propofol[24]
  - Nucleoside reverse transcriptase inhibitors: stavudine, didanosine[23]
  - Clenbuterol[26]
  - Isoniazid
- Systemic disease
  - Liver failure
  - Malignancy

Box 12-5 Causes of lactic acidosis.

pH or [HCO_3^-] should be avoided. Acute hemodialysis is rarely beneficial for lactic acidosis induced by tissue hypoperfusion. The hemodynamic instability that can occur with hemodialysis in these critically ill patients may worsen the underlying difficulty in tissue oxygenation.

Diabetic Ketoacidosis

Diabetic ketoacidosis results from the accumulation of acetoacetic acid and β-hydroxybutyric acid. The development of ketoacidosis is the result of insulin deficiency and a relative or absolute increase in glucagon.[28] These hormonal changes lead to increased fatty acid mobilization from adipose tissue and alter the oxidative machinery of the liver such that delivered fatty acids are primarily metabolized into keto acids. In addition, peripheral glucose use is impaired, and the gluconeogenic pathway in the liver is maximally stimulated. The resultant hyperglycemia causes an osmotic diuresis and volume depletion.

Ketoacidosis results when the rate of hepatic keto acid generation exceeds renal excretion, causing increased blood keto acid concentrations. The H^+ accumulation in the extracellular fluid (ECF) decreases HCO_3^- concentration, whereas the keto acid anion concentration increases. An anion gap metabolic acidosis is the more common finding in the patient with diabetic ketoacidosis, but a normal gap metabolic acidosis can also be seen. In early stages of ketoacidosis, when the ECF volume is almost normal, keto acid anions that are produced are rapidly excreted by the kidney as Na^+ and K^+ salts. Excretion of these salts is equivalent to the loss of potential HCO_3^-. This loss of potential HCO_3^- in the urine at the same time that the kidney is retaining NaCl results in a normal gap metabolic acidosis. As volume depletion develops, renal keto acid excretion cannot match production rates, and keto acid anions are retained within the body, thus increasing the anion gap.

During treatment, the anion gap metabolic acidosis transforms once again into a normal gap acidosis. Treatment leads to a termination in keto acid production. As the ECF volume is restored, there is increased renal excretion of the Na^+ salts of the keto acid anions. The loss of this potential HCO_3^-, combined with the retention of administered NaCl, accounts for the redevelopment of the hyperchloremic normal gap acidosis. In addition, K^+ and Na^+ administered in solutions containing NaCl and KCl enter cells in exchange for H^+. The net effect is infusion of HCl into the ECF. The reversal of the hyperchloremic acidosis takes several days as the HCO_3^- deficit is corrected by the kidney.

Diabetic ketoacidosis can result in a severe metabolic acidosis with serum bicarbonate levels below 5 mmol/l. This diagnosis should be considered in patients with simultaneous metabolic acidosis and hyperglycemia. Diagnosis is confirmed by demonstration of retained keto acids with nitroprusside tablets or reagent strips. However, these tests detect only acetone and acetoacetate and not β-hydroxybutyrate. In the patient with lactic acidosis or alcoholic ketoacidosis, acetoacetate may be converted to β-hydroxybutyrate to an extent that depends on the NADH-NAD^+ ratio. With treatment of the diabetic ketoacidosis, acetoacetate is generated as this ratio falls, and the nitroprusside test result may suddenly become strongly positive.

The limitations of the nitroprusside test can be prevented by direct measurement of β-hydroxybutyrate. With uncontrolled diabetes, a serum β-hydroxybutyrate level above 3.0 mmol/l in adults and above 3.8 mmol/l in children confirms diabetic ketoacidosis.[29] Compared with urinary ketone measurements, capillary blood levels of β-hydroxybutyrate better correlate with both the degree of acidosis and the response to therapy.[30]

Treatment consists of insulin and IV fluids to correct volume depletion. Deficiencies in K^+, Mg^{2+}, and phosphate are common; therefore, these electrolytes are typically added to IV solutions. However, diabetic ketoacidosis typically presents with hyperkalemia due to the insulin deficiency. Potassium should be administered only as hypokalemia develops, usually during insulin treatment of diabetic ketoacidosis. If there is significant hypokalemia at presentation, potassium supplementation may be needed before insulin administration to avoid life-threatening worsening of hypokalemia. Alkali therapy is generally not required because administration of insulin leads to the metabolic conversion of keto acid anions to HCO_3^- and allows partial correction of the acidosis. However, HCO_3^- therapy may be indicated in those patients who present with severe acidemia (pH < 7.1).[31]

D-Lactic Acidosis

D-Lactic acidosis is a unique form of metabolic acidosis that can occur in the patient with small bowel resections or in patients with a jejunoileal bypass. Such short bowel syndromes create a situation in which carbohydrates that are normally extensively reabsorbed in the small intestine are delivered in large amounts to the colon. In the presence of colonic bacterial overgrowth, these substrates are metabolized into D-lactate and absorbed into the systemic circulation. Accumulation of D-lactate produces an anion gap metabolic acidosis in which the serum lactate concentration is normal because the standard test for lactate is specific for L-lactate. These patients typically present after ingestion of a large, high-carbohydrate meal, with neurologic abnormalities including confusion, slurred speech, and ataxia. Ingestion of low-carbohydrate meals and antimicrobial agents to decrease the degree of bacterial overgrowth are the principal treatments.

Starvation Ketosis

Abstinence from food can lead to a mild anion gap metabolic acidosis secondary to increased production of keto acids. The pathogenesis of this disorder is similar to that of diabetic ketoacidosis in that starvation leads to relative insulin deficiency and glucagon excess. As a result, there is increased mobilization of fatty acids while the liver is set to oxidize fatty acids to keto acids. With prolonged starvation, the blood keto acid level can reach 5 to 6 mmol/l. The serum [HCO_3^-] is rarely less than 18 mmol/l. More fulminant ketoacidosis is aborted because ketone bodies stimulate the pancreatic islets to release insulin, and lipolysis is held in check. This break in the ketogenic process is notably absent in patients with insulin-dependent diabetes. No specific therapy is indicated in starvation ketosis.

Alcoholic Ketoacidosis

Ketoacidosis develops in patients with a history of chronic ethanol abuse, decreased food intake, and often a history of nausea and vomiting. As with starvation ketosis, a decrease in the insulin to glucagon ratio leads to accelerated fatty acid mobilization and alters the enzymatic machinery of the liver to favor keto acid production. However, features unique to this disorder differentiate alcoholic ketoacidosis from simple starvation ketosis. First, the alcohol withdrawal combined with volume depletion and starvation greatly increases the levels of circulating catecholamines. As a result, the peripheral mobilization of fatty acids is much greater than typically found with starvation alone. This sometimes massive mobilization of fatty acids can lead to marked keto acid production and severe metabolic acidosis. Second, the metabolism of ethanol leads to

accumulation of NADH. The increase in NADH/NAD^+ is reflected by a higher β-hydroxybutyrate–acetoacetate ratio. As mentioned previously, the nitroprusside reaction may be diminished by this redox shift despite the presence of severe ketoacidosis. Treatment of patients with alcoholic ketoacidosis focuses on glucose administration, which leads to the rapid resolution of the acidosis; stimulation of insulin release leads to diminished fatty acid mobilization from adipose tissue, as well as decreased hepatic output of keto acids.

Ethylene Glycol and Methanol Intoxications

Ethylene glycol and methanol intoxications are characteristically associated with the development of a severe anion gap metabolic acidosis. Metabolism of ethylene glycol by alcohol dehydrogenase generates various acids, including glycolic, oxalic, and formic acids. Ethylene glycol is present in antifreeze and solvents and is ingested by accident or as a suicide attempt. The initial effects of intoxication are neurologic and begin with drunkenness but can quickly progress to seizures and coma. If left untreated, cardiopulmonary symptoms such as tachypnea, noncardiogenic pulmonary edema, and cardiovascular collapse may appear. From 24 to 48 hours after ingestion, patients may develop flank pain and acute kidney injury, often accompanied by abundant calcium oxalate crystals in the urine (Box 12-6). A fatal dose of ethyl glycol is approximately 100 ml.

Methanol is also metabolized by alcohol dehydrogenase and forms formaldehyde, which is then converted to formic acid. Methanol is found in a variety of commercial preparations, such as shellac, varnish, and de-icing solutions, and is also known as wood alcohol.

Ethylene Glycol and Methanol Poisoning

Time course of clinical symptoms and signs after ingestion

Ethylene glycol

- 0–12 hours: inebriation progressing to coma
- 12–24 hours: tachypnea, noncardiogenic pulmonary edema
- 24–36 hours: flank pain, renal failure, urinary calcium oxalate crystals

Methanol

- 0–12 hours: inebriation followed by asymptomatic period
- 24–36 hours: pancreatitis, retinal edema progressing to blindness, seizures
- >48 hours: putamen and white matter hemorrhage leading to Parkinson-like state

Increased anion gap metabolic acidosis

Increased osmolar gap

Treatment

Supportive care

Fomepizole (4-methylpyrazole) is agent of choice (competitor of alcohol dehydrogenase): 15 mg/kg IV loading dose, then 10 mg/kg every 12 hours for 48 hours. After 48 hours, increase dose to 15 mg/kg every 12 hours; increase frequency of dosing to 4 hours during hemodialysis.

Intravenous ethanol (5% or 10% solution) if fomepizole unavailable: loading dose of 0.6 g/kg, followed by hourly maintenance dose of 66 mg/kg. Increase maintenance dose when the patient has history of chronic alcohol use and during hemodialysis.

Hemodialysis to accelerate removal of parent compound and metabolites

Bicarbonate therapy to treat acidosis

Box 12-6 Ethylene glycol and methanol poisoning.

As with ethylene glycol, methanol can be ingested either by accident or as a suicide attempt. Clinically, methanol ingestion is associated with an acute inebriation followed by an asymptomatic period lasting 24 to 36 hours. Abdominal pain caused by pancreatitis, seizures, blindness, and coma may develop. The blindness is caused by direct toxicity of formic acid on the retina. Methanol intoxication is also associated with hemorrhage in the white matter and putamen, which can lead to the delayed onset of a Parkinson disease–like syndrome (Box 12-6). The lethal dose of methanol is 60 to 250 ml.

Lactic acidosis is also a feature of methanol and ethylene glycol poisoning and contributes to the elevated anion gap. Together with an elevated anion gap, an osmolar gap is an important clue to the diagnosis of ethylene glycol and methanol poisoning. The osmolar gap is the difference between the measured and calculated osmolality. The formula for the calculated osmolality is as follows:

$$\text{Calculated osmolality} = 2 \times Na^+ + BUN/2.8 + \text{glucose}/18 + EtOH/4.6$$

where the blood urea nitrogen (BUN), glucose, and ethanol concentrations are in milligrams per deciliter. Inclusion of the ethanol concentration in this calculation is important because many patients ingest ethylene glycol or methanol while inebriated from ethanol ingestion. The normal value for the osmolar gap is less than 10 mOsm/kg. Each 100 mg/dl (161 mmol/l) of ethylene glycol will increase the osmolar gap by 16 mOsm/kg. Methanol contributes 32 mOsm/kg for each 100 mg/dl (312 mmol/l).

In addition to supportive measures, the patient with ethylene glycol and methanol poisoning is treated with fomepizole (4-methylpyrazole), which inhibits alcohol dehydrogenase and prevents formation of toxic metabolites[32] (Box 12-6). If fomepizole is unavailable, IV ethanol can be used to prevent the formation of toxic metabolites. Ethanol has more than a 10-fold greater affinity for alcohol dehydrogenase than that of other alcohols. Ethanol has its greatest efficacy when levels of 100 to 200 mg/dl are obtained. In addition to both fomepizole and ethanol therapy, the patient should receive hemodialysis to remove both the parent compound and its metabolites. Correction of the acidosis is accomplished with an HCO_3^--containing dialysate or by IV infusion of $NaHCO_3$.

Salicylate

Aspirin (acetylsalicylic acid) is associated with a large number of accidental or intentional poisonings. At toxic concentrations, salicylate uncouples oxidative phosphorylation and, as a result, leads to increased lactic acid production. In children, keto acid production may also be increased. The accumulation of lactic, salicylic, keto, and other organic acids leads to the development of an anion gap metabolic acidosis. At the same time, salicylate has a direct stimulatory effect on the respiratory center. Increased ventilation lowers the carbon dioxide tension (P_{CO_2}), contributing to the development of a respiratory alkalosis. Children primarily manifest an anion gap metabolic acidosis with toxic salicylate levels; a respiratory alkalosis is most evident in adults.

In addition to conservative management, the initial goals of therapy for salicylate poisoning are to correct systemic acidemia and increase the urine pH. By increasing systemic pH, the ionized fraction of salicylic acid will increase, resulting in less accumulation of the drug in the central nervous system. Similarly, an alkaline urine pH favors increased urinary excretion because the ionized fraction of the drug is poorly reabsorbed by the tubule. At serum concentrations above 80 mg/dl or in the setting of severe clinical toxicity, hemodialysis can be used to accelerate drug elimination.

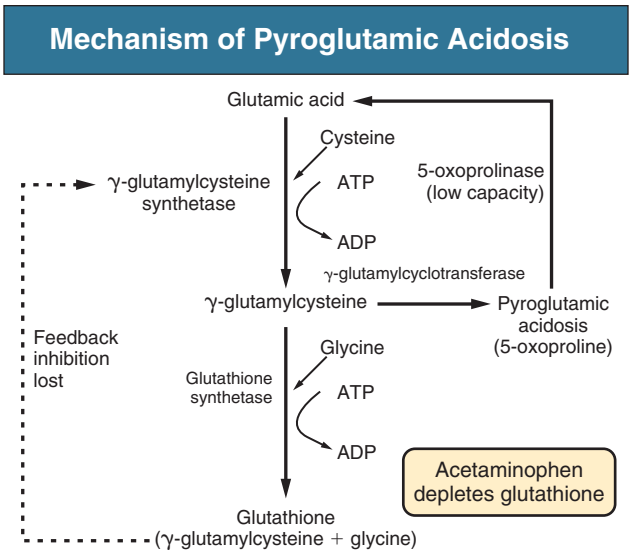

Figure 12-4 Mechanism of pyroglutamic acidosis. Glutathione is formed from γ-glutamylcysteine and glycine in the presence of glutathione synthetase. Glutathione normally regulates the activity of γ-glutamylcysteine synthetase through feedback inhibition. Depletion of glutathione results in increased formation of γ-glutamylcysteine, which in turn is metabolized to pyroglutamic acid (5-oxoproline) and cystine through γ-glutamylcyclotransferase. Pyroglutamic acid accumulates because the enzyme responsible for its metabolism (5-oxoprolinase) is low capacity. *ADP,* Adenosine diphosphate; *ATP,* adenosine triphosphate.

Pyroglutamic Acidosis

Pyroglutamic acid, also known as 5-oxoproline, is an intermediate in glutathione metabolism. An anion gap acidosis caused by pyroglutamic acid has been described rarely in critically ill patients receiving therapeutic doses of acetaminophen[33,34] (Fig. 12-4). Patients present with severe anion gap metabolic acidosis accompanied by alterations in mental status ranging from confusion to coma. High concentrations of pyroglutamic acid are found in the blood and urine. In this setting, glutathione levels are reduced because of the oxidative stress associated with critical illness and by the metabolism of acetaminophen. The reduction in glutathione secondarily leads to increased production of pyroglutamic acid. The diagnosis of pyroglutamic acidosis should be considered in patients with unexplained anion gap metabolic acidosis and recent acetaminophen ingestion.

ALKALI TREATMENT OF METABOLIC ACIDOSIS

Treatment of metabolic acidosis usually involves either sodium bicarbonate or citrate[31] (Table 12-2). $NaHCO_3$ can be taken orally as tablets or powder or given intravenously as a hypertonic bolus or an isotonic infusion, which can be created by adding 150 mmol $NaHCO_3$ to 1 liter of 5% dextrose in water (D5W). This solution is useful if treatment requires both volume expansion and alkali administration.

Citrate may be taken orally as a liquid, as sodium citrate, potassium citrate, or citric acid, or a combination. Many patients find citrate-containing solutions more palatable than oral $NaHCO_3$ as a source of oral alkali therapy. Oral citrate therapy should not be combined with medications that include aluminum. Citrate, which has a −3 charge under normal conditions, can complex with aluminum (Al^{3+}) in the intestinal tract, resulting in an uncharged moiety that is rapidly absorbed across the intestinal tract and then can dissociate

Alkali Treatment Options

Therapy	Route	Usual Dose per Unit	Comments
Sodium bicarbonate tablet	PO	650 mg = 8 mmol	May cause gastric gas
Sodium bicarbonate	IV	50 mmol in 50 ml	Hypertonic, may cause hypernatremia
D5W with $NaHCO_3$	IV	150 mmol/l	Useful for simultaneous intravascular volume expansion and alkali administration
Sodium citrate/ citric acid (liquid)	PO	1 mmol of Na^+ and citrate per milliliter	1 mmol citrate equivalent to 1 mmol HCO_3^- Avoid concomitant aluminum-containing medications such as antacids and sucralfate.
Potassium citrate (tablet)	PO	5 and 10 mmol per tablet	Useful for simultaneous K^+ and alkali therapy
Citric acid/ potassium citrate/sodium citrate (liquid)	PO	1 mmol of Na^+ and K^+ and 2 mmol of citrate per milliliter	Avoid concomitant aluminum-containing medications.
Potassium citrate (liquid)	PO	2 mmol of K^+ and 2 mmol of citrate per milliliter	Avoid concomitant aluminum-containing medications.

Table 12-2 Alkali treatment options. *D5W,* 5% Dextrose in water; *IV,* intravenous; *PO,* oral.

to release free aluminum. This can increase the rate of aluminum absorption dramatically and in some patients, particularly those with severe CKD, has resulted in acute aluminum encephalopathy.

The dose of alkali therapy administered is based on both the total body bicarbonate deficit and the desired rapidity of treatment. Under normal circumstances, the volume of distribution (V_D) for bicarbonate is approximately 0.5 l/kg total body weight. Thus, the bicarbonate deficit, in millimoles, can be estimated from the following formula:

$$\text{Bicarbonate deficit} = (0.5 \times \text{LBW}_{kg}) \times (24 - \text{HCO}_3^-)$$

where LBW_{kg} is the lean body weight in kilograms and 24 is the desired resultant bicarbonate concentration.

Several caveats regarding this equation should be understood. First, edema fluid contributes to the volume of distribution of bicarbonate. Accordingly, an estimation of the amount of edema fluid should be included in this calculation. Second, the volume of distribution for bicarbonate increases as the severity of the metabolic acidosis worsens. When serum [HCO_3^-] is 5 mmol/l or less, the volume of distribution may increase to 1 l/kg or more.

When acute treatment is desired, 50% of the bicarbonate deficit should be replaced during the first 24 hours. If hypertonic $NaHCO_3$ is administered, the increase in serum [HCO_3^-] will be mirrored by an increase in serum [Na^+]. After the initial 24 hours of therapy, the response to therapy and the patient's current clinical condition are reevaluated before future therapy is decided. Acute hemodialysis solely for the treatment of metabolic acidosis, other than that associated with renal failure, is rarely beneficial.

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CHAPTER 13

Metabolic Alkalosis

F. John Gennari

DEFINITION

Metabolic alkalosis is caused by retention of excess alkali and is defined by a venous total carbon dioxide concentration ([total CO_2]) greater than 30 mmol/l or an arterial bicarbonate concentration ($[HCO_3^-]$) greater than 28 mmol/l. The increase in pH that results from the elevation in $[HCO_3^-]$ induces hypoventilation, producing a secondary increase in arterial CO_2 tension ($Paco_2$). Thus, metabolic alkalosis is characterized by coexisting elevations in serum $[HCO_3^-]$, arterial pH, and $Paco_2$. Because the kidney normally responds to an increase in $[HCO_3^-]$ by rapidly excreting excess alkali, sustained metabolic alkalosis occurs *only* when some additional factor impairs bicarbonate excretion. This chapter reviews the normal process of bicarbonate reabsorption by the kidney and how it is impaired in metabolic alkalosis, the various clinical settings in which this disorder occurs, and its diagnosis and management.

BICARBONATE TRANSPORT IN THE KIDNEY

Bicarbonate ions are freely filtered across the glomerulus and under normal conditions must be completely recaptured from the tubule urine to conserve body alkali stores. In addition, acid excretion must occur to regenerate any HCO_3^- consumed in buffering of endogenously produced acids. Both tasks are accomplished by secretion of hydrogen ions (H^+) into the renal tubules.[1] Bicarbonate ions are recaptured when secreted H^+ combines with filtered HCO_3^- to produce CO_2 and water, removing HCO_3^- from the urine. Acid excretion occurs in the collecting duct when secreted H^+ combines with filtered phosphate, converting HPO_4^{2-} to $H_2PO_4^-$, or with ammonia (NH_3) to form ammonium (NH_4^+), and these ions are excreted. Whenever excess alkali is ingested or administered, HCO_3^- is secreted into the tubule urine as well as being filtered, and acid excretion decreases, all changes that result in rapid bicarbonate excretion.

Figure 13-1 illustrates the key epithelial transporters and channels that participate in HCO_3^- reabsorption and secretion. In the proximal tubule, where most of the filtered HCO_3^- is reabsorbed, H^+ is secreted into the tubule urine both by a Na^+-linked transporter (Na^+-H^+ exchanger, NHE3) and an H^+-ATPase (not shown in figure). In the thick ascending limb of Henle loop (TAL), H^+ is secreted via NHE3, and in the collecting duct, H^+ secretion is accomplished primarily by an apical membrane H^+-ATPase. The activity of this collecting duct proton transporter is regulated by aldosterone and by the rate of Na^+ delivery to and reabsorption at this site in the nephron. When body K^+ stores are low, an apical membrane H^+,K^+-ATPase is activated in the cortical collecting duct, further promoting H^+ secretion linked to K^+ reabsorption.[2] Excretion of excess bicarbonate is facilitated by secretion of HCO_3^- into the tubule urine in the cortical collecting duct through an apical membrane Cl^--HCO_3^- exchanger (pendrin).[3] This transporter is activated by alkalemia and requires Cl^- reabsorption in exchange for secreted HCO_3^-. The HCO_3^- secreted into the urine by this transporter can be recaptured again by H^+ secretion further along in the collecting duct, so that excretion of excess alkali requires both stimulation of the Cl^--HCO_3^- exchanger and suppression of the normally active collecting duct H^+-ATPase.

PATHOPHYSIOLOGY OF METABOLIC ALKALOSIS

With the exception of alkali administration in the setting of severe impairment of kidney function (GFR <30 ml/min), sustained metabolic alkalosis is always the result of dysregulation of the transporters that control bicarbonate reabsorption and acid excretion by the kidney. A key feature of this dysregulation is abnormal stimulation of collecting duct ion transport[4] (Box 13-1). This stimulation usually is secondary to abnormalities in Na^+ and Cl^- reabsorption that occur before the urine reaches the collecting duct. More rarely, metabolic alkalosis is the result of primary stimulation of collecting duct ion transport resulting from abnormal signaling or genetic abnormalities.

Secondary Stimulation of Collecting Duct Ion Transport

Chloride Depletion

The most common clinical presentation of metabolic alkalosis is generated by Cl^- depletion. Although the term *contraction alkalosis* is sometimes used as a synonym for Cl^- depletion alkalosis, this phrase is confusing because it implies that volume contraction is responsible for the disorder. The term refers specifically to the increase in serum $[HCO_3^-]$ that follows *only one type* of extracellular fluid (ECF) volume contraction, that caused by selective Cl^- losses. Moreover, volume contraction is neither necessary nor instrumental in inducing this change in serum $[HCO_3^-]$.[5]

Selective Cl^- depletion, induced by vomiting or nasogastric suction, increases serum $[HCO_3^-]$.[6] The degree of alkalosis generated is greater when H^+ loss also occurs, as shown in the example in Figure 13-2, but it may occur even when H^+ loss is minimized by administration of a proton pump inhibitor. In either setting, maintenance of the metabolic alkalosis depends on sustained depletion of body Cl^- stores. Serum $[HCO_3^-]$ returns to normal when sufficient Cl^- is given to replenish losses. Chloride-depletion metabolic alkalosis always causes concomitant K^+ depletion through renal K^+ losses, but Cl^- administration can correct the alkalosis even if the K^+ deficit is deliberately maintained.[7] Despite this experimental finding, secondary K^+ depletion plays a key role in maintaining alkalosis. When K^+ depletion is maintained, much larger amounts of Cl^- are needed to correct the disorder completely.[8] The metabolic alkalosis induced by gastrointestinal Cl^- losses can be very severe, with reports of

Key Apical Membrane Ion Transporters Along the Nephron

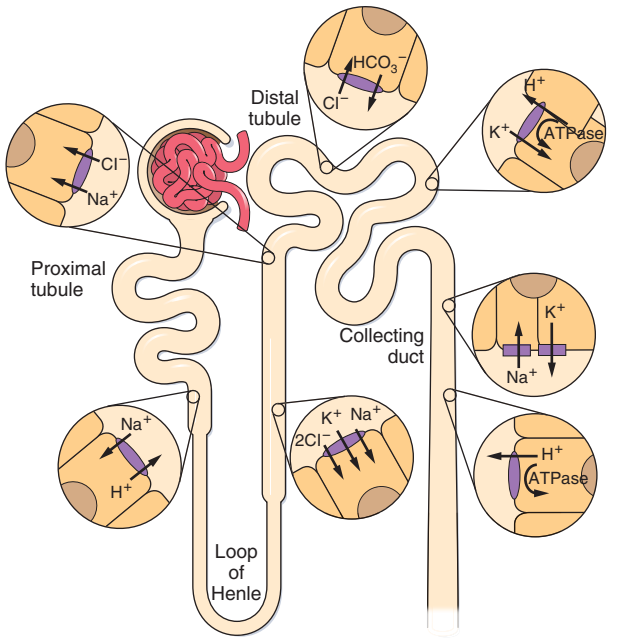

Figure 13-1 Key apical membrane ion transporters along the nephron. Bicarbonate ions (HCO_3^-) are recaptured by H^+ secretion throughout the renal tubules. In the proximal tubule and loop of Henle, H^+ secretion is directly linked to Na^+ reabsorption through the Na^+/H^+ exchanger. In addition, H^+ secretion occurs in the proximal tubule through an apical membrane H^+-ATPase (not shown). In the collecting duct, H^+ secretion is indirectly coupled to Na^+ uptake through a Na^+ channel and parallel H^+-ATPase. Chloride-linked Na^+ reabsorption in the loop of Henle and early distal tubule affects H^+ secretion by determining Na^+ delivery to the collecting duct. Bicarbonate secretion occurs in the distal tubule and cortical collecting duct under conditions of alkalemia through a Cl^--linked exchanger (pendrin). Potassium reabsorption in states of K^+ depletion is linked to H^+ secretion through a H^+/K^+-ATPase.

Pathophysiologic Classification of Causes of Metabolic Alkalosis

- Primary stimulation of collecting duct ion transport (Na^+ uptake, H^+ and K^+ secretion)
  - Mineralocorticoid induced
  - Activating genetic mutations of ENaC or its signal pathway
- Secondary stimulation of collecting duct ion transport (Na^+ uptake, H^+ and K^+ secretion)
  - Extrarenal Cl^- losses and secondary K^+ losses
  - Renal Cl^- losses and secondary K^+ losses
    - Pharmacologic (diuretics)
    - Inactivating gene mutations of Cl^--linked Na^+ cotransporters
- Alkali administration in settings in which HCO_3^- excretion is impaired (e.g., kidney failure)

Box 13-1 Pathophysiologic classification of causes of metabolic alkalosis. *ENaC,* Epithelial sodium channel in collecting duct.

serum [HCO_3^-] greater than 60 mmol/l.[9,10] A less severe Cl^--dependent metabolic alkalosis, without evident H^+ loss, is generated by administration of thiazide or loop diuretics and by two genetic abnormalities in Cl^- reabsorption, Bartter and Gitelman syndromes, as discussed later.

Effects of Gastric Drainage with NaCl-Restricted Diet

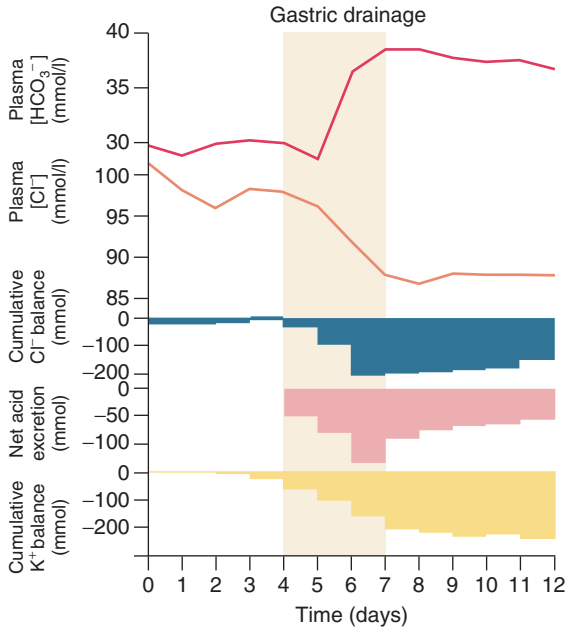

Figure 13-2 Effect of gastric drainage with salt-restricted diet. Effect on plasma [HCO_3^-] and [Cl^-] and on the net balance of [Cl^-] and [K^+] in the body in a normal individual ingesting a NaCl-restricted diet. Changes in net acid excretion are also shown. Gastric drainage on three consecutive nights in this patient increased plasma [HCO_3^-] by 9 mmol/l, a change that persisted after gastric drainage was stopped. Potassium depletion results from renal K^+ losses during the period of gastric drainage. These losses are not regained, however, after the drainage is discontinued, despite the continued daily ingestion of 70 mmol of K^+. Net acid excretion decreases transiently during drainage but then returns to control levels despite sustained metabolic alkalosis. Chloride depletion is maintained by the low dietary intake of this ion.

When metabolic alkalosis is induced by Cl^- depletion and dietary Cl^- intake is restricted, a characteristic sequence of changes in electrolyte excretion occurs (see Fig. 13-2).[6] Sodium and HCO_3^- excretion increase transiently, then decrease rapidly to low levels, accompanied by an abnormal increase in K^+ excretion. The increase in K^+ excretion is also transient but still induces significant K^+ depletion. In the new steady state, urinary K^+ excretion matches intake despite depletion of body K^+ stores (see Fig. 13-2). As a result, hypokalemia is a cardinal feature of Cl^--depletion alkalosis. Potassium depletion stimulates H^+ secretion in the collecting duct (through H^+,K^+-ATPase; see Fig. 13-1) and HCO_3^- reabsorption in the ascending limb of the loop of Henle.[11] Potassium depletion also downregulates both the Na^+-K^+-2Cl^- cotransporter and the Na^+- Cl^- cotransporter,[11] increasing Na^+ delivery to the collecting duct and further stimulating collecting duct H^+ secretion (Fig. 13-3). When K^+ deficiency is severe, this effect results in measurable Cl^- excretion despite Cl^- depletion and sustained metabolic alkalosis even when NaCl is administered.[12] Finally, K^+ depletion stimulates renal NH_4^+ production, facilitating the acid excretion needed to sustain metabolic alkalosis. Although the Cl^--HCO_3^- exchanger is activated by metabolic alkalosis, its activation in turn stimulates collecting duct H^+ secretion, resulting in reabsorption of all the secreted HCO_3^- and continued acid excretion.[13] In the steady state, acid excretion matches net acid production despite systemic alkalemia, indicating a failure of downregulation of collecting duct ion transport. The contribution of Cl^- and K^+ depletion to the maintenance of metabolic alkalosis is

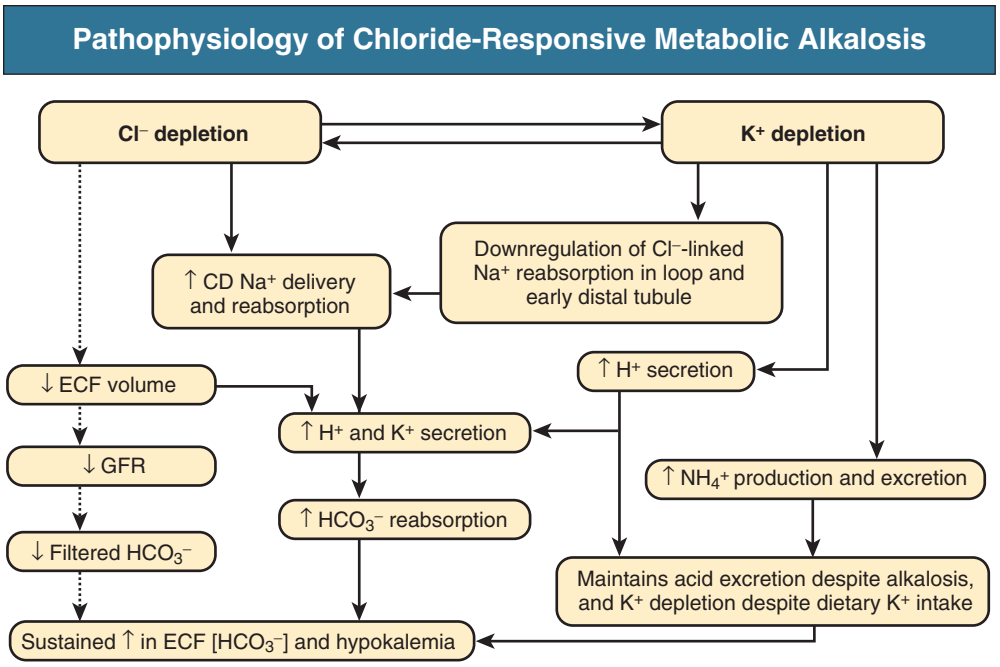

Figure 13-3 Pathophysiology of metabolic alkalosis caused by depletion of body chloride stores. Chloride depletion stimulates H^+ and K^+ secretion into the collecting duct *(CD)* as a result of disproportionate distal Na^+ delivery and reabsorption. The resultant K^+ depletion further stimulates H^+ secretion and promotes ammonium (NH_4^+) production and excretion, as well as downregulating Na^+ reabsorption in Henle loop. These events all contribute to a sustained increase in serum [HCO_3^-]. Chloride depletion also reduces glomerular filtration rate *(GFR)* and therefore HCO_3^- filtration, reducing potential alkali losses. As indicated by the *dashed lines,* the role of this effect in sustaining metabolic alkalosis remains controversial. *ECF,* Extracellular fluid.

of little importance in the clinic because treatment is dictated by the particular setting; some patients need NaCl to replenish ECF volume, and most need KCl to treat K^+ depletion.

Potassium Depletion

Induction of net K^+ loss by severe restriction of dietary K^+ intake produces a small but significant increase in serum [HCO_3^-].[8] When dietary Cl^- intake is concomitantly restricted, however, the resultant alkalosis is four times as great, illustrating the complementary roles of Cl^- and K^+ in regulating renal HCO_3^- reabsorption. Depletion of body K^+ stores is probably the most important factor in producing and sustaining the rarer forms of metabolic alkalosis induced by mineralocorticoid excess or apparent mineralocorticoid excess (see later discussion).

Primary Stimulation of Collecting Duct Ion Transport

Metabolic alkalosis produced by primary stimulation of collecting duct ion transport accounts for less than 1% of the clinical incidence of this disorder, and by far the most common cause is primary hyperaldosteronism.[14] Primary hyperaldosteronism is characterized by persistently high and unregulated aldosterone secretion, which activates both the epithelial sodium channel (ENaC) and H^+-ATPase, regardless of body fluid volume and acid-base status (Fig. 13-4; see also Fig. 13-1). As a result, Na^+ reabsorption and H^+ secretion are increased directly, and K^+ secretion is increased secondarily, depleting body K^+ stores. The resultant K^+ depletion promotes NH_4^+ production and activates H^+,K^+-ATPase activity, further facilitating acid excretion. Sodium retention leads to hypertension and also ensures continued Na^+ delivery to the collecting duct, sustaining the cycle of increased reabsorption and increased K^+ and H^+ secretion. As a result of all these events, metabolic alkalosis is sustained despite normal Cl^- intake. Not surprisingly, the degree of alkalosis induced by primary hyperaldosteronism is modulated by both Cl^- and K^+ intake. Much more rarely, metabolic alkalosis is caused by genetic mutations in the regulation and function of ENaC in the collecting duct (see Etiology and Chapter 49).

Exogenous Alkali

The kidney responds rapidly to excess alkali by increasing HCO_3^- excretion, and sustained metabolic alkalosis does not occur unless massive amounts are administered in individuals with normal kidney function. When lesser amounts of $NaHCO_3$ are ingested daily, serum [HCO_3^-] does not increase unless dietary Cl^- intake is severely restricted.[15] If HCO_3^- excretion is impaired as a result of kidney failure, even minimal daily alkali administration can cause a sustained metabolic alkalosis independent of Cl^- intake.[16] End-stage renal disease is the ultimate model of impaired HCO_3^- excretion, and any added alkali remains in the body until it is consumed by buffering the strong acids produced by protein metabolism (endogenous acid production).

Secondary Response to Alkalemia Induced by Bicarbonate Retention

Regardless of the cause, blood pH increases in patients with metabolic alkalosis and elicits secondary hypoventilation, increasing P_{CO_2}. The response is a potent one, occurring despite the concomitant development of hypoxemia. On average, P_{CO_2} increases by 0.7 mm Hg (0.1 kP) for each 1 mmol/l increase in serum [HCO_3^-]. Assuming a normal [HCO_3^-] of 24 mmol/l and P_{CO_2} of 40 mm Hg, the predicted P_{CO_2} for any given serum [HCO_3^-] in metabolic alkalosis can be calculated as follows:

$$P_{CO_2}(\text{mm Hg}) = 40 + 0.7 \times ([HCO_3^-](\text{mmol/l}) - 24)$$

Although this formula is helpful in determining whether the ventilatory response to metabolic alkalosis is appropriate, it implies a precision that does not exist in nature. Variations of up to 5 to 7 mm Hg between the observed and calculated P_{CO_2} may occur. When serum [HCO_3^-] exceeds 60 mmol/l, moreover, the formula is not a reliable predictor of the respiratory response. Even when metabolic alkalosis is severe (serum [HCO_3^-] >50 mmol/l), however, the P_{CO_2} (in mm Hg) virtually always exceeds the value for the serum [HCO_3^-] (in mmol/l).[10] Figure 13-5 illustrates the ameliorating effect of increasing P_{CO_2} on pH in metabolic alkalosis. While it mitigates the alkalemia, the increase in P_{CO_2}, when sustained, also directly

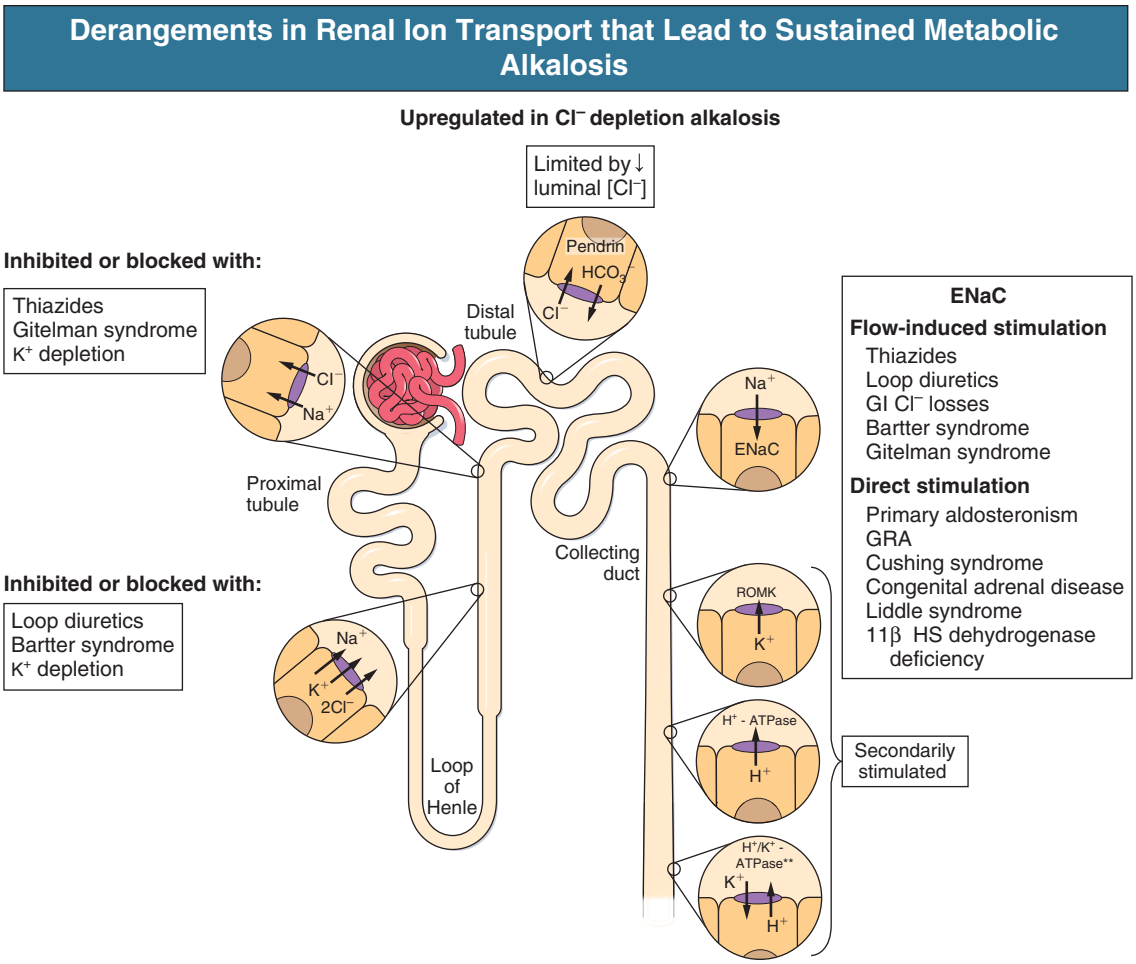

Figure 13-4 Sustained metabolic alkalosis from renal ion transport derangements. Schematic of key apical membrane transport proteins in the loop of Henle and distal nephron and the ways their function is altered to impair renal HCO_3^- excretion and sustain K^+ excretion in the face of K^+ depletion. Bartter and Gitelman syndromes are caused by genetic abnormalities that impede or inactivate Cl^--linked Na^+ reabsorption in Henle loop and early distal tubule, respectively. The epithelial Na^+ channel *(ENaC)* in the collecting duct is stimulated directly in primary hyperaldosteronism and in several genetic abnormalities. Glucocorticoid-remediable aldosteronism *(GRA)* causes aldosterone secretion to respond to corticotropin (ACTH) rather than to angiotensin II; Liddle syndrome blocks downregulation of the channel, and 11β-hydroxysteroid *(HS)* dehydrogenase deficiency allows cortisol to act as a mineralocorticoid. *ROMK,* Renal outer medulla K^+ (channel).

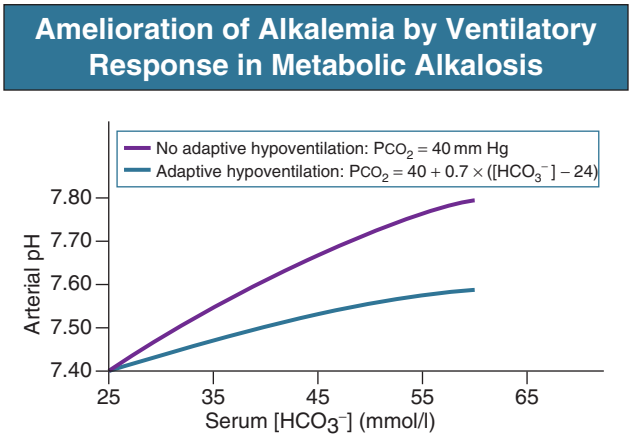

Figure 13-5 Alkalemia in metabolic alkalosis. Amelioration of alkalemia by the normal ventilatory response to increased serum $[HCO_3^-]$. *Upper line* in the graph illustrates the relationship between arterial pH and serum $[HCO_3^-]$ in the absence of adaptive hypoventilation (P_{CO_2} maintained at 40 mm Hg). *Lower line shows* the relationship when P_{CO_2} is increased by the expected level of hypoventilation.

stimulates renal HCO_3^- reabsorption, increasing serum $[HCO_3^-]$ further.[17] This effect is small and unimportant in the clinical setting.

ETIOLOGY

The major causes of metabolic alkalosis are subdivided into three groups based on pathophysiology[4] (see Box 13-1). The most common causes are induced and sustained by chloride depletion resulting from abnormal losses from the gut or the kidney. The second subgroup, much rarer, includes the metabolic alkaloses induced and sustained by excess corticosteroids, or by collecting duct transport abnormalities that mimic excess mineralocorticoid activity. The third subgroup includes the causes of metabolic alkalosis due to alkali administration or ingestion. This newer classification replaces the traditional separation of causes based on treatment response (chloride-responsive and chloride-resistant) with a more straightforward and inclusive grouping that logically combines the causes of metabolic alkalosis that have the same pathophysiology (e.g., Bartter and Gitelman syndromes and diuretic-induced metabolic alkalosis).

Metabolic Alkalosis from Secondary Stimulation of Ion Transport
Chloride loss from the stomach (common)
Vomiting
Nasogastric suction
Chloride-depleting diarrheas (rare)
Congenital chloridorrhea
Some villous adenomas of the colon
High-volume ileostomy losses
Diuretic administration (common)
Thiazides
Metolazone
Loop diuretics: furosemide, bumetanide, torsemide, ethacrynic acid
Impaired chloride-linked sodium transport (rare)
Bartter syndrome
Gitelman syndrome
Rare causes
Recovery from chronic hypercapnia
Gastrocystoplasty
Cystic fibrosis
Severe potassium deficiency

Box 13-2 Causes of metabolic alkalosis resulting from secondary stimulation of collecting duct ion transport.

Secondary Stimulation of Collecting Duct Ion Transport

Box 13-2 lists the causes of metabolic alkalosis resulting from stimulation of collecting duct ion transport by abnormal transport events occurring earlier in the nephron. Specific examples are discussed next.

Vomiting or Nasogastric Drainage

Loss of chloride from the upper gastrointestinal (GI) tract, often accompanied by concomitant H^+ losses, produces a metabolic alkalosis that is sustained until body Cl^- stores are replenished (see Fig. 13-2). With continued emesis or nasogastric suction and without replacement of Cl^- losses, serum [HCO_3^-] may rise to extremely high levels.[9,10]

Diuretic Administration

Diuretics that inhibit Cl^- transport proteins in the kidney are the most common cause of metabolic alkalosis (see Box 13-2). The thiazides and metolazone inhibit the Na^+-Cl^- cotransporter in the early distal tubule, and the loop diuretics inhibit the Na^+-K^+-$2Cl^-$ cotransporter in the TAL (see Fig 13-1). These agents all impair Cl^- reabsorption, causing selective Cl^- depletion, and stimulate K^+ excretion by increasing Na^+ delivery to the collecting duct. The alkalosis produced is typically mild (serum [HCO_3^-] <38 mmol/l), except in patients who continue to ingest excess salt and have extreme renal Na^+ avidity. Hypokalemia caused by K^+ depletion is more prominent and is the major management problem.[18]

Genetic Impairment of Cl^--Linked Na^+ Transport

Bartter and Gitelman syndromes are two hereditary disorders manifested by metabolic alkalosis and hypokalemia without hypertension (see Chapter 49). Bartter syndrome is caused by several mutations, all of which have the effect of impeding Cl^--associated Na^+ reabsorption in the TAL[19] (through Na^+-K^+-$2Cl^-$ cotransporter; see Fig. 13-4). Patients with Bartter syndrome usually become ill early in life with metabolic alkalosis and volume depletion, features similar to those seen in individuals abusing loop diuretic agents. Gitelman syndrome is caused by genetic mutations that inactivate the thiazide-sensitive Na^+-Cl^- cotransporter in the early distal tubule (see Fig. 13-3), leading to hypokalemia and metabolic alkalosis similar to that caused by thiazide diuretics. Gitelman syndrome becomes clinically apparent later in life and, unlike Bartter syndrome, has hypomagnesemia and hypocalciuria as prominent features.[20]

Recovery from Chronic Hypercapnia

The renal response to sustained hypercapnia results in an increase in HCO_3^- reabsorption and a decrease in Cl^- reabsorption (see Chapter 14). As a result, serum [HCO_3^-] increases and body Cl^- stores are reduced. When P_{CO_2} is restored to normal, renal excretion of excess HCO_3^- requires repletion of the Cl^- losses incurred during adaptation. If these losses are not replaced, recovery from hypercapnia can result in a persistent metabolic alkalosis.

Congenital Chloridorrhea

This rare form of diarrhea is caused by an inactivating mutation in the "downregulated in adenoma" *(DRA)* gene, an apical membrane Cl^--HCO_3^- exchanger in the small intestine.[21] The result is a large-volume diarrhea that is rich in Cl^-, causing selective loss of this ion as well as H^+ and K^+ losses. The resultant metabolic alkalosis is ameliorated by K^+ and Cl^- administration, but correction is difficult because of continuing losses. Interestingly, the volume of diarrhea is reduced dramatically by proton pump inhibition, which reduces gastric Cl^- secretion and presumably reduces Cl^- delivery to the small intestine.[22]

Other Causes of Excessive Chloride Losses

Villous adenomas occur in the distal colon and typically secrete 1 to 3 l/day of fluid that is rich in Na^+, Cl^-, and K^+. Because the volume of secreted fluid is relatively low, these tumors are only occasionally associated with metabolic alkalosis, which is usually mild when present.[23] Cystic fibrosis is characterized by high sweat [Cl^-] and, with excessive sweating, Cl^- losses can be large enough to cause metabolic alkalosis. In children and adolescents, this acid-base disorder can be the presenting symptom.[24] Patients with high-volume ileostomy losses can sometimes develop severe metabolic alkalosis,[25] and their fluid contains abnormally high [Na^+] and [Cl^-]. The use of gastric tissue to augment bladder size (gastrocystoplasty) can occasionally lead to transient metabolic alkalosis as a result of gastrin-induced Cl^- secretion into the urine.[26]

Severe Potassium Deficiency

In patients with severe K^+ depletion (serum [K^+] <2 mmol/l), metabolic alkalosis can be sustained despite Cl^- administration.[12] Chloride resistance in this setting is probably caused by impairment of renal Cl^- reabsorption induced by K^+ depletion (see earlier discussion). Even partial repletion of K^+ stores rapidly reverses this problem and makes the alkalosis Cl^- responsive.

Primary Stimulation of Collecting Duct Ion Transport

Box 13-3 lists the causes of metabolic alkalosis caused by primary stimulation of collecting duct ion transport. Specific examples are discussed next.

Metabolic Alkalosis from Primary Stimulation of Ion Transport

- Mineralocorticoid excess
  - Primary hyperaldosteronism: adenoma, hyperplasia
  - Cushing syndrome
  - Corticotropin-secreting tumor
  - Renin-secreting tumor
  - Glucocorticoid-remediable aldosteronism
  - Adrenogenital syndromes
  - Fludrocortisone treatment
  - 9α-Fluoroprednisolone (inhaled)
- Apparent mineralocorticoid excess
  - Licorice
  - Carbenoxolone
  - Liddle syndrome
  - 11β-Hydroxysteroid dehydrogenase deficiency
- Glucocorticoids (high dose)
  - Methylprednisolone

Box 13-3 Causes of metabolic alkalosis resulting from primary stimulation of collecting duct ion transport.

Mineralocorticoid Excess

Aldosterone and other mineralocorticoids cause metabolic alkalosis by directly stimulating both the H^+-ATPase and the ENaC in the collecting duct, promoting Na^+ retention, K^+ loss, and metabolic alkalosis (see Figs. 13-1 and 13-4). The metabolic alkalosis is typically mild (serum [HCO_3^-] 30 to 35 mmol/l) and is associated with more severe hypokalemia (K^+ often <3 mmol/l) than observed with Cl^- depletion alkalosis.[11,14] Primary hyperaldosteronism is by far the most common cause of this form of metabolic alkalosis (see Chapter 40), but it can also occur with rarer hereditary defects in cortisol synthesis or in the regulation of aldosterone secretion (Box 13-3). Glucocorticoid-remediable aldosteronism (GRA) is caused by a mutation that results in stimulation of aldosterone secretion by adrenocorticotropic hormone (ACTH) rather than by angiotensin.[27] The oral mineralocorticoid fludrocortisone, as well as inhaled 9α-fluoroprednisolone, can induce metabolic alkalosis if used inappropriately. Corticosteroids, when administered in high doses, increase renal K^+ excretion nonspecifically and produce a mild increase in serum [HCO_3^-].

Apparent Mineralocorticoid Excess Syndromes

Several inherited abnormalities produce a metabolic alkalosis that is clinically indistinguishable from hyperaldosteronism but without measurable aldosterone (see Chapter 49). Liddle syndrome results from a genetic mutation that prevents the removal of ENaCs from the urinary membrane of collecting duct epithelial cells[28] (see Fig. 13-3). As a result, Na^+ reabsorption cannot be downregulated, causing the same cascade of events seen in hyperaldosteronism. Because continuous stimulation of Na^+ reabsorption expands ECF volume, however, aldosterone levels are vanishingly low. In another rare familial disorder, confusingly termed "the syndrome of apparent mineralocorticoid excess," a mutation inactivates 11β-hydroxysteroid dehydrogenase, an enzyme adjacent to the mineralocorticoid receptor that rapidly converts cortisol to cortisone, minimizing cortisol binding to this receptor.[29] When this enzyme is inactivated, cortisol activates the receptor, stimulating Na^+ reabsorption and K^+ secretion and producing metabolic alkalosis and hypertension with low aldosterone levels. Glycyrrhizic acid (a component of natural licorice), carbenoxolone, and gossypol (an agent that inhibits spermatogenesis) inhibit the activity of 11β-hydroxysteroid dehydrogenase and can cause the same clinical picture.[11]

Metabolic Alkalosis from Alkali Administration

Renal Status	Causes
Normal renal function (only in association with K^+ depletion or low NaCl intake)	Alkali intake: $NaHCO_3$, citrate, lactate, acetate, amino acid anions
Renal failure	Milk-alkali syndrome Alkali intake Aluminum hydroxide with K^+ exchange resin

Table 13-1 Causes of metabolic alkalosis associated with alkali administration.

Potential Sources of Alkali

Alkali or Alkali Precursors	Source
Bicarbonate	$NaHCO_3$: pills, intravenous solutions Proprietary preparations (e.g., Alka-Seltzer), baking soda $KHCO_3$: pills, oral solutions
Lactate	Ringer solutions Peritoneal dialysis solutions
Acetate Glutamate Propionate	Parenteral nutrition solutions
Citrate	Blood products Plasma exchange, K^+ supplements Alkalinizing agents
Calcium compounds*	Calcium supplements and phosphate binders ($CaCO_3$, calcium acetate, calcium citrate)

Table 13-2 Potential sources of alkali. *Alkalinizing effect minimal when given orally.

Alkali Administration

Table 13-1 lists the causes of metabolic alkalosis induced by alkali administration. Exogenous alkali produces metabolic alkalosis in individuals with normal kidney function only when body K^+ or Cl^- stores are deficient, because these deficiencies impair HCO_3^- excretion by the kidney[15] (see Fig. 13-3). In acute or chronic kidney disease, alkali administration or ingestion can produce metabolic alkalosis independent of K^+ and Cl^- stores if the damage is severe enough to impair excretion of the excess alkali.[16] *Milk-alkali syndrome* is characterized by the concomitant presence of metabolic alkalosis and kidney damage, initiated by the ingestion of $NaHCO_3$ in combination with excess calcium (either in milk or as $CaCO_3$).[30,31] In this disorder, kidney damage is caused by calcium deposition, facilitated by an alkaline urine. The renal damage in turn facilitates the maintenance of metabolic alkalosis by limiting HCO_3^- excretion in the face of continued ingestion. Metabolic alkalosis is usually relatively mild in these patients unless they develop concomitant vomiting. In hospitalized patients with kidney failure, a wide variety of alkali sources or alkali precursors can cause metabolic alkalosis (Table 13-2). Although aluminum hydroxide is now administered only rarely, its use in combination with sodium polystyrene sulfonate (Kayexalate) can cause metabolic alkalosis because aluminum binds to the resin in exchange for Na^+. As a result, the HCO_3^- normally secreted into the duodenum is not titrated by H^+, which was

neutralized by the aluminum hydroxide, nor does bicarbonate form an insoluble salt with aluminum. Instead, it is completely reabsorbed from the gut, increasing serum [HCO_3^-].[32]

Other Causes

Refeeding after starvation causes an abrupt increase in serum [HCO_3^-] from the low concentrations characteristic of the fasting state. In some patients, serum [HCO_3^-] increases transiently above normal, causing a mild metabolic alkalosis. The causes are multiple, including HCO_3^- generation from metabolism of accumulated organic anions and K^+ and Cl^- depletion. Administration of either vitamin D or parathyroid hormone causes a small but significant increase in serum [HCO_3^-].[33,34] Despite this experimental finding, hyperparathyroidism is not associated with clinically significant metabolic alkalosis. Hypercalcemia and vitamin D intoxication have been associated with metabolic alkalosis, but in most cases, the alkalosis can be explained by the vomiting that characteristically accompanies these disorders. High aldosterone levels induced by hyperreninemia in renovascular or malignant hypertension are associated with hypokalemia and occasionally with very minor increases in serum [HCO_3^-].

CLINICAL MANIFESTATIONS

Mild to moderate metabolic alkalosis is well tolerated, with few clinically important adverse effects. Patients with serum [HCO_3^-] as high as 40 mmol/l are usually asymptomatic. The adverse effect of most concern is hypokalemia, which increases the likelihood of cardiac arrhythmias in patients with coronary heart disease.[33] With more severe metabolic alkalosis (serum [HCO_3^-] >45 mmol/l), arterial oxygen tension (Pa_{O_2}) often falls to less than 50 mm Hg (<6.6 kP) secondary to hypoventilation, and ionized calcium decreases (due to alkalemia). Patients with serum [HCO_3^-] greater than 50 mmol/l may develop seizures, tetany, delirium, or stupor. These changes in mental status are probably multifactorial in origin, resulting from alkalemia, hypokalemia, hypocalcemia, and hypoxemia.

DIAGNOSIS

Diagnosis of metabolic alkalosis involves three steps (Fig. 13-6). The first step, detection, is most often based on the finding of an elevated venous [total CO_2]. The second step is evaluation of the secondary response (hypoventilation), excluding the possibility that a respiratory acid-base abnormality is also present. This step requires measurement of arterial pH and $Paco_2$. The third step is determination of the cause.

Serum [total CO_2] greater than 30 mmol/l in association with hypokalemia is virtually pathognomonic of metabolic alkalosis. The only other cause of an elevated value is chronic respiratory acidosis, and hypokalemia is not a feature (see Chapter 14). Because the diagnosis is usually evident and metabolic alkalosis is almost always uncomplicated, measurement of arterial pH and $Paco_2$ is unnecessary in most patients. If the alkalosis is severe (serum [HCO_3^-]

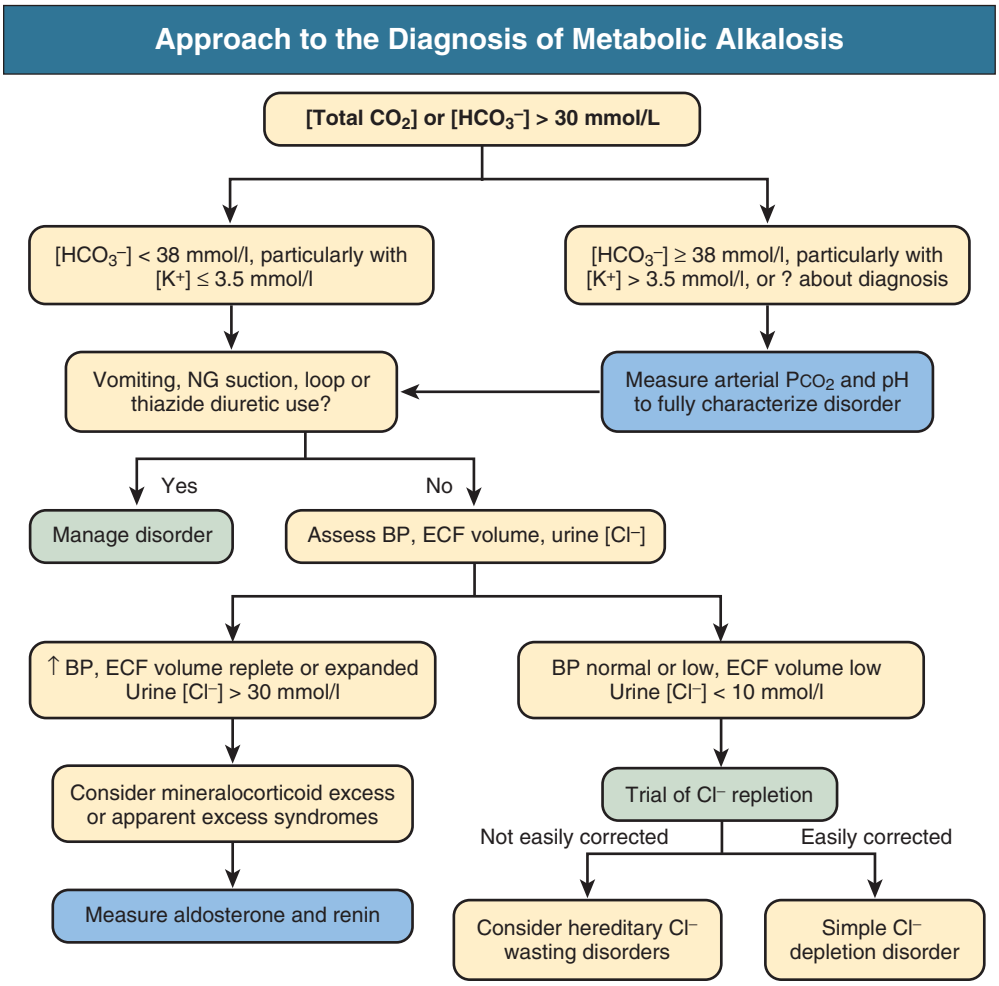

Figure 13-6 Approach to diagnosis of metabolic alkalosis. If the increase in [total CO_2] (or serum [HCO_3^-]) is mild and hypokalemia is present, arterial gas measurements are usually not necessary, and a simple algorithm can be used to diagnose the cause of the metabolic alkalosis. If hypokalemia is not present, if the increase in serum [total CO_2] is severe, or if there is a question about the diagnosis, arterial measurement of pH and Pco_2 is recommended to determine whether the condition is caused by metabolic alkalosis, respiratory acidosis, or a mixed disorder. *BP,* Blood pressure; *ECF,* extracellular fluid; *NG,* nasogastric.

>38 mmol/l), if the cause of the elevated [HCO_3^-] is unclear, or if a mixed acid-base disorder is suspected, however, the clinician should always measure pH and $Paco_2$ to characterize the disorder fully (see Fig. 13-6). These measurements confirm the presence of alkalosis and allow an estimation of whether the degree of hypoventilation is appropriate for the serum [HCO_3^-] (see earlier equation). A major deviation in $Paco_2$ from the expected value indicates the presence of a complicating respiratory acid-base disorder, either respiratory acidosis or respiratory alkalosis (see Chapter 14). The anion gap, [Na^+] – ([Cl^-] + [HCO_3^-]), is not increased in mild to moderate metabolic alkalosis, but it can be increased by as much as 3 to 5 mmol/l when alkalosis is severe. If the anion gap is more than 20 mmol/l, metabolic alkalosis is most likely complicated by superimposed metabolic acidosis (see Chapter 12).

The third step, elucidation of the cause, is straightforward in most patients. In more than 95%, metabolic alkalosis is caused either by diuretic use or by Cl^- losses from the GI tract. This information is usually easily obtained from the patient history, and attention can be directed toward the appropriate treatment. If the cause is unclear from the history, measurement of urine [Cl^-] can help. Unless the patient has recently taken a diuretic agent, urine [Cl^-] should be less than 10 mmol/l if the metabolic alkalosis is caused by Cl^- depletion. A confounding problem can be self-induced vomiting (bulimia) or the surreptitious use of diuretics, which presents the greater diagnostic dilemma because continued diuretic-induced Cl^- excretion may lead one to undertake an extensive workup for rarer forms of metabolic alkalosis. Urinary screens for specific diuretic compounds may be necessary to establish the correct diagnosis. In bulimic patients, urine Cl^- excretion should be low (spot urine [Cl^-] <10 mmol/l). If the cause is not apparent from this analysis, rarer forms of metabolic alkalosis caused by tubule transport abnormalities should be considered. In these forms of metabolic alkalosis, urine [Cl^-] is typically greater than 30 mmol/l.

In the patient with hypertension and adequate chloride intake who is not taking a diuretic agent, the most common cause of metabolic alkalosis is primary hyperaldosteronism. Measurement of serum renin and serum or urine aldosterone levels can distinguish mineralocorticoid excess syndromes from the rarer syndromes of apparent mineralocorticoid excess (see Box 13-3). The details of such a workup are presented in Chapter 40. In the normotensive or hypotensive patient who is not taking a diuretic agent, and who has metabolic alkalosis despite adequate chloride intake, the diagnosis of Bartter or Gitelman syndrome should be considered. Aldosterone and renin levels are not helpful in making these diagnoses because the levels can be low or high, depending on the patient's ECF volume at the time of measurement. Familial genetic studies can establish these diagnoses with high specificity.

TREATMENT

Chloride Depletion Alkalosis

In the patient with metabolic alkalosis caused by nasogastric drainage or vomiting, ECF volume depletion is virtually always a concomitant feature and treatment is straightforward. Administration of intravenous NaCl will correct both the alkalosis and the volume depletion. Potassium losses should also be replaced by oral or intravenous KCl. Typically the K^+ deficit is 200 to 400 mmol in patients with mild to moderate metabolic alkalosis induced by Cl^- losses in the upper GI tract. When nasogastric drainage must be continued, H^+ and Cl^- losses can be reduced by drugs that inhibit gastric acid secretion. In contrast to patients with GI losses, NaCl administration is not usually required in patients with metabolic alkalosis caused by diuretics, unless clinical signs of volume depletion are present. Potassium chloride supplements should be given to minimize K^+ depletion and mitigate the severity of the metabolic alkalosis. The addition of a potassium-sparing diuretic, such as amiloride, triamterene, spironolactone, or eplerenone, can assist in minimizing these abnormalities. Complete resolution of diuretic-induced metabolic alkalosis is often difficult because of continued Cl^- and K^+ losses. Fortunately, such a therapeutic goal is not necessary in most patients. A mild metabolic alkalosis is well tolerated, with no clinically significant adverse effects. If possible, the diuretic should be discontinued; the disorder then will resolve as long as the diet contains adequate K^+ and Cl^-.

The metabolic alkalosis and hypokalemia seen in Bartter and Gitelman syndromes is the most difficult to manage. In addition to oral KCl supplements (and magnesium supplements in Gitelman syndrome), nonsteroidal anti-inflammatory drugs have been used with moderate success. NSAIDs minimize renal Cl^- losses.

Corticosteroid and Apparent Corticosteroid-Induced Metabolic Alkalosis

Management of patients with metabolic alkalosis caused by corticosteroids or tubule transport abnormalities that mimic mineralocorticoid excess depends on the underlying cause. If the alkalosis is caused by an adrenal adenoma, the disorder is corrected by surgical removal of the tumor (see Chapter 40). In other forms of primary hyperaldosteronism, the alkalosis can be minimized by dietary NaCl restriction and by aggressive replacement of body K^+ stores with supplemental KCl. Spironolactone or eplerenone, competitive inhibitors of aldosterone, can also correct the disorder. In patients with GRA, the disorder is corrected by dexamethasone administration, which suppresses ACTH secretion and thereby reduces aldosterone secretion. In the hereditary forms of apparent mineralocorticoid excess (Liddle syndrome and 11β-hydroxysteroid dehydrogenase deficiency), amiloride is the most effective treatment.

Alkali Ingestion

Treatment for the patient ingesting alkali is directed at identification and discontinuation of the offending alkali (see Table 13-2). In the intensive care unit, sources of exogenous alkali should be carefully sought. A common offender is acetate used as a replacement for Cl^- in parenteral nutrition solutions.

SPECIAL PROBLEMS IN MANAGEMENT

Management of metabolic alkalosis is more difficult in patients with severe congestive heart failure or kidney failure. In patients with congestive heart failure and fluid overload who still have adequate kidney function, acetazolamide can be used to reduce serum [HCO_3^-]. This carbonic anhydrase inhibitor blocks H^+-linked Na^+ reabsorption, leading to excretion of both Na^+ and HCO_3^-. Acetazolamide decreases ECF volume and lowers serum [HCO_3^-] but stimulates K^+ excretion, exacerbating hypokalemia. When used, acetazolamide should be accompanied by aggressive K^+ replacement therapy.

In patients with kidney failure, serum [HCO_3^-] can be reduced in a timely manner by the appropriate form of renal replacement therapy. Continuous venovenous hemofiltration can remove as much as 20 to 30 l/day of an ultrafiltrate of plasma, and a bicarbonate-free replacement solution can be used to reduce serum [HCO_3^-] and increase serum [Cl^-]. Serum [HCO_3^-] can also be lowered by

continuous slow, low-efficiency dialysis, with the dialysate [HCO_3^-] adjusted to 23 mmol/l. Standard hemodialysis or peritoneal dialysis is less useful because these treatments are designed to add alkali to the blood, and the alkali concentration in the dialysate is set at 35 to 40 mmol/l. However, newer machines allow adjustment of the dialysate [HCO_3^-] to as low as 30 mmol/l, and this form of treatment has been used to successfully treat patients with severe metabolic alkalosis.[10]

If renal replacement therapy cannot be instituted, titration with hydrochloride is an alternative therapy. This approach is limited by the concentration of HCl that can be administered without producing hemolysis or venous coagulation. Although some have used higher concentrations, the recommended safe level of H^+ is 100 mmol/l (0.1N HCl). Even at this concentration, HCl must be administered through a central vein. Because the apparent space of distribution of HCO_3^- is approximately 50% of body weight, 350 mmol of H^+ is required to reduce serum [HCO_3^-] by 10 mmol/l in a 70-kg patient. The volume of fluid required for this titration using HCl, unfortunately, is 3.5 liters.

Ammonium chloride (NH_4Cl) and arginine monohydrochloride are not recommended for the treatment of metabolic alkalosis because of their life-threatening complications of NH_3 intoxication and severe hyperkalemia, respectively.[35]

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CHAPTER 14

Respiratory Acidosis, Respiratory Alkalosis, and Mixed Disorders

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Deviations of systemic acidity in either direction can have adverse consequences and, when severe, can be life threatening to the patient. Therefore, it is essential for the clinician to recognize and properly diagnose acid-base disorders, to understand their impact on organ function, and to be familiar with their treatment and the potential complications of treatment.[1,2]

RESPIRATORY ACIDOSIS (PRIMARY HYPERCAPNIA)

Definition

Respiratory acidosis is the acid-base disturbance initiated by an increase in carbon dioxide tension (P_{CO_2}) of body fluids and in whole-body CO_2 stores. The secondary increment in plasma bicarbonate ion concentration (plasma [HCO_3^-]) observed in acute and chronic hypercapnia is an integral part of the respiratory acidosis.[3] The level of arterial CO_2 tension (Pa_{CO_2}) is greater than 45 mm Hg in patients with simple respiratory acidosis, as measured at rest and at sea level. (To convert values from millimeters Hg to kilopascals [kP], multiply by 0.1333.) An element of respiratory acidosis may still occur with lower Pa_{CO_2} in patients residing at high altitude (e.g., 4000 m or 13,000 ft) or with metabolic acidosis, in whom a normal Pa_{CO_2} is inappropriately high for this condition.[4] Another special case of respiratory acidosis is the presence of arterial eucapnia, or even hypocapnia, occurring together with severe venous hypercapnia, in patients having an acute, profound decrease in cardiac output but relative preservation of respiratory function.[5,6] This disorder is known as pseudorespiratory alkalosis and is discussed under respiratory alkalosis.

Etiology and Pathogenesis

The ventilatory system is responsible for eucapnia by adjustment of alveolar minute ventilation ($\dot{V}_A$) to match the rate of CO_2 production. Its main elements are the respiratory pump, which generates a pressure gradient responsible for airflow, and the loads that oppose such action.

Carbon dioxide retention can occur from an imbalance between the strength of the respiratory pump and the extent of respiratory load (Fig. 14-1). When the respiratory pump is unable to balance the opposing load, respiratory acidosis develops. Respiratory acidosis may be acute or chronic (Tables 14-1 and 14-2). Life-threatening acidemia of respiratory origin can occur during severe, acute respiratory acidosis or during respiratory decompensation in patients with chronic hypercapnia.

A simplified form of the alveolar gas equation at sea level and on breathing of room air (Fi_{O_2}, 21%) is as follows:

$$Pa_{O_2} = 150 - 1.25\, Pa_{CO_2}$$

where P_{AO_2} is alveolar O_2 tension (mm Hg). This equation demonstrates that patients breathing room air cannot reach Pa_{CO_2} levels much greater than 80 mm Hg (10.6 kP) because the hypoxemia that would occur at greater values is incompatible with life. Therefore, extreme hypercapnia occurs only during O_2 therapy, and severe CO_2 retention is often the result of uncontrolled O_2 administration.

Secondary Physiologic Response

Adaptation to acute hypercapnia elicits an immediate increment in plasma [HCO_3^-] due to titration of non-HCO_3^- body buffers; such buffers generate HCO_3^- by combining with H^+ derived from the dissociation of carbonic acid, as follows:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+ \text{ and } H^+ + B^- \leftrightarrow HB$$

where B^- refers to the base component and HB refers to the acid component of non-HCO_3^- buffers. This adaptation is completed within 5 to 10 minutes from the increase in Pa_{CO_2}, and assuming a stable level of hypercapnia, no further change in acid-base equilibrium is detectable for a few hours.[7] Moderate hypoxemia does not alter the adaptive response to acute respiratory acidosis. However, preexisting hypobicarbonatemia (whether it is caused by metabolic acidosis or chronic respiratory alkalosis) enhances the magnitude of the HCO_3^- response to acute hypercapnia; this response is diminished in hyperbicarbonatemic states, whether caused by metabolic alkalosis or chronic respiratory acidosis.[8,9]

The adaptive increase in plasma [HCO_3^-] observed in acute hypercapnia is amplified greatly during chronic hypercapnia as a result of HCO_3^- generation by the kidney.[10] In addition, the renal response to chronic hypercapnia includes a reduction in the rate of Cl^- reabsorption, resulting in depletion of body Cl^- stores. Complete adaptation to chronic hypercapnia requires 3 to 5 days.[7] Table 14-3 provides quantitative aspects of the secondary physiologic responses to acute and chronic hypercapnia. More recently, a substantially steeper slope for the change in plasma [HCO_3^-] in chronic respiratory acidosis was reported (0.51 mmol/l for each 1 mm Hg chronic increase in Pa_{CO_2}), but the small number of arterial blood gas (ABG) measurements, one for each of 18 patients, calls in question the validity of the conclusion reached.[11] The renal response to chronic hypercapnia is not altered appreciably by dietary Na^+ or Cl^- restriction, moderate K^+ depletion, alkali loading, or moderate hypoxemia. However, recovery from chronic hypercapnia is crippled by a diet deficient in Cl^-; in this circumstance, despite correction of the level of Pa_{CO_2}, plasma [HCO_3^-] remains elevated as long as the state of Cl^- deprivation persists, leading to posthypercapnic metabolic alkalosis.

Clinical Manifestations

Because clinical hypercapnia almost always occurs in association with hypoxemia, it is often difficult to determine whether a specific

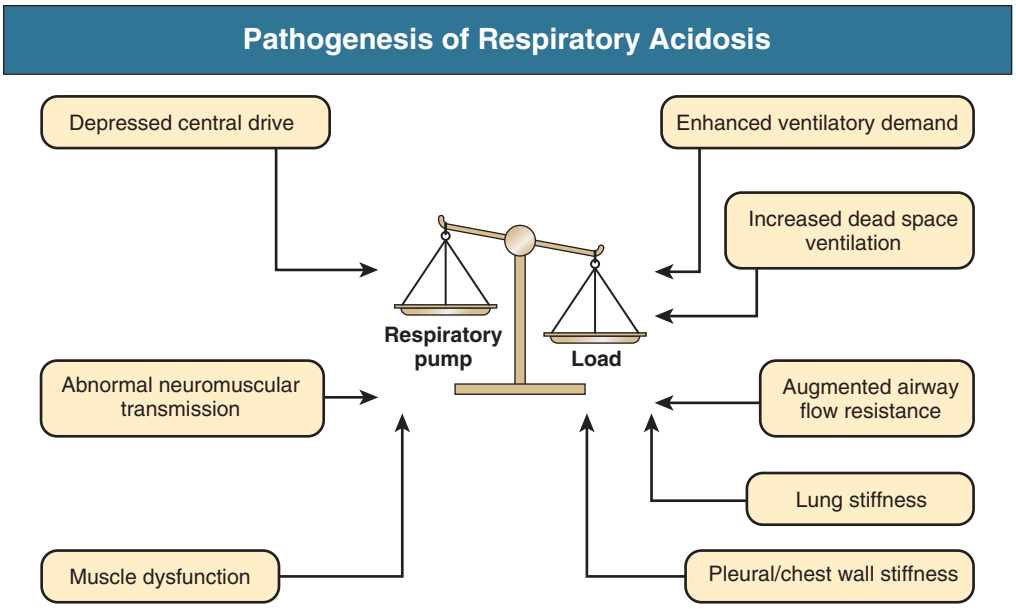

Figure 14-1 Pathogenesis of respiratory acidosis.

manifestation is the consequence of elevated $Paco_2$ or reduced Pao_2. Nevertheless, the clinician should bear in mind several characteristic manifestations of neurologic or cardiovascular dysfunction to diagnose the condition accurately and to treat it effectively.[4,7]

Neurologic Symptoms

Acute hypercapnia is often associated with marked anxiety, severe breathlessness, disorientation, confusion, incoherence, and combativeness. A narcotic-like effect can occur in patients with chronic hypercapnia, and drowsiness, decreased alertness, inattention, forgetfulness, loss of memory, irritability, confusion, and somnolence may be observed. Motor disturbances, including tremor, myoclonic jerks, and asterixis, are frequently observed with both acute and chronic hypercapnia. Sustained myoclonus and seizure activity can also develop. Signs and symptoms of increased intracranial pressure (ICP) such as pseudotumor cerebri are occasionally evident in patients with either acute or chronic hypercapnia and appear to be related to the vasodilating effects of CO_2 on cerebral blood vessels. Headache is a frequent complaint. Blurring of the optic discs and frank papilledema can be found when hypercapnia is severe. Hypercapnic coma characteristically occurs in patients with acute exacerbations of chronic respiratory insufficiency who are treated injudiciously with high-flow O_2.[12]

Cardiovascular Symptoms

Acute hypercapnia of mild to moderate degree is usually characterized by warm and flushed skin, bounding pulse, sweating, increased cardiac output, and normal or increased blood pressure. By comparison, severe hypercapnia might be attended by decreases in both cardiac output and blood pressure. Cardiac arrhythmias occur frequently in patients with either acute or chronic hypercapnia, especially those receiving digoxin.

Renal Symptoms

Mild to moderate hypercapnia results in renal vasodilation, but acute increments in $Paco_2$ to levels above 70 mm Hg (9.3 kP) can induce renal vasoconstriction and hypoperfusion. Salt and water retention typically attend sustained hypercapnia, especially in the presence of cor pulmonale. In addition to the effects of heart failure on the kidney, multiple other factors might be at play, including the prevailing stimulation of the sympathetic nervous system and the renin-angiotensin-aldosterone axis, the increased renal vascular resistance, and the elevated levels of antidiuretic hormone (ADH) and cortisol.[12]

Diagnosis

Whenever CO_2 retention is suspected, ABG values should be obtained.[12] If the patient's acid-base profile reveals hypercapnia in association with acidemia, at least an element of respiratory acidosis must be present. However, hypercapnia can be associated with a normal or even an alkaline pH if certain additional acid-base disorders are also present. Information from the patient history, physical examination, and ancillary laboratory data should be used to assess whether part or all of the increase in $Paco_2$ reflects an adaptive response to metabolic alkalosis rather than being primary in origin.

Treatment

As previously noted, CO_2 retention, whether acute or chronic, is always associated with hypoxemia in patients breathing room air. Consequently, O_2 administration represents a critical element in the management of respiratory acidosis.[1,13] However, supplemental O_2 may lead to worsening hypercapnia, especially in patients with chronic obstructive pulmonary disease (COPD). Although a depressed respiratory drive in CO_2 retention seems to play a role, other factors might account for the worsening hypercapnia in response to supplemental O_2 therapy. These include an increase in dead space ventilation and ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch caused by the loss of hypoxic pulmonary vasoconstriction and the Haldane effect (decreased hemoglobin affinity for CO_2 in the presence of increased O_2 saturation), which mandates an increase in ventilation to eliminate the excess CO_2.[7]

Figures 14-2 and 14-3 outline the management of acute respiratory acidosis and chronic respiratory acidosis. Whenever possible, treatment must be directed at removal or amelioration of the underlying cause. Immediate therapeutic efforts should focus on securing a patent airway and restoring adequate oxygenation by delivery of an O_2-rich inspired mixture. Supplemental oxygen can be administered to the spontaneously breathing patient with nasal cannulas,

Causes of Acute Respiratory Acidosis	
Increased Load	**Depressed Pump**
Enhanced Ventilatory Demand	**Depressed Central Drive**
High-carbohydrate diet High-carbohydrate dialysate (peritoneal dialysis) Sorbent-regenerative hemodialysis	General anesthesia Sedative overdose Head trauma Cerebrovascular accident Obesity-hypoventilation syndrome Cerebral edema Brain tumor Encephalitis Brainstem lesion
Increased Dead Space Ventilation	**Abnormal Neuromuscular Transmission**
Acute lung injury Multilobar pneumonia Cardiogenic pulmonary edema Pulmonary embolism Positive-pressure ventilation Supplemental oxygen	High spinal cord injury Guillain–Barré syndrome Status epilepticus Botulism, tetanus Crisis in myasthenia gravis Familial periodic paralysis Drugs or toxic agents (e.g., curare, succinylcholine, aminoglycosides, organophosphate poisoning)
Augmented Airway Flow Resistance ***Upper Airway Obstruction***	**Muscle Dysfunction**
Coma-induced hypopharyngeal obstruction Aspiration of foreign body or vomitus Laryngospasm Angioedema Inadequate laryngeal intubation Laryngeal obstruction after intubation	Fatigue Hyperkalemia Hypokalemia
Lower Airway Obstruction	
Status asthmaticus Exacerbation in chronic obstructive pulmonary disease	
Lung Stiffness **Atelectasis** **Pleural/Chest Wall Stiffness**	
Pneumothorax Hemothorax Flail chest Abdominal distention Peritoneal dialysis	

Table 14-1 **Causes of acute respiratory acidosis.**

Causes of Chronic Respiratory Acidosis	
Increased Load	**Depressed Pump**
Increased Dead Space Ventilation	**Depressed Central Drive**
Emphysema Pulmonary fibrosis Pulmonary vascular disease	Central sleep apnea Obesity-hypoventilation syndrome Methadone/heroin addiction Brain tumor Bulbar poliomyelitis Hypothyroidism
Augmented Airway Flow Resistance ***Upper Airway Obstruction***	**Abnormal Neuromuscular Transmission**
Tonsillar and peritonsillar hypertrophy Paralysis of vocal cords Tumor of vocal cords or larynx Airways stenosis after prolonged intubation Thymoma, aortic aneurysm	High spinal cord injury Poliomyelitis Multiple sclerosis Muscular dystrophy Amyotrophic lateral sclerosis Diaphragmatic paralysis
Lower Airway Obstruction	
Chronic obstructive pulmonary disease	
Lung Stiffness	**Muscle Dysfunction**
Severe chronic interstitial lung disease	Myopathic disease (e.g., polymyositis)
Pleural/Chest Wall Stiffness	
Kyphoscoliosis Thoracic cage disease Thoracoplasty Obesity	

Table 14-2 **Causes of chronic respiratory acidosis.**

Secondary Response to Alterations in Acid-Base Status			
Condition	**Initiating Mechanism**	**Expected Response: Change (Δ) in $[HCO_3^-]$ or $Paco_2$**	**Maximal Level of Response**
Respiratory acidosis	Increase in $Paco_2$		
Acute		Increase in $[HCO_3^-] \approx 0.1\ \Delta Paco_2$	30 mmol/l
Chronic		Increase in $[HCO_3^-] \approx 0.35\ \Delta Paco_2$	45 mmol/l
Respiratory alkalosis	Decrease in $Paco_2$		
Acute		Decrease in $[HCO_3^-] \approx 0.2\ \Delta Paco_2$	16-18 mmol/l
Chronic		Decrease in $[HCO_3^-] \approx 0.4\ \Delta Paco_2$	12-15 mmol/l
Metabolic acidosis	Decrease in $[HCO_3^-]$	Decrease in $Paco_2 \approx 1.2\ \Delta[HCO_3^-]$	10 mm Hg (1.3 kP)
Metabolic alkalosis	Increase in $[HCO_3^-]$	Increase in $Paco_2 \approx 0.7\ \Delta[HCO_3^-]$	65 mm Hg (8.7 kP)

Table 14-3 **Secondary response to alterations in acid-base status.** $[HCO_3^-]$, Plasma HCO_3^-; $Paco_2$, arterial carbon dioxide tension.

Venturi masks, or non-rebreathing masks. Oxygen flow rates up to 5 l/min can be used with nasal cannulas; each increment of 1l/min increases the fraction of inspired O_2 concentration (Fio_2) by approximately 4%. Venturi masks, calibrated to deliver Fio_2 between 24% and 50%, are most useful in patients with COPD because the Po_2 can be titrated, thus minimizing the risk of CO_2 retention. Oxygen saturation of hemoglobin of approximately 80% to 90% can be achieved with nonbreathing masks.

If the target Po_2 is not achieved with these measures and the patient is conscious, cooperative, hemodynamically stable, and able to protect the lower airway, a method of noninvasive ventilation through a mask can be used, including bilevel positive airway pressure (BiPAP). With BiPAP, the inspiratory-pressure support decreases the work of breathing, and the expiratory-pressure support improves gas exchange by preventing alveolar collapse.

Endotracheal intubation and mechanical ventilatory support should be initiated if adequate oxygenation cannot be secured by noninvasive measures, if progressive hypercapnia or obtundation

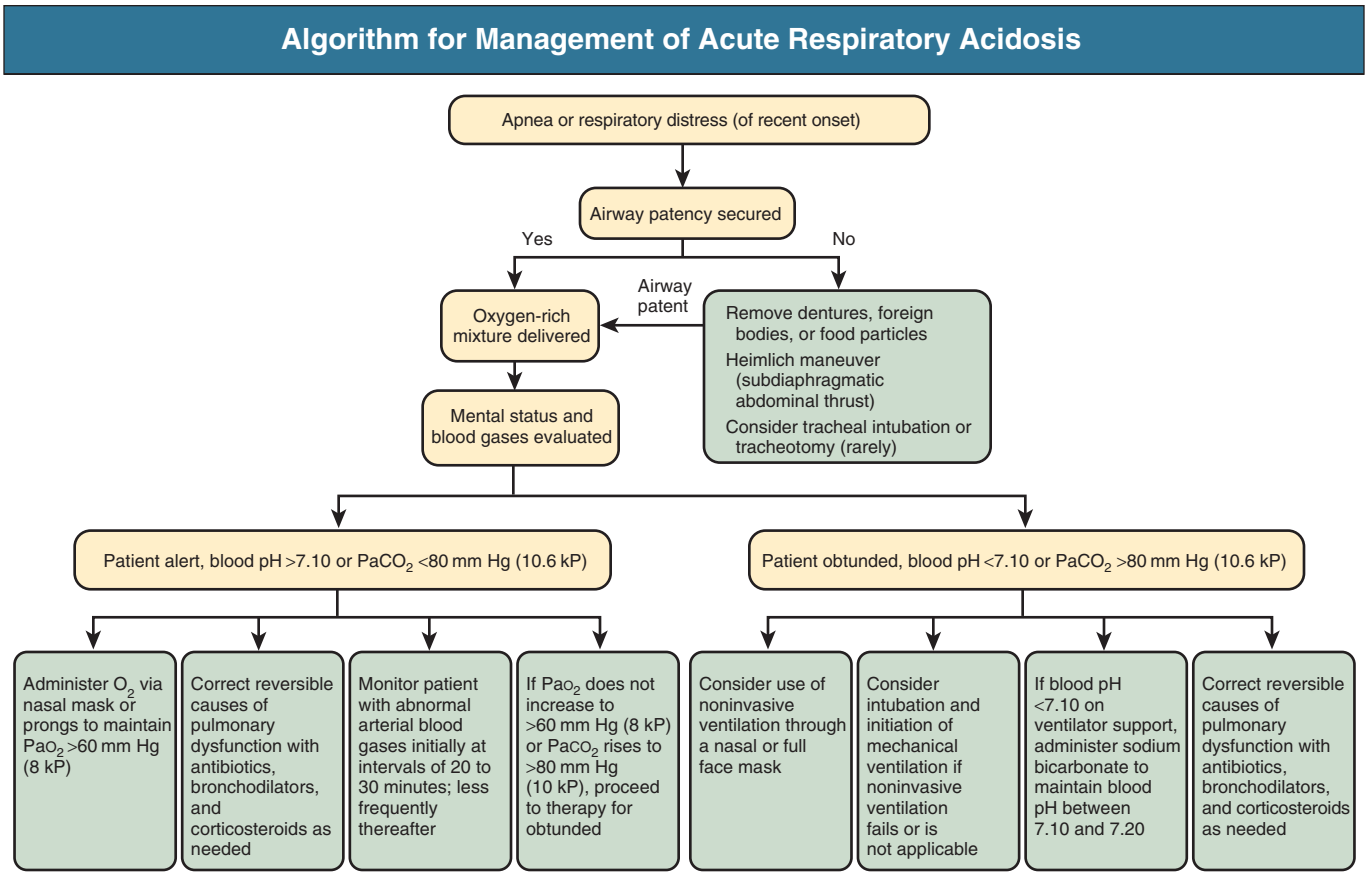

Figure 14-2 **Algorithm for management of the patient with acute respiratory acidosis.**

develops, or if the patient is unable to cough and clear secretions. Minute ventilation should be raised so that the $Paco_2$ gradually returns to near its long-term baseline and excretion of excess HCO_3^- by the kidneys is accomplished (assuming that Cl^- is provided). By contrast, overly rapid reduction in the $Paco_2$ risks the development of posthypercapnic alkalosis, with potentially serious consequences. If it develops, posthypercapnic alkalosis can be ameliorated by providing Cl^-, usually as the potassium salt, and administering the HCO_3^--wasting diuretic acetazolamide at doses of 250 to 500 mg once or twice daily. Vigorous treatment of pulmonary infections, bronchodilator therapy, and removal of secretions can offer considerable benefit. Naloxone will reverse the suppressive effect of narcotic agents on ventilation. Avoidance of tranquilizers and sedatives, gradual reduction of supplemental oxygen, aiming at a Pao_2 of about 60 mm Hg (8 kP), and treatment of a superimposed metabolic alkalosis will optimize the ventilatory drive.

Mechanical ventilation with tidal volumes of 10 to 15 ml/kg body weight often leads to alveolar overdistention and volutrauma. Therefore, an alternative approach called *permissive hypercapnia* (or controlled mechanical hypoventilation) has been successfully applied to prevent barotrauma and cardiovascular collapse.[4,14] In this form of treatment, lower tidal volumes of less than 6 ml/kg and lower peak inspiratory pressures are used. Further, $Paco_2$ is allowed to increase, but rarely exceeds 80 mm Hg, and blood pH can decrease to as low as 7.00 to 7.10, while adequate oxygenation is maintained. Because the patient usually requires neuromuscular blockade as well, accidental disconnection from the ventilator can cause sudden death. Contraindications to permissive hypercapnia include cerebrovascular disease, brain edema, increased ICP, convulsions, depressed cardiac function, arrhythmias, and severe pulmonary hypertension. Correction of acidemia attenuates the adverse hemodynamic effects of permissive hypercapnia.[15] It appears prudent, although still controversial, to keep the blood pH at approximately 7.30 by the administration of intravenous alkali when controlled hypoventilation is prescribed.[1,16]

RESPIRATORY ALKALOSIS (PRIMARY HYPOCAPNIA)

Definition

Respiratory alkalosis is the acid-base disturbance initiated by a reduction in CO_2 tension of body fluids. The secondary decrease in plasma $[HCO_3^-]$ observed in acute and chronic hypocapnia is an integral part of the respiratory alkalosis. Whole-body CO_2 stores are decreased and $Paco_2$ is less than 35 mm Hg (4.7 kP) in patients with simple respiratory alkalosis (at rest and at sea level). An element of respiratory alkalosis may still occur with higher levels of $Paco_2$ in patients with metabolic alkalosis, in whom a normal $Paco_2$ is inappropriately low for this primary metabolic disorder.

Etiology and Pathogenesis

Respiratory alkalosis is the most frequent acid-base disorder encountered because it occurs in normal pregnancy and with high-altitude residence.[2,17,18] It is also the most common acid-base abnormality in critically ill patients, occurring either as the simple disorder or as a component of mixed disturbances; indeed, in such patients, its

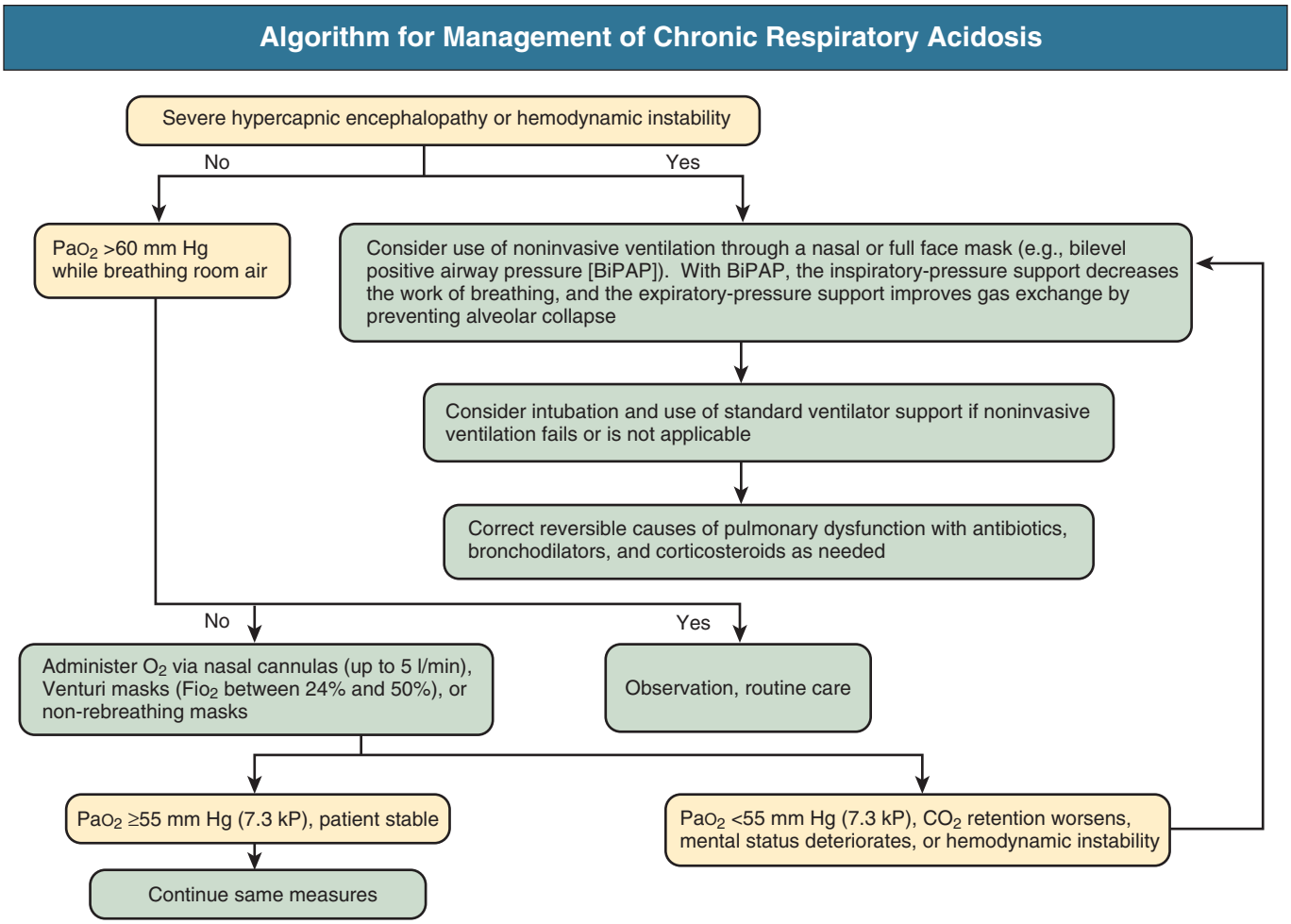

Figure 14-3 **Algorithm for management of the patient with chronic respiratory acidosis.**

presence may constitute a serious prognostic sign, especially if P_{aCO_2} level is below 20 to 25 mm Hg (2.7 to 3.3 kP). The presence of hypocapnia signifies transient or persistent alveolar hyperventilation relative to the prevailing CO_2 production, thus leading to negative CO_2 balance. Primary hypocapnia might also originate from the extrapulmonary elimination of CO_2 by dialysis or other extracorporeal circulation (e.g., heart-lung machine).

Table 14-4 provides the major causes of respiratory alkalosis.[12] In most patients, primary hypocapnia reflects alveolar hyperventilation caused by increased ventilatory drive. This is a result of signals arising from the lung, the peripheral chemoreceptors (carotid and aortic), or the brainstem chemoreceptors, or signals originating in other brain centers.

The response of the brainstem chemoreceptors to CO_2 can be augmented by systemic diseases (e.g., liver disease, sepsis), pharmacologic agents, and volition. Hypoxemia is a major stimulus of alveolar ventilation, but P_{AO_2} values below 60 mm Hg (8 kP) are required to elicit this effect consistently. Alveolar hyperventilation can be the result of maladjusted mechanical ventilators, psychogenic hyperventilation, and lesions involving the central nervous system.

In states of severe circulatory failure, arterial hypocapnia may coexist with venous and therefore tissue hypercapnia; under these conditions, the body CO_2 stores have been enriched so that there is respiratory acidosis rather than respiratory alkalosis. This entity, which we have termed *pseudorespiratory alkalosis,* develops in patients with profound depression of cardiac function and pulmonary perfusion but relative preservation of alveolar ventilation, including patients with advanced circulatory failure and those undergoing cardiopulmonary resuscitation (CPR). The severely reduced pulmonary blood flow limits the CO_2 delivered to the lungs for excretion, thereby increasing the venous P_{CO_2}. However, the increased ventilation-perfusion ratio causes a larger than normal removal of CO_2 per unit of blood traversing the pulmonary circulation, thereby giving rise to arterial eucapnia or frank hypocapnia. A progressive widening of the arteriovenous difference in pH and P_{CO_2} develops in two settings of cardiac dysfunction, circulatory failure and cardiac arrest (Fig. 14-4). In both situations, there is severe tissue O_2 deprivation, and it can be completely disguised by the reasonably preserved arterial O_2 values. Appropriate monitoring of acid-base composition and oxygenation in patients with advanced cardiac dysfunction requires mixed (or central) venous blood sampling in addition to the sampling of arterial blood.

Secondary Physiologic Response

Adaptation to acute hypocapnia is characterized by an immediate decrement in plasma [HCO_3^-] that results totally from nonrenal mechanisms and is explained principally by alkaline titration of the non-HCO_3^- body buffers (see second equation under Respiratory Acidosis). This adaptation is completed within 5 to 10 minutes of the

Causes of Respiratory Alkalosis	
Hypoxemia or Tissue Hypoxia	**Drugs and Hormones**
Decreased inspired O_2 tension High altitude Bacterial or viral pneumonia Aspiration of food, foreign body, or vomitus Laryngospasm Drowning Cyanotic heart disease Severe anemia Left shift deviation of oxyhemoglobin (HbO_2) dissociation curve Hypotension Severe circulatory failure Pulmonary edema Pseudorespiratory alkalosis	Respiratory stimulants (doxapram, nikethamide, ethamivan, progesterone, medroxyprogesterone) Salicylates Nicotine Xanthines Dinitrophenol Pressor hormones (epinephrine, norepinephrine, angiotensin II)
Central Nervous System Stimulation	**Miscellaneous**
Voluntary Pain Anxiety-hyperventilation syndrome Psychosis Fever Subarachnoid hemorrhage Cerebrovascular accident Meningoencephalitis Tumor Trauma	Exercise Pregnancy Gram-positive septicemia Gram-negative septicemia Hepatic failure Mechanical hyperventilation Heat exposure Recovery from metabolic acidosis Hemodialysis with acetate dialysate
Pulmonary Diseases with Stimulation of Chest Receptors	
Pneumonia Asthma Pneumothorax Hemothorax Flail chest Acute respiratory distress syndrome Cardiogenic and noncardiogenic pulmonary edema Pulmonary embolism Pulmonary fibrosis	

Table 14-4 Causes of respiratory alkalosis.

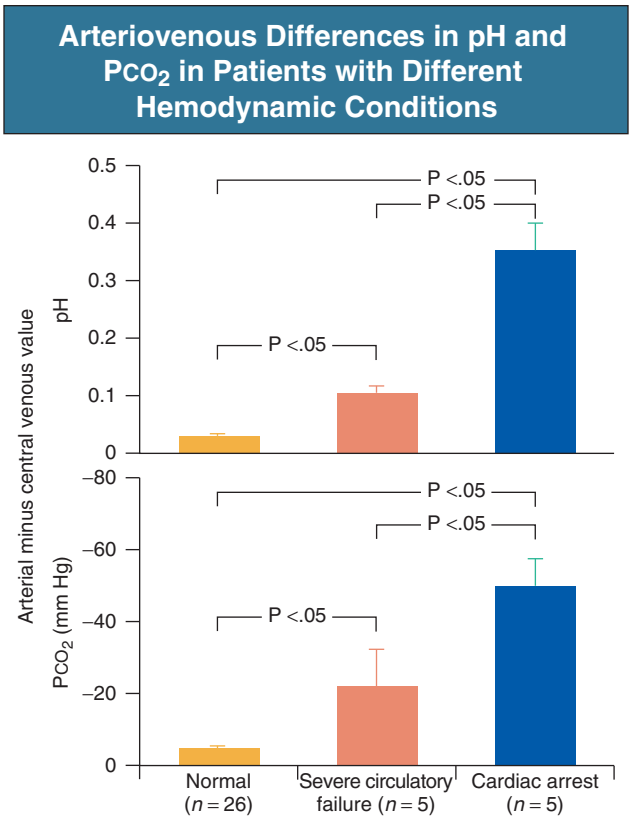

Figure 14-4 Arteriovenous differences in pH and P_{CO_2} in patients with different hemodynamic conditions.

onset of hypocapnia, and if there is no further change in P_{aCO_2}, no additional detectable changes in acid-base equilibrium occur for several hours.[7]

Adaptation to chronic hypocapnia entails an additional, larger decrease in plasma [HCO_3^-] as a consequence of renal adjustments that reflect a dampening of H^+ secretion by the renal tubule.[10] Approximately 2 to 3 days are required for completion of the adaptation to chronic hypocapnia. Quantitative aspects of the secondary physiologic responses to acute and chronic hypocapnia are shown in Table 14-3.

Clinical Manifestations

A rapid decrease in P_{aCO_2} to half-normal values or lower is typically accompanied by numbness and paresthesias of the extremities, chest discomfort (especially in patients manifesting increased airway resistance), circumoral numbness, lightheadedness, and mental confusion. Muscle cramps, increased deep tendon reflexes, carpopedal spasm, and generalized seizures occur infrequently. Cerebral vasoconstriction and reduced cerebral blood flow have been well documented during acute hypocapnia; in severe cases, cerebral blood flow might decrease to below 50% of normal values. Hypocapnia can have deleterious effects on the brain of premature infants; in patients with traumatic brain injury, acute stroke, or general anesthesia; and after sudden exposure to very high altitude.[19] Long-term neurologic sequelae can develop when immature brains are exposed to P_{aCO_2} levels below 15 mm Hg (2 kP) for even short periods. Furthermore, abrupt correction of hypocapnia in these patients leads to cerebral vasodilation, which might cause reperfusion injury or intraventricular hemorrhage.

Brain injury caused by hypocapnia probably results from cerebral ischemia. Other factors include hypocapnia itself, alkalemia, pH-induced shift of the oxyhemoglobin (HbO_2) dissociation curve, decreased levels of ionized calcium and potassium, depletion of the antioxidant glutathione by cytotoxic excitatory amino acids, increases in anaerobic metabolism, cerebral oxygen demand, neuronal dopamine, and seizure activity. If sepsis is present, brain damage worsens with the release of lipopolysaccharide, interleukin-1β, and tumor necrosis factor α.[19]

The cardiovascular manifestations of respiratory alkalosis differ in passive and active hyperventilation. The induction of acute hypocapnia in anesthetized patients (i.e., passive hyperventilation) results in a decrease in cardiac output, an increase in peripheral resistance, and a decrease in the systemic blood pressure. By contrast, active hyperventilation does not change or might even increase cardiac output and leaves systemic blood pressure virtually unchanged. The discrepant response of cardiac output during hyperventilation probably reflects the decrease in venous return caused by mechanical ventilation in passive hyperventilation and the reflex tachycardia consistently observed in active hyperventilation. Sustained hypocapnia induced by exposure to high altitude for several weeks results in a cardiac output within control values or higher. Although it does not lead to cardiac arrhythmias in normal individuals, acute

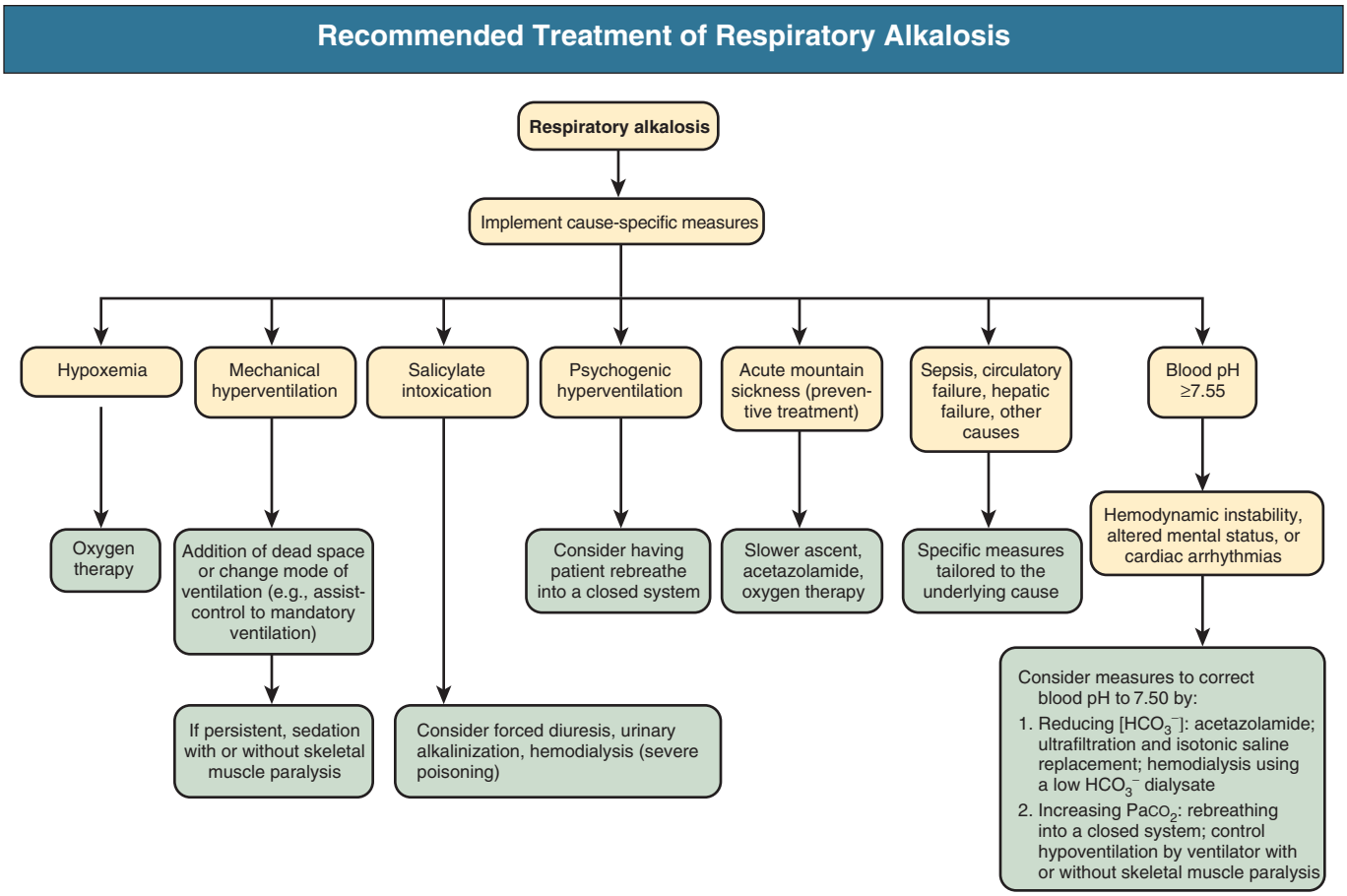

Figure 14-5 **Recommended management of the patient with respiratory alkalosis.**

hypocapnia appears to contribute to the generation of both atrial and ventricular tachyarrhythmias in patients with ischemic heart disease; such arrhythmias are frequently resistant to standard forms of therapy. Chest pain and ischemic ST-T wave changes have been observed in acutely hyperventilating patients with no evidence of fixed lesions on coronary angiography.

Diagnosis

Evaluation of the patient history, physical examination, and ancillary laboratory data are required to establish the diagnosis of respiratory alkalosis.[12,17] Careful observation can detect abnormal patterns of breathing in some patients, although marked hypocapnia can occur without a clinically evident increase in respiratory effort. ABG determinations are required to confirm the presence of hyperventilation.

The diagnosis of respiratory alkalosis, especially the chronic form, is frequently missed; physicians often misinterpret the electrolyte pattern of hyperchloremic hypobicarbonatemia as indicative of normal anion gap metabolic acidosis. If the patient's acid-base profile reveals hypocapnia in association with alkalemia, at least an element of respiratory alkalosis must be present. However, hypocapnia might be associated with a normal or an acidic pH because of the concomitant presence of additional acid-base disorders. The clinician should also note that mild degrees of chronic hypocapnia leave blood pH within the high-normal range. The diagnosis of respiratory alkalosis can have important clinical implications; it often provides a clue to the presence of an unrecognized, serious disorder or signals the threat of a known underlying disease.

Treatment

Figure 14-5 provides a synopsis of the management of patients with respiratory alkalosis. The view that hypocapnia poses minimal risk to health under most conditions is not accurate. Substantial hypocapnia in hospitalized patients, whether spontaneous or deliberately induced, may result in transient or permanent damage in the brain as well as the respiratory and cardiovascular systems.[19] Furthermore, rapid correction of severe hypocapnia leads to vasodilation of ischemic areas, resulting in reperfusion injury in the brain and lung. Consequently, severe hypocapnia in hospitalized patients must be prevented whenever possible, and if it is present, abrupt correction should be avoided. Severe alkalemia caused by acute primary hypocapnia requires corrective measures that depend on whether serious clinical manifestations are present. Such measures can be directed at reducing plasma [HCO_3^-], increasing $Paco_2$, or both. Even if baseline plasma [HCO_3^-]is moderately decreased, reducing it further can be particularly rewarding in these patients because this maneuver combines effectiveness with relatively little risk. For patients with the anxiety-hyperventilation syndrome, in addition to reassurance or sedation, rebreathing into a closed system (e.g., paper bag) might prove helpful by interrupting the vicious cycle that can result from the reinforcing effects of the symptoms of hypocapnia.

Respiratory alkalosis resulting from severe hypoxemia requires O_2 therapy. The oral administration of 250 to 500 mg acetazolamide twice daily can be beneficial in the management of signs and symptoms of high-altitude sickness, a syndrome characterized by hypoxemia and respiratory alkalosis.[17] Patients undergoing mechanical ventilation can facilitate effective correction of hypocapnia, whether from maladjusted ventilator or other factors, by resetting the device.

MIXED ACID-BASE DISTURBANCES

Definition

Mixed acid-base disturbances are defined as the simultaneous presence of two or more acid-base disorders. Such association might include two or more simple acid-base disorders (e.g., metabolic acidosis and respiratory alkalosis), two or more forms of a simple disturbance having different time course or pathogenesis (e.g., acute and chronic respiratory acidosis or high anion gap and hyperchloremic metabolic acidosis, respectively), or a combination of these two forms.[20] The secondary or adaptive response to a simple acid-base disorder cannot be taken as one of the components of a mixed disorder.

Etiology and Pathogenesis

Mixed acid-base disturbances are usually observed in hospitalized patients, especially those in critical care units.[21] Characterization of these disorders and proper identification of their pathogenesis can be challenging and are a prerequisite for taking sound corrective action. Certain clinical settings are often associated with mixed acid-base disorders, including cardiorespiratory arrest, sepsis, drug intoxications, diabetes mellitus, and organ failure (especially renal, hepatic, and pulmonary failure). Patients with severe renal impairment or end-stage renal disease (ESRD) are prone to mixed acid-base disturbances of great complexity and severity.[22] In these conditions, metabolic acidosis of the high anion gap type is frequently accompanied by a component of hyperchloremic acidosis, inability to mount an appropriate secondary response to chronic respiratory acidosis or alkalosis, inability to respond to a load of fixed acids (e.g., lactic acid) or a primary loss of alkali (e.g., diarrhea) with the expected increase in net acid excretion, and inability to respond to an alkali load with bicarbonaturia despite the presence of increased plasma [HCO_3^-]. As a result, these patients are particularly vulnerable to the development of both extreme acidemia and extreme alkalemia.

A practical classification of mixed acid-base disorders recognizes three main groups of disturbances in accordance with the preceding definition (Fig. 14-6). Representative examples are depicted in Table 14-5, and some of these mixed disorders are reviewed next.

Metabolic Acidosis and Respiratory Acidosis

The expected hypocapnia secondary to metabolic acidosis is estimated by $\Delta Pa_{CO_2}/\Delta[HCO_3^-]$ = 1.2 mm Hg/mEq/l (Δ indicates change). If measured Pa_{CO_2} exceeds 5 mm Hg of the estimated value, respiratory acidosis is also present. Clinical examples of metabolic acidosis combined with respiratory acidosis include untreated cardiopulmonary arrest, circulatory failure in patients with COPD, severe renal failure associated with hypercapnic respiratory failure, various intoxications, and hypokalemic (or less frequently hyperkalemic) paralysis of respiratory muscles in patients with diarrhea or renal tubular acidosis (RTA) (Fig. 14-7 and Table 14-5, example 4).

Metabolic Alkalosis and Respiratory Alkalosis

Metabolic alkalosis combined with respiratory alkalosis might be encountered in patients with primary hypocapnia associated with chronic liver disease who develop metabolic alkalosis from a variety of causes, including vomiting, nasogastric drainage, diuretics, profound hypokalemia, and alkali administration (e.g., absorption of antacids; infusion of lactated Ringer solution, alimentation solutions, citrated blood products), especially in the patient with renal impairment. Mixed metabolic/respiratory alkalosis also occurs in critically ill patients, particularly those undergoing mechanical ventilation, and in patients with respiratory alkalosis, caused by either pregnancy or heart failure, who experience metabolic alkalosis attributable to diuretics or vomiting (Fig. 14-8 and Table 14-5, example 6).

Metabolic Alkalosis and Respiratory Acidosis

Metabolic alkalosis with respiratory acidosis is one of the most frequently encountered mixed acid-base disorders. The usual clinical setting involves COPD in conjunction with diuretic therapy, but it can occur with other causes of metabolic alkalosis (e.g., vomiting, administration of corticosteroids) (Fig. 14-9 and Table 14-5, example 5). Critically ill patients with respiratory failure caused by acute respiratory distress syndrome and occasionally those with profound hypokalemia with diaphragmatic muscle weakness also might develop mixed metabolic alkalosis and respiratory acidosis.

Metabolic Acidosis and Respiratory Alkalosis

As with respiratory acidosis and metabolic alkalosis, the combination of metabolic acidosis and respiratory alkalosis is characterized

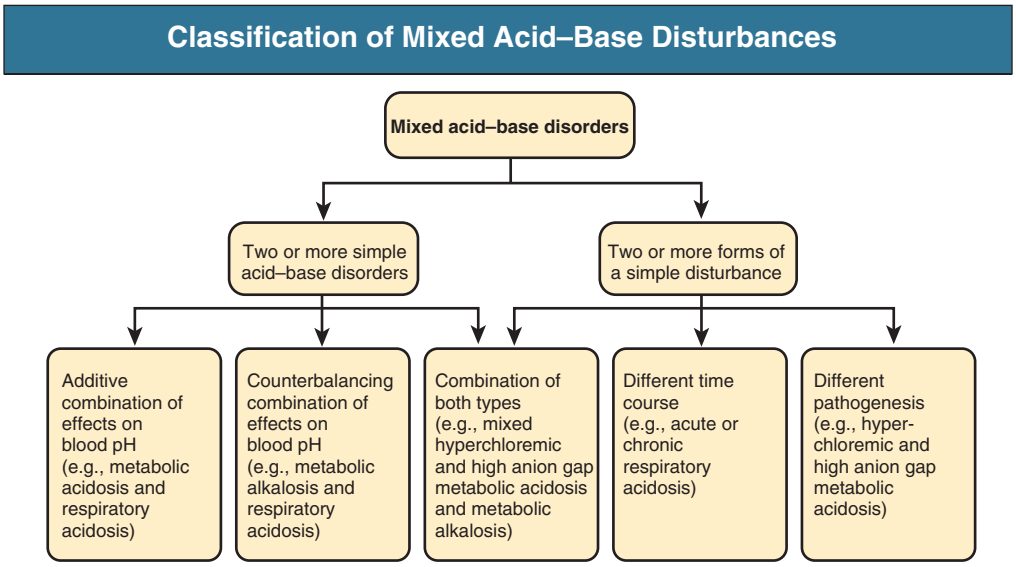

Figure 14-6 Classification of mixed acid-base disturbances.

Representative Examples of Mixed Acid-Base Disorders

Type of Mixed Disorder	No.*	pH	$Paco_2$† (mm Hg)	HCO_3^- (mmol/l)	Na^+ (mmol/l)	K^+ (mmol/l)	Cl^- (mmol/l)	Anion gap (mmol/l)	Clinical Circumstances
Hyperchloremic and high anion gap metabolic acidosis	1	7.12	16	5	137	3.6	114	18	Diabetic ketoacidosis with adequate salt and water balance
Mixed high anion gap metabolic acidosis and metabolic alkalosis	2	7.36	31	17	132	4.0	89	26	Alcoholic liver disease, vomiting, and lactic acidosis
	3	7.40	40	24	143	5.5	95	24	Diabetic ketoacidosis and lactic acidosis after bicarbonate therapy
Mixed high anion gap metabolic acidosis and respiratory acidosis	4	7.18	44	16	133	5.7	100	17	Hepatic, renal, and pulmonary failure
Metabolic alkalosis and respiratory acidosis	5	7.44	55	36	135	3.8	84	15	COPD and diuretics
Metabolic alkalosis and respiratory alkalosis	6	7.60	40	38	131	3.6	77	16	Congestive heart failure and diuretics
Acute or chronic respiratory acidosis	7	7.22	80	32	141	4.3	99	10	COPD and therapy with O_2-rich mixtures

Table 14-5 Representative examples of mixed acid-base disorders. Anion gap is calculated as $[Na^+] - ([Cl^-] + [HCO_3^-])$. *COPD,* Chronic obstructive pulmonary disease. *Number for representative example as cited in text. †To convert to kP, multiply by 0.1333.

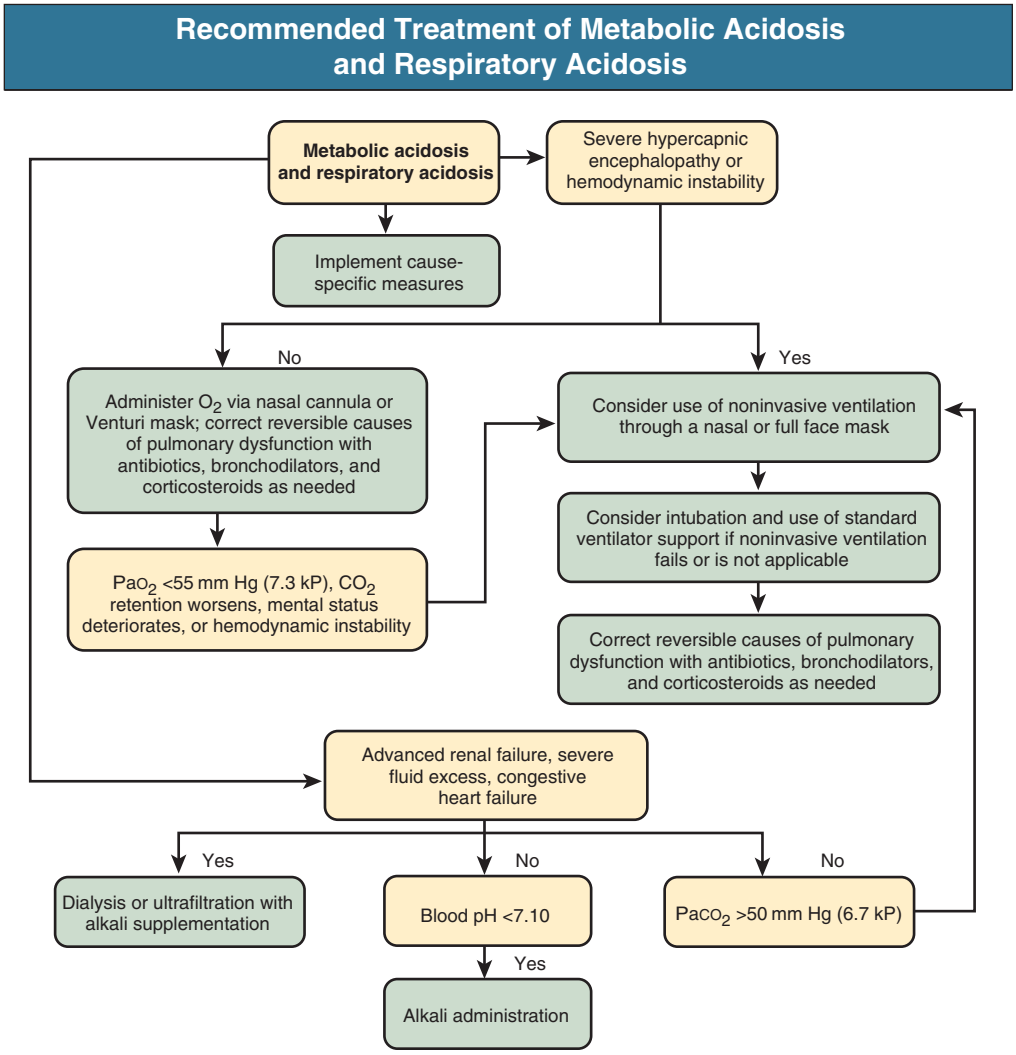

Figure 14-7 Recommended management of the patient with metabolic acidosis and respiratory acidosis.

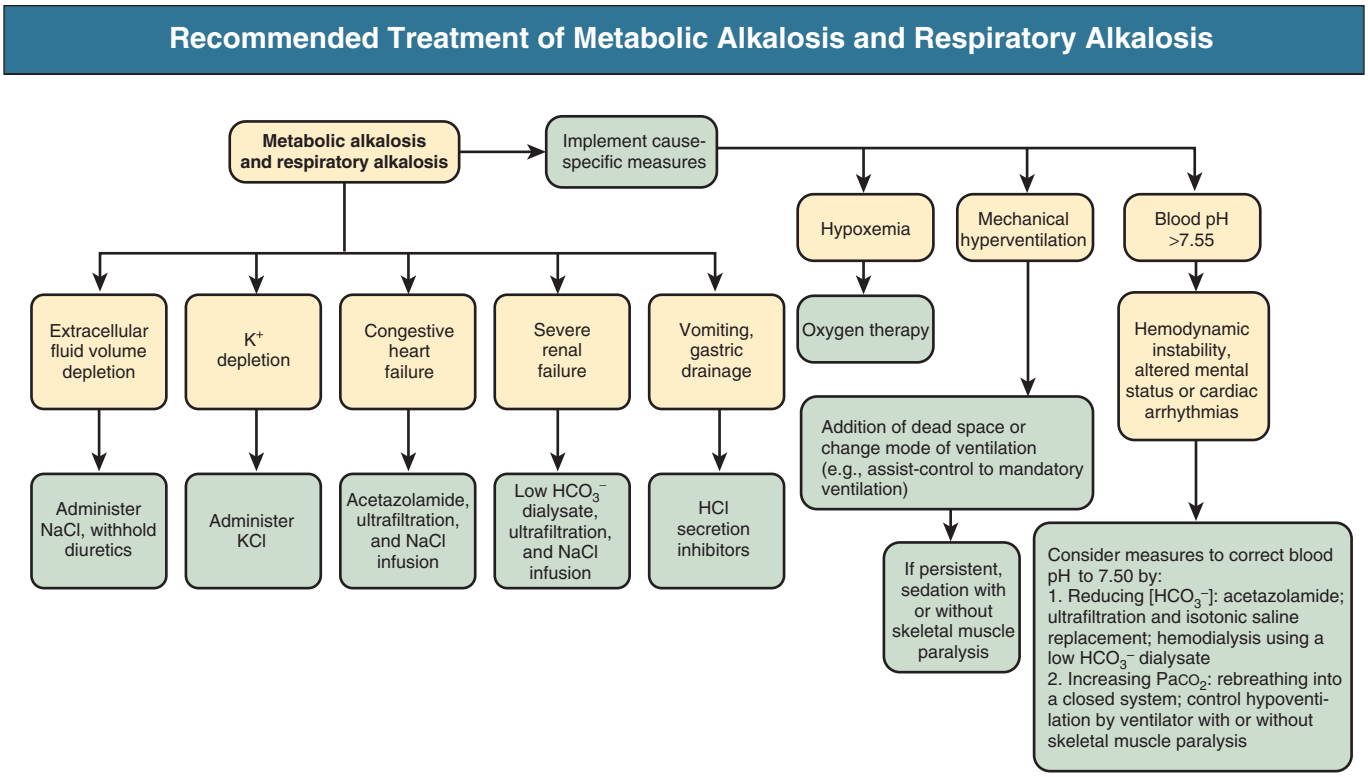

Figure 14-8 **Recommended management of the patient with metabolic alkalosis and respiratory alkalosis.**

by normal or near-normal blood pH; its two components exert offsetting effects on systemic acidity (Fig. 14-10). This disorder is common in intensive care unit patients and is generally associated with high mortality. Causes of the primary hypocapnia include fever, hypotension, gram-negative septicemia, pulmonary edema, hypoxemia, and mechanical hyperventilation. The component of metabolic acidosis in turn might be lactic acidosis (e.g., complicating shock, hepatic failure) or renal acidosis. A considerable fraction of adults and children develop respiratory alkalosis and lactic acidosis in the course of acute severe asthma. In some patients, the lactic acidosis appears to be caused by excessive use of β_2-adrenergic agonists and corticosteroids. The resulting increased ventilatory demands might worsen abnormal lung mechanics and precipitate ventilatory failure.[23,24] Salicylate intoxication is another cause of mixed metabolic acidosis and respiratory alkalosis. Stimulation of the ventilatory center in the brainstem accounts for the respiratory alkalosis, whereas the accelerated production of organic acids, including pyruvic, lactic, and keto acids, and to a lesser extent the accumulation of salicylic acid itself are responsible for the metabolic acidosis.

Metabolic Acidosis and Metabolic Alkalosis

Metabolic acidosis and metabolic alkalosis are typically observed in patients with alcoholic liver disease who develop fasting ketoacidosis or lactic acidosis in conjunction with metabolic alkalosis caused by vomiting, diuretics, or other causes (Table 14-5, examples 2 and 3). Protracted vomiting or nasogastric suction superimposed on uremic acidosis, diabetic ketoacidosis, or metabolic acidosis caused by diarrhea might also generate this offsetting metabolic combination. A similar picture might develop after administration of alkali during CPR or as therapy for diabetic ketoacidosis.

Mixed Metabolic Acidosis

Mixed high anion gap metabolic acidosis in patients with diabetic or alcoholic ketoacidosis may be combined with lactic acidosis resulting from circulatory failure. Uremic patients with associated lactic acidosis or ketoacidosis provide another example of mixed high anion gap acidosis. Mixed hyperchloremic metabolic acidosis is seen in patients with RTA or those receiving carbonic anhydrase inhibitors who also have substantial fecal losses of HCO_3^- caused by severe diarrhea. Mixed hyperchloremic and high anion gap metabolic acidosis occurs in patients with profuse diarrhea whose circulation becomes sufficiently compromised to generate in turn a high anion gap metabolic acidosis, as a result of renal failure or lactic acidosis. Patients with diabetic ketoacidosis whose renal function is maintained at reasonable levels by adequate salt and water intake might develop an element of hyperchloremic metabolic acidosis because of preferential excretion of ketone anions and conservation of Cl^- (Table 14-5, example 1).[25]

Mixed Metabolic Alkalosis

The coexistence of several processes with each contributing to a primary increase in plasma [HCO_3^-], including diuretic therapy, vomiting, mineralocorticoid excess, and severe potassium depletion, will give rise to mixed metabolic alkalosis.

Triple Disorders

The most frequent triple disorders comprise two cardinal metabolic disturbances in conjunction with either respiratory acidosis or respiratory alkalosis, such as severely ill patients with COPD and CO_2 retention who simultaneously develop metabolic alkalosis (usually caused by diuretics and a Cl^--restricted diet) and metabolic acidosis (usually lactic acidosis caused by hypoxemia, hypotension, or sepsis). This type of triple disorder also might be encountered during CPR when an element of metabolic alkalosis caused by alkali administration is superimposed on preexisting respiratory acidosis and metabolic (lactic) acidosis. Patients with respiratory alkalosis caused by advanced congestive heart failure also might have diuretic-induced metabolic alkalosis and lactic acidosis from tissue hypoperfusion.

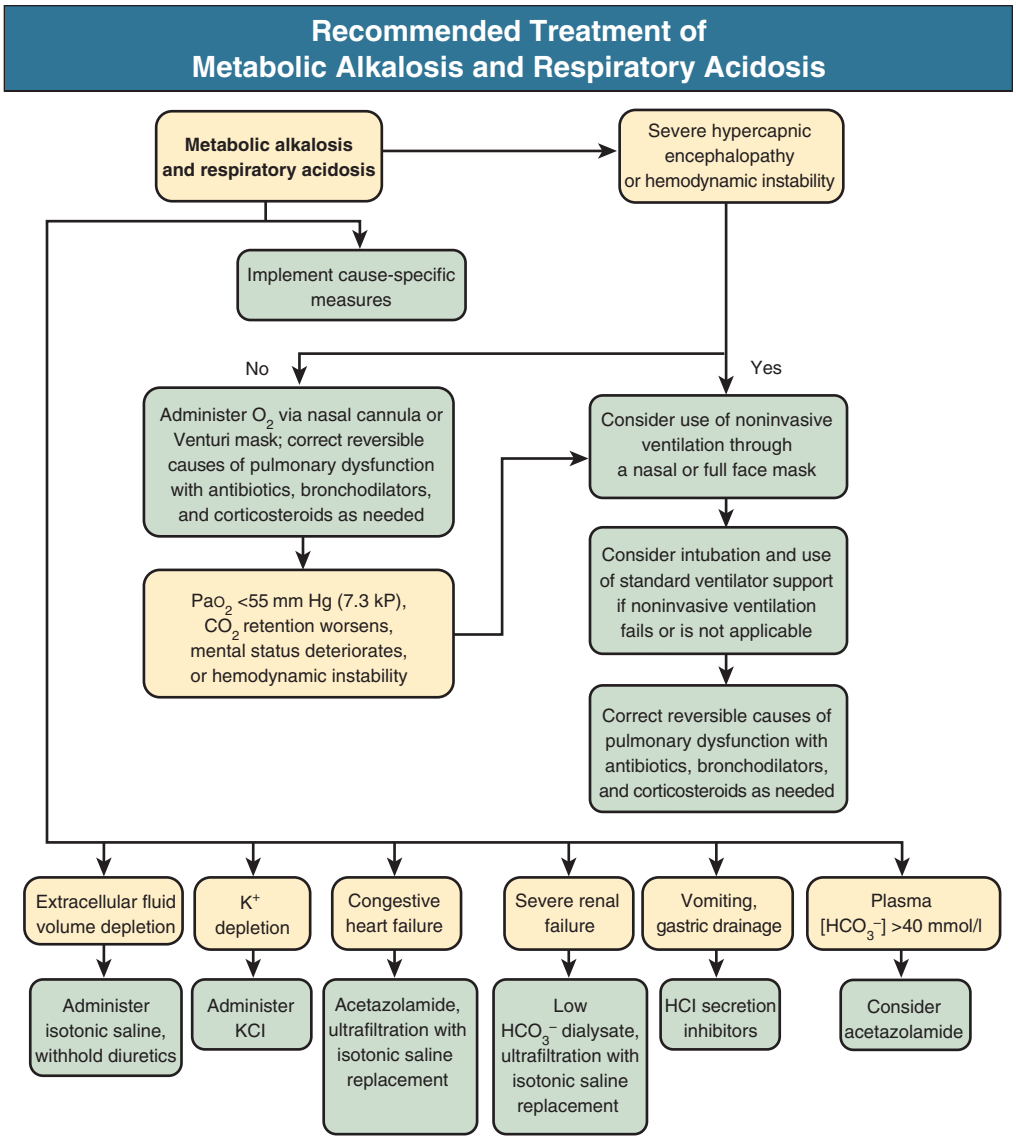

Figure 14-9 Recommended management of the patient with metabolic alkalosis and respiratory acidosis.

Such triple acid-base disorders can also be seen in patients with chronic alcoholism who develop metabolic alkalosis from vomiting, lactic acidosis from volume depletion or ethanol intoxication, and respiratory alkalosis from hepatic encephalopathy or sepsis.

Less common triple disorders encompass two cardinal respiratory disturbances in combination with either metabolic acidosis or metabolic alkalosis. The typical presentation involves critically ill patients with chronic respiratory acidosis who experience an abrupt reduction in $Paco_2$ because of mechanical ventilation and superimposed metabolic acidosis (usually lactic acidosis, reflecting circulatory failure) or metabolic alkalosis (e.g., from gastric fluid loss or diuretics). With superimposed metabolic alkalosis, extreme alkalemia might ensue because of the concomitant presence of hypocapnia and hyperbicarbonatemia. Even more infrequently, this same clinical setting might lead to a quadruple acid-base disorder in which all four cardinal acid-base disturbances coexist.

Clinical Manifestations

The symptoms and signs of the underlying disease that give rise to the observed mixed acid-base disorder dominate the clinical picture, but the development of severe abnormalities in either $Paco_2$ (severe hypocapnia or hypercapnia) or systemic acidity (profound acidemia or alkalemia) might be responsible for the superimposition of additional clinical manifestations. On the one hand, profound hypocapnia might induce obtundation, generalized seizures, and occasionally even coma or death as a result of a critical reduction in cerebral blood flow and other mechanisms. Rarely, angina pectoris also might occur. On the other hand, severe hypercapnia might generate a profound encephalopathy with the classic features of pseudotumor cerebri, including headaches, obtundation, vomiting, and bilateral papilledema, caused by increased ICP. Extreme acidemia results in depression of the central nervous system as well as the cardiovascular system.[7] Reduction in myocardial contractility and peripheral vascular resistance triggered by acidemia might result in severe hypotension. Profound alkalemia might elicit paresthesias, tetany, cardiac dysrhythmias, or generalized seizures.

Diagnosis

The basic principles underlying the diagnosis of mixed acid-base disorders are identical to those required for the identification of simple acid-base disturbances. These include assessment of the accuracy of the acid-base data by ensuring that the available values

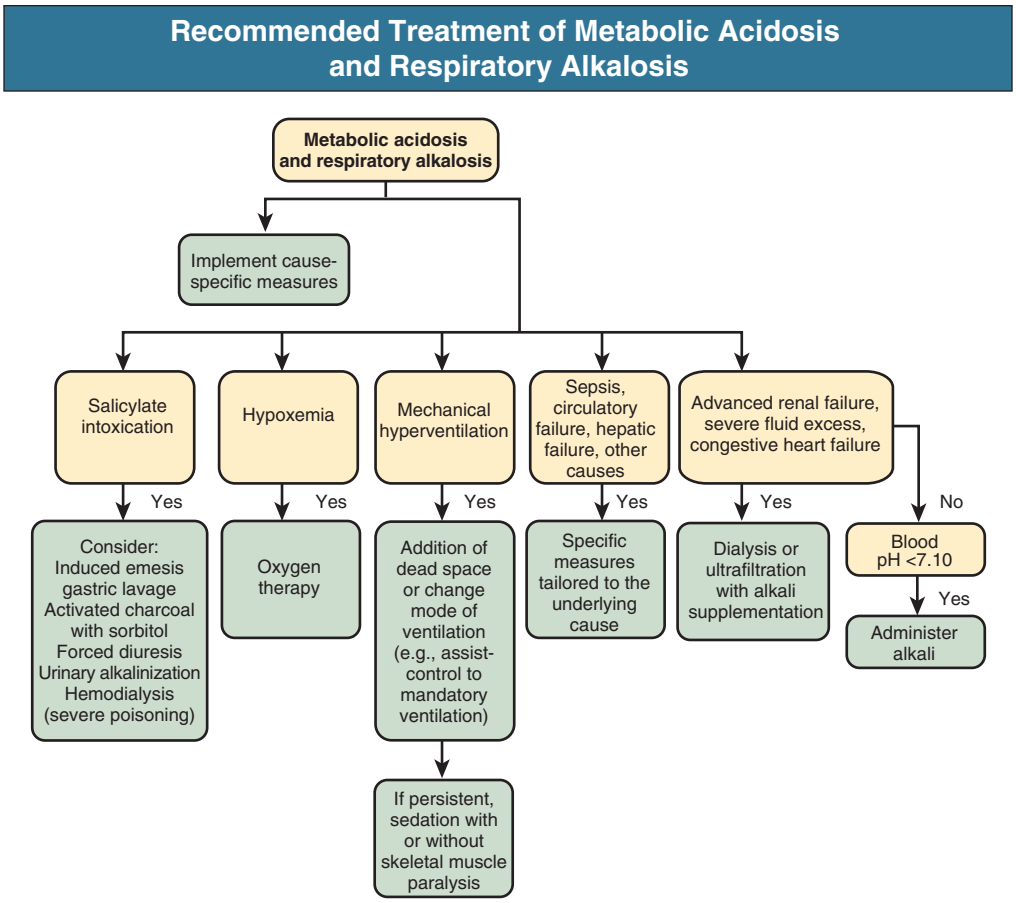

Figure 14-10 Recommended management of the patient with metabolic acidosis and respiratory alkalosis.

Blood Parameters in Diagnosis of Mixed Metabolic Acid-Base Disorders

Blood Composition	Normal	High Anion Gap Acidosis	High Anion Gap and Normal Anion Gap Acidosis	Metabolic Alkalosis	High Anion Gap Acidosis and Metabolic Alkalosis
pH	7.40	7.29	7.10	7.50	7.38
$Paco_2$ (mm Hg)	40	30	20	45	35
Bicarbonate (mmol/l)	24	14	6	34	20
Anion gap (mmol/l)	10	20	20	12	26
ΔBicarbonate	0	−10	−18	+10	−4
ΔAnion gap	0	+10	+10	+2	+16

Table 14-6 Blood parameters in diagnosis of patients with mixed metabolic acid-base disorders.

for pH, $Paco_2$, and plasma [HCO_3^-] satisfy the mathematical constraints of the Henderson-Hasselbalch equation; a careful history and performance of a complete physical examination; analysis of the plasma anion gap and other ancillary laboratory data; and knowledge of the quantitative aspects of the adaptive response to each of the four simple acid-base disturbances. Adherence to these principles cannot be overemphasized. Even experienced clinicians risk misdiagnosis of the prevailing acid-base status by bypassing this systematic approach.[3]

Normality of the acid-base parameters is not in itself sufficient for diagnosis of normal acid-base status; indeed, normal acid-base values might be the fortuitous result of mixed acid-base disorders (e.g., high anion gap acidosis treated with alkali infusion, diarrhea-induced metabolic acidosis in conjunction with vomiting-induced metabolic alkalosis). A given set of acid-base parameters is never diagnostic of a particular acid-base disorder, whether it is simple or mixed in nature; rather, it is consistent with a range of acid-base abnormalities. What on the surface appears to be a clear-cut simple acid-base disorder might actually reflect the interplay of a number of coexisting acid-base disturbances. The patient history and physical examination frequently provide important insights into the prevailing acid-base status as well as useful clues to the differential diagnosis.

A critical component of the diagnostic process is the examination of the plasma anion gap (Table 14-6). This derived parameter provides important insights into the nature of the prevailing changes in plasma [HCO_3^-]. An elevated plasma anion gap might offer the first clue to the presence of disordered acid-base status despite

normal acid-base parameters. With a plasma HCO_3^- concentration deficit ($\Delta[HCO_3^-]_p$), a normal or subnormal value for the plasma anion gap denotes that the entire decrease in HCO_3^- can be attributed to acidifying processes resulting in the loss of alkali (e.g., diarrhea, RTA) or to respiratory alkalosis. By comparison, with a high anion gap metabolic acidosis, there is usually a close reciprocal stoichiometry between the decrease in serum HCO_3^- and the increase in the anion gap, termed the Δ(anion gap). A reduction in serum HCO_3^- of 10 mmol/l is therefore associated with a Δ(anion gap) of 10 mmol/l. Addition of the value for the Δ(anion gap) to the prevailing level of serum HCO_3^- allows the derivation of the basal value of HCO_3^- existing before the development of the high anion gap metabolic acidosis. Appreciation of this reciprocal relationship between the $\Delta[HCO_3^-]_p$ and the Δ(anion gap) is important in distinguishing between a pure high anion gap metabolic acidosis and a mixed high and normal anion gap metabolic acidosis and in detecting a mixed high anion gap metabolic acidosis and metabolic alkalosis. Additional diagnostic insights are often obtained by examination of other laboratory data, including the serum potassium, glucose, urea nitrogen, and creatinine concentrations; semiquantitative measures for ketonemia or ketonuria; screening of blood or urine for toxins; and estimation of the serum osmolar gap.

Mild acid-base disorders pose particular diagnostic difficulty because of the overlap of values for the simple disturbances near the normal range. In such patients, any of several simple disorders or a variety of mixed disturbances might fully account for the acid-base data under evaluation. Again, careful correlation of all available clinical information should guide the diagnostic process.

Treatment

The management of mixed acid-base disturbances is aimed at restoration of the altered acid-base status by treatment of each simple acid-base disorder involved.[1,2,20,26] Figures 14-7 to 14-10 provide recommendations for treatment of patients with some common mixed acid-base disturbances.

Given the variable response time to therapy of the individual components, it is crucial to be aware of the effect that graded correction might have on systemic acidity. The asynchronous reversal of the individual components might be used at times to therapeutic advantage; on other occasions, such a practice might prove catastrophic. For example, extreme acidemia caused by metabolic acidosis and respiratory acidosis, or extreme alkalemia caused by metabolic alkalosis and respiratory alkalosis, might be safely corrected by a rapid return of $Paco_2$ toward normal. By comparison, an asynchronous return of $Paco_2$ to normal in a patient with profound metabolic acidosis and superimposed respiratory alkalosis might prove disastrous. Similarly, extreme caution should be exercised in treating patients with respiratory acidosis and metabolic alkalosis, one of the most common mixed acid-base disorders. Although therapeutic measures intended to improve alveolar ventilation should be instituted, an abrupt decrease in $Paco_2$ risks development of severe alkalemia. Therefore, aggressive measures should be taken to treat metabolic alkalosis, making certain that reversal of the metabolic component does not lag behind treatment of the respiratory element. In fact, because the ventilatory drive in patients with chronic respiratory acidosis depends in part on the prevailing acidemia, reversal of a complicating element of metabolic alkalosis regularly results in improved alveolar ventilation, thus achieving a decrease in $Paco_2$ and an increase in Pao_2.

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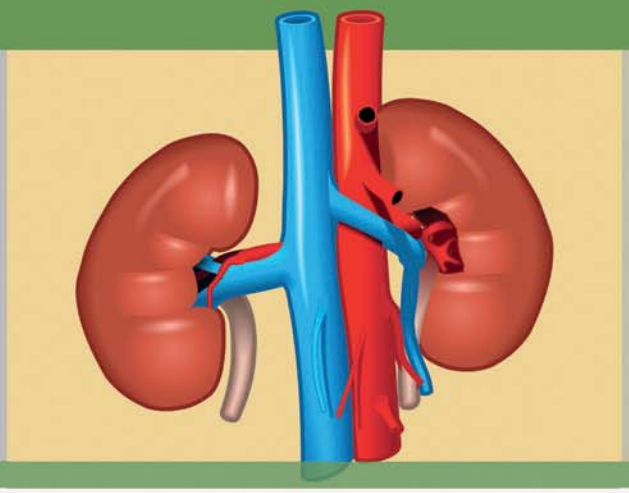

SECTION IV

Glomerular Disease

CHAPTER 15

Introduction to Glomerular Disease: Clinical Presentations

Jürgen Floege and John Feehally

DEFINITION

Glomerular disease has clinical presentations that vary from the asymptomatic individual who is found to have hypertension, edema, hematuria, or proteinuria at a routine medical assessment to a patient who has fulminant illness with acute kidney injury possibly associated with life-threatening extrarenal disease (Fig. 15-1). The most dramatic symptomatic presentations are uncommon. Asymptomatic urine abnormalities are much more common, but less specific, and may also indicate a wide range of nonglomerular urinary tract disease.

CLINICAL EVALUATION OF GLOMERULAR DISEASE

The history, physical examination, and investigations are aimed at excluding nonglomerular disease, finding evidence of associated multisystem disease, and establishing renal function.

History

The majority of glomerular diseases do not lead to symptoms that patients will report. However, specific questioning may reveal edema, hypertension, foamy urine, or urinary abnormalities during prior routine testing (e.g., during scheduled medical examinations). Multisystem diseases associated with glomerular disease include diabetes, hypertension, amyloid, lupus, and vasculitis. Apart from the individual history suggestive of these diseases, a positive family history may also be obtained in some cases. Other causes of familial renal disease may include Alport syndrome, especially if associated with hearing loss (see Chapter 48); uncommon familial forms of IgA nephropathy (see Chapter 23); focal segmental glomerulosclerosis (FSGS; see Chapters 18 and 19); complement-mediated glomerulonephritis (see Chapter 22); hemolytic uremic syndrome (HUS; see Chapter 29); and other rare conditions (see Chapter 28). Morbid obesity can be associated with FSGS. Certain drugs and toxins may cause glomerular disease, including nonsteroidal anti-inflammatory agents (NSAIDs) and interferon in minimal change disease (MCD); penicillamine, NSAIDs, and mercury (e.g., in skin-lightening creams) in membranous nephropathy; pamidronate and heroin in FSGS; and cyclosporine, tacrolimus, mitomycin C, and oral contraceptives in HUS. Recent or persistent infection, especially streptococcal infection, infective endocarditis, and certain viral infections (see Chapters 21, 57, and 58), may also be associated with a variety of glomerular diseases.

Malignant neoplasms associated with glomerular disease include lung, breast, and gastrointestinal (GI) carcinoma in membranous nephropathy; Hodgkin disease in MCD; non-Hodgkin lymphoma in membranoproliferative glomerulonephritis; and renal carcinoma in amyloid disease (see Chapter 27). Patients will occasionally present with the renal disease as the first manifestation of a tumor.

Physical Examination

The presence of dependent pitting edema suggests the nephrotic syndrome, heart failure, or cirrhosis. In the nephrotic patient, edema is often periorbital in the morning (Fig. 15-2), whereas the face is not affected overnight in edema associated with heart failure (edema distributes by gravity, and patient with heart failure cannot lie flat because of orthopnea resulting from pulmonary congestion) or cirrhosis (patient cannot lie flat because of pressure on the diaphragm from ascites). As it progresses, edema of genitals and abdominal wall becomes apparent, and accumulation of fluid in body spaces leads to ascites and pleural effusions. Edema is unpleasant, leading to feelings of tightness in the limbs and a bloated abdomen, with practical problems of clothes and shoes no longer fitting. Surprisingly, however, edema may become massive in nephrotic syndrome before patients seek medical help; fluid gains of 20 kg (44 lb) or more are not unusual (Fig. 15-3). The edema becomes firm and stops pitting only when it is longstanding. In children, fluid retention may also be striking with nephritic syndrome. Chronic hypoalbuminemia is also associated with loss of normal pink color under the nails, resulting in white nails or white bands if the nephrotic syndrome is transient (Muehrcke lines, Fig. 15-4). Xanthelasmas may also be present as a result of the hyperlipidemia associated with longstanding nephrotic syndrome (Fig. 15-5).

The presence of pulmonary signs should suggest one of the pulmonary-renal syndromes (see Boxes 24-3 and 24-4). Palpable purpura may be seen in vasculitis, systemic lupus, cryoglobulinemia, or endocarditis.

Laboratory Studies

Assessment of renal function and careful examination of the urine are critical (see Chapters 3 and 4). The quantity of urine protein and the presence or absence of dysmorphic red cells and casts will help classify the clinical presentation (see Fig. 15-1).

Certain serologic tests are also helpful. These include antinuclear and anti-DNA antibodies for lupus, cryoglobulins and rheumatoid factor suggesting cryoglobulinemia, anti–glomerular basement membrane (anti-GBM) antibodies for Goodpasture disease, antineutrophil cytoplasmic autoantibody (ANCA) for vasculitis, and antistreptolysin O titer or streptozyme test for poststreptococcal glomerulonephritis. Serum and urine electrophoresis will detect monoclonal light chains or heavy chains and assays for free light chains in serum or urine may aid in their quantification, as in myeloma-associated amyloid or light-chain deposition disease.

Testing for the presence of ongoing bacterial or viral infections is also useful. This includes blood cultures and testing for hepatitis

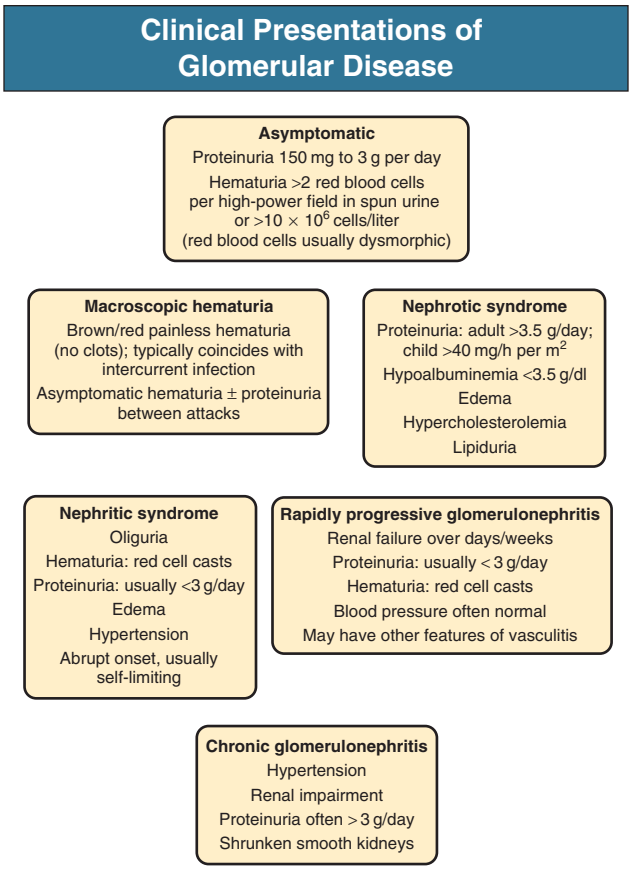

Figure 15-1 Clinical presentation of various glomerular diseases.

Figure 15-2 Nephrotic edema. Periorbital edema in the early morning in a nephrotic child. The edema resolves during the day under the influence of gravity.

Figure 15-3 Nephrotic edema. Severe peripheral edema in nephrotic syndrome; note the blisters caused by intradermal fluid.

Figure 15-4 Muehrcke lines (bands) in nephrotic syndrome. The white line grew during a transient period of hypoalbuminemia caused by the nephrotic syndrome.

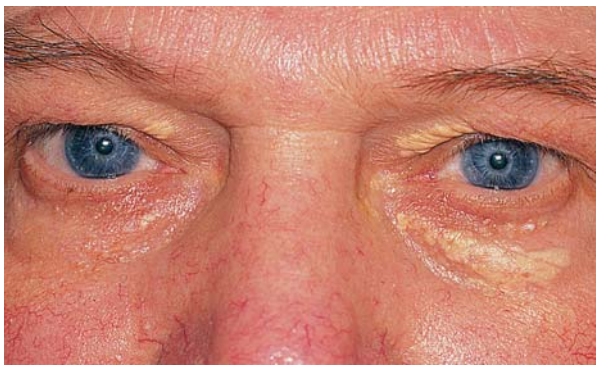

Figure 15-5 Xanthelasmas in nephrotic syndrome. These prominent xanthelasmas developed within 2 months in a patient with recent onset of severe nephrotic syndrome and serum cholesterol level of 550 mg/dl (14.2 mmol/l).

B, hepatitis C, and human immunodeficiency virus (HIV) infection.

Measurement of systemic complement pathway activation by testing for serum C3, C4, and CH50 (50% hemolyzing dose of complement) is often helpful in limiting the differential diagnosis (Table 15-1).

The emerging role for genetic evaluation in patients with glomerulonephritis (GN) is discussed in Chapters 19 and 22.

Imaging

Ultrasound scanning is recommended in the workup to ensure the presence of two kidneys, to rule out obstruction or anatomic abnormalities, and to assess kidney size. Renal size is often normal in GN,

Hypocomplementemia in Glomerular Disease			
Pathways Affected	**Complement Changes**	**Glomerular Disease**	**Nonglomerular Disease**
Classical pathway activation	C3 ↓, C4 ↓, CH50 ↓	Lupus nephritis (especially Class IV) Cryoglobulinemia Membranoproliferative GN type 1	
Alternative pathway activation	C3 ↓, C4 normal, CH50 ↓	Poststreptococcal GN GN associated with other infection* (e.g., endocarditis, shunt nephritis) HUS	Atheroembolic renal disease
	plus C3 nephritic factor	Dense deposit disease (formerly membranoproliferative GN type 2)	
Reduced complement synthesis	Acquired		Hepatic disease Malnutrition
	Hereditary C2 or C4 deficiency Factor H deficiency	Lupus nephritis Familial HUS Dense deposit disease	

Table 15-1 Hypocomplementemia in glomerular disease. *Glomerulonephritis *(GN)* with visceral abscesses is generally associated with normal or increased complement (elevations occur because complement components are acute-phase reactants). *CH50,* 50% Hemolyzing dose of complement; *HUS,* hemolytic uremic syndrome.

although large kidneys (>14 cm) are sometimes seen in nephrotic syndrome associated with diabetes, amyloid disease, or HIV infection. Large kidneys can also occasionally be seen with any acute severe GN. The occurrence of small kidneys (<9 cm) suggests advanced chronic kidney disease (CKD) and should limit enthusiasm for renal biopsy or aggressive immunosuppressive therapies.

Renal Biopsy

Renal biopsy is generally required to establish the type of glomerular disease and to guide treatment decisions (see Chapter 6). In some patients, however, renal biopsy is not performed. If nephrotic children have no unusual clinical features, the probability of MCD is so high that corticosteroids can be initiated without biopsy (see Chapter 17). In patients with acute nephritic syndrome, if all features point to poststreptococcal GN, especially in an epidemic, biopsy can be reserved for the minority who do not show early spontaneous improvement (see Chapter 57). In Goodpasture disease (see Chapter 24), the presence of lung hemorrhage and rapidly progressive renal failure with urinary red cell casts and high levels of circulating anti-GBM antibody establishes the diagnosis without the need for a biopsy, although a biopsy may still provide valuable prognostic information. In patients with systemic features of vasculitis, a positive ANCA titer, negative blood cultures, and a tissue biopsy specimen from another site showing vasculitis are sufficient to secure a diagnosis of renal vasculitis. Again, however, renal biopsy may provide important clues to disease activity and chronicity. Biopsy is also not generally performed in patients with longstanding diabetes with characteristic findings suggestive of diabetic nephropathy and other evidence of microvascular complications of diabetes (see Chapter 30). Biopsy may also not be indicated in many patients with glomerular disease presenting with minor, asymptomatic urine abnormalities and well-preserved renal function because the prognosis is excellent, and histologic findings will not alter management.

ASYMPTOMATIC URINE ABNORMALITIES

Urine testing that detects proteinuria or microhematuria is often the first evidence of glomerular disease. The random nature of urine testing in most communities inevitably means that much mild glomerular disease remains undetected. In some countries, symptomless individuals may have a urine test only if they require medical approval for some key life event, such as obtaining life insurance, joining the armed forces, or sometimes for employment purposes. In other countries, for example, Japan, urinalysis is performed routinely in school or for employment. These different practices may partly account for the apparently variable incidence of certain diseases, such as IgA nephropathy. Asymptomatic low-grade proteinuria and microhematuria and the combination of the two, increase in prevalence with age[1] (Fig. 15-6). Nevertheless, there is no evidence to justify routine population-wide screening for asymptomatic urine abnormalities as renal biopsy and therapeutic intervention are rarely required when renal function is preserved. Screening, in particular for microalbuminuria, may be indicated for high-risk populations, for example, patients with diabetes, hypertension, or cardiovascular disease, and those with a family history of renal disease.

Asymptomatic Microhematuria

Microhematuria is defined as the presence of more than two red blood cells (RBCs) per high-power field in a spun urine sediment (3000 rpm for 5 minutes) or more than 10×10^6 RBCs/l. Microhematuria is common in many glomerular diseases, especially IgA nephropathy and thin basement membrane nephropathy, although there are many other causes of hematuria (see Chapter 48). A glomerular origin should especially be considered if more than 5% of RBCs are acanthocytes (see Chapter 4) or if the hematuria is accompanied by RBC casts or proteinuria (Fig. 15-7).

Pathogenesis

Glomerular hematuria is thought to result from small breaks in the glomerular basement membrane that allow extravasation of RBCs into the urinary space. This may occur in the peripheral capillary wall but more often occurs in the paramesangial basement membrane, particularly in diseases involving injury to the mesangium (mesangiolysis). As long as the renal tubules are intact, low amounts of serum proteins lost together with RBCs in damaged glomeruli can be fully reabsorbed, resulting in "isolated" microhematuria.

Evaluation

The evaluation of microhematuria, discussed further in Chapters 48 and 61, begins with a thorough history. Urine culture should exclude urinary or prostatic infection. Phase contrast microscopy should follow in cases of persistent microhematuria to search for dysmorphic RBCs and RBC casts. In the absence of urine infection or a

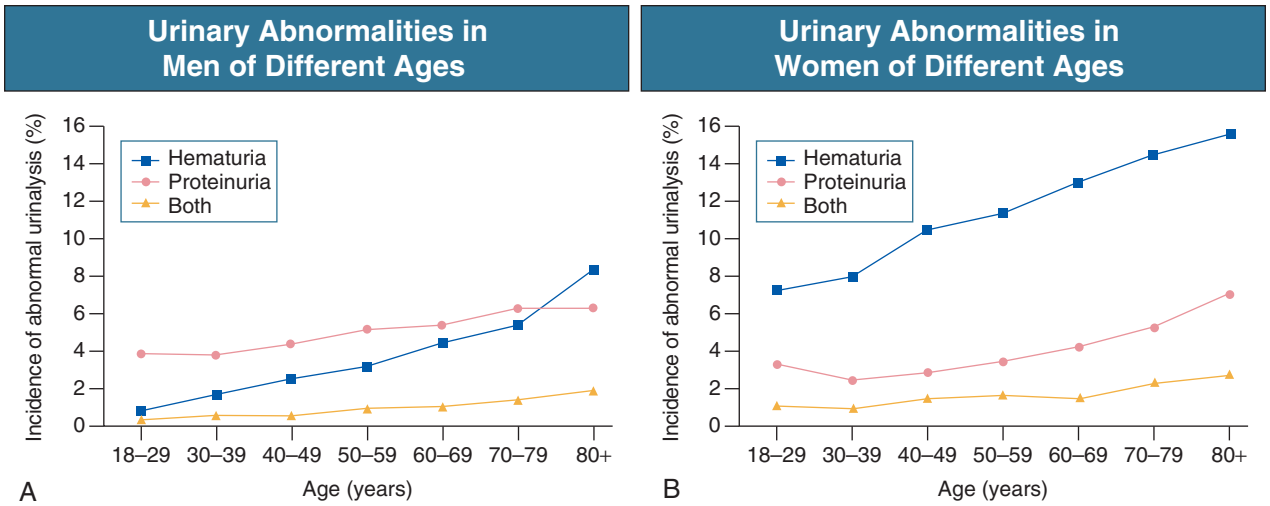

Figure 15-6 Prevalence of asymptomatic proteinuria and hematuria with age. Mass screening of a population of 107,192 adult men (**A**) and women (**B**) in Okinawa, Japan. Hematuria is more common in women. *(Modified from reference 1.)*

Figure 15-7 Red blood cell cast. An RBC cast typical of glomerular hematuria.

bladder catheter, any detectable proteinuria in the patient with asymptomatic microhematuria virtually excludes "urologic" bleeding and strongly suggests a glomerular origin. If this evaluation is nondiagnostic, renal imaging is performed to exclude anatomic lesions such as stones, tumors, polycystic kidneys, or arteriovenous malformations.

In those older than 40 years who have persistent isolated microhematuria without evidence of a glomerular origin (see previous discussion), cystoscopy is mandatory to exclude uroepithelial malignant disease. In people younger than 40 years, such malignant disease is so rare that cystoscopy is not recommended. If all the prior study results are normal, a glomerular etiology is likely.[2] The glomerular etiology can be determined only by renal biopsy, but this is rarely done because the prognosis is excellent in patients with normal renal function, normal blood pressure, and low-grade proteinuria (<0.5 g/day). However, repeated evaluation and prolonged follow-up are mandatory.

Asymptomatic Non-nephrotic Proteinuria

The hallmark of glomerular disease is the excretion of protein in the urine. Normal urine protein excretion is less than 150 mg/24 h, consisting of 20 to 30 mg of albumin, 10 to 20 mg of low-molecular-weight proteins that undergo glomerular filtration, and 40 to 60 mg of secreted proteins (e.g., Tamm-Horsfall, IgA). Proteinuria is identified and quantified by dipstick testing or by assay in timed urine collections; Chapter 4 discusses test interpretation.

Microalbuminuria is defined as the excretion of 30 to 300 mg of albumin per day, equivalent to a urine albumin to creatinine (g/g) ratio of 0.03 to 0.3, and is detected by quantitative immunoassay or by special urine dipsticks because this is below the sensitivity of the normal dipstick (see Chapter 30). This measurement is primarily used to identify diabetic subjects at risk for development of nephropathy and to assess cardiovascular risk, for example, in patients with hypertension.

Non-nephrotic proteinuria is usually defined as a urine protein excretion of less than 3.5 g/24 h or a urine protein-creatinine ratio of less than 3 g/g. Whereas nephrotic-range proteinuria is absolutely characteristic of glomerular disease, asymptomatic proteinuria (<3.5 g/24 h) is much less specific and may occur with a wide range of nonglomerular parenchymal diseases as well as with nonparenchymal renal and urinary tract conditions that must be excluded by clinical evaluation and investigation.

Increased urine protein excretion may result from alterations in glomerular permeability or tubulointerstitial disease, although only in glomerular disease will it be in the nephrotic range. Protein excretion can also increase from increased filtration through normal glomeruli (overflow proteinuria).

Overflow Proteinuria

Overflow proteinuria is typical of urinary light-chain excretion. It is seen in myeloma but can occur in other settings (e.g., release of lysozyme by leukemic cells) and should be suspected when the urine dipstick is negative for albumin despite detection of large amounts of proteinuria by other tests.

Tubular Proteinuria

Tubulointerstitial disease can be associated with low-grade proteinuria (usually <2 g/day). In addition to the loss of tubular proteins such as α_1- or β_2-microglobulin, there will also be some albuminuria due to impaired tubular reabsorption of filtered albumin. Tubular proteinuria accompanying glomerular proteinuria is an adverse prognostic sign in various glomerular diseases because it usually indicates advanced tubulointerstitial damage.

Glomerular Proteinuria

Glomerular proteinuria is further classified into transient or hemodynamic (functional), that present only during the day (orthostatic), and persistent or fixed.

Functional Proteinuria Functional proteinuria refers to the transient non-nephrotic proteinuria that can occur with fever, exercise, heart failure, and hyperadrenergic or hyperreninemic states. Functional proteinuria is benign, usually assumed to be hemodynamic in origin and the result of increases in single-nephron flow or pressure.

Orthostatic Proteinuria In children and young adults, low-grade glomerular proteinuria may be orthostatic, meaning that proteinuria is absent when urine is generated in the recumbent position. If there is no proteinuria in early-morning urine, the diagnosis of orthostatic proteinuria can be made. In patients with fixed orthostatic proteinuria, renal plasma flow and glomerular filtration rate (GFR) decrease in the upright position because of a lower systemic blood pressure. As recently proposed, the decreased GFR translates into a lower *streaming potential* across the filtration barrier, and albumin can no longer be excluded as efficiently from the filter by electrophoresis.[3]

Total urine protein in the patient with orthostatic proteinuria is usually less than 1 g/24 h; hematuria and hypertension are absent. Renal biopsy usually shows normal morphology or occasionally mild glomerular change. The prognosis is uniformly good, and renal biopsy is not indicated.[4]

Fixed Non-nephrotic Proteinuria Fixed non-nephrotic proteinuria is usually caused by glomerular disease. If GFR is preserved and proteinuria is less than 0.5 to 1 g/day, biopsy is not indicated but prolonged follow-up is necessary if significant proteinuria persists, to rule out the possibility of disease progression. Previous studies indicate that the biopsy findings in these patients can be similar to those seen in nephrotic syndrome (e.g., FSGS or membranous GN), although milder lesions are more common, particularly mesangial proliferative GN or IgA nephropathy. In general, other than regular monitoring and blood pressure control as needed, no treatment is necessary.

Although it is controversial, many nephrologists will perform a renal biopsy in patients with normal GFR if non-nephrotic proteinuria exceeds 1 g/day, in particular if it persists after initiation of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy.

Figure 15-8 summarizes the evaluation of isolated asymptomatic proteinuria.

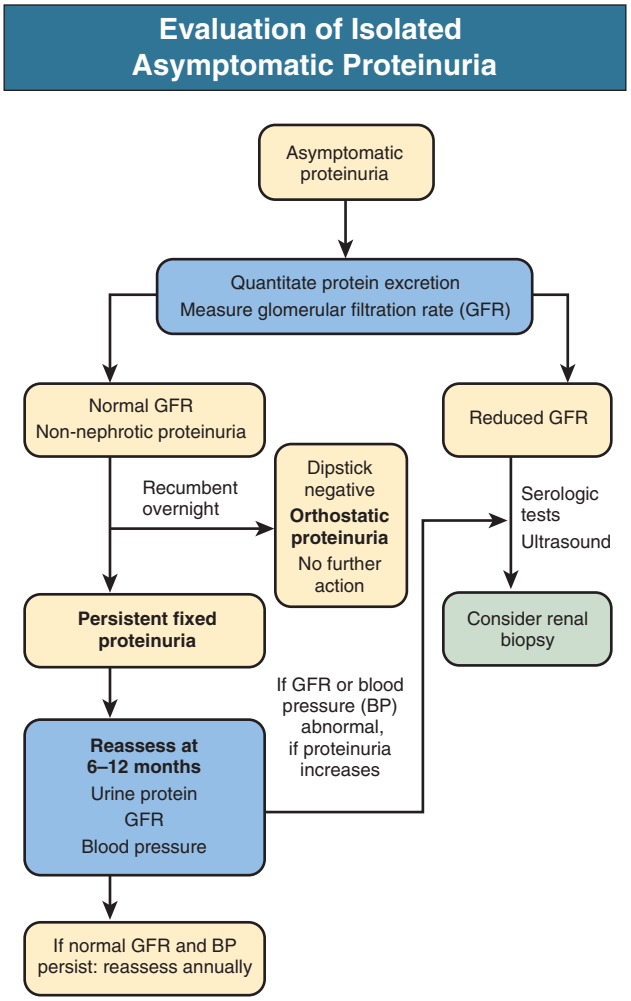

Figure 15-8 Evaluation of patients with isolated asymptomatic proteinuria.

Asymptomatic Proteinuria with Hematuria

Patients with coincident asymptomatic hematuria and proteinuria have a much greater risk of significant glomerular injury, hypertension, and progressive renal dysfunction. Minor histologic changes are less common. Renal biopsy is indicated even if urine protein is only 0.5 to 1 g/24 h if there is also persistent microhematuria with casts.

MACROHEMATURIA

Episodic painless macrohematuria associated with glomerular disease is often brown or "smoky" rather than red, and clots are unusual. Macrohematuria must be distinguished from other causes of red or brown urine, including hemoglobinuria, myoglobinuria, porphyrias, consumption of food dyes (particularly beetroot), and intake of drugs (especially rifampin).

Macrohematuria caused by glomerular disease is observed primarily in children and young adults and rarely is seen after age 40. Most cases are caused by IgA nephropathy, but hematuria may occur with other glomerular and nonglomerular renal diseases, including acute interstitial nephritis. Although macrohematuria is typically painless, the patient may have an accompanying dull loin ache that suggests other diagnoses, such as stone disease or loin-pain hematuria syndrome. In IgA nephropathy, the frank hematuria is usually episodic, occurring within a day of an upper respiratory infection. The clear distinction between this history and the 2- to 3-week latency between an upper respiratory tract infection and hematuria is highly suggestive of postinfectious (usually poststreptococcal) GN; furthermore, patients with poststreptococcal disease usually will have other features of nephritic syndrome.

Macrohematuria requires urologic evaluation, including cystoscopy, at any age unless the history (as shown previously) is characteristic of glomerular hematuria.

NEPHROTIC SYNDROME

Definition

Nephrotic syndrome is pathognomonic of glomerular disease. It is a clinical syndrome with a characteristic pentad[5] (see Fig. 15-1). Patients may be nephrotic with preserved renal function, but in

many, progressive renal failure will become superimposed when nephrotic syndrome is prolonged.

Independent of the risk of progressive renal failure, the nephrotic syndrome has far-reaching metabolic effects that can influence the general health of the patient. Fortunately, some episodes of nephrotic syndrome are self-limited, and a few patients respond completely to specific treatment (e.g., corticosteroids in MCD). For most patients, however, it is a relapsing or chronic condition. Not all patients with proteinuria above 3.5 g/24 h will have a full nephrotic syndrome; some have a normal serum albumin concentration and no edema. This difference presumably reflects the varied response of protein metabolism; some patients sustain an increase in albumin synthesis in response to heavy proteinuria that may even normalize serum albumin.

Etiology

Table 15-2 shows the major causes of nephrotic syndrome. Proteinuria in the nephrotic range in the absence of edema and hypoalbuminemia has similar etiologies. The relative frequency of the different glomerular diseases varies with age (Table 15-3). Although it is predominant in childhood, MCD remains common at all ages.[6] Prevalence of FSGS in African Americans has increased, which may explain why FSGS is becoming more common in U.S. adults but not in European adults.[7,8]

Hypoalbuminemia

Hypoalbuminemia is mostly a consequence of urinary losses. The liver responds by increasing albumin synthesis, but this compensatory mechanism appears to be blunted in nephrotic syndrome.[9] The end result is that serum albumin falls further. White bands in the nails (Muehrcke lines) are a characteristic clinical sign of hypoalbuminemia (see Fig. 15-4). The increase in protein synthesis in response to proteinuria is not discriminating; as a result, proteins not being lost in the urine may actually increase in concentration in plasma. This is chiefly determined by molecular weight; large molecules will not spill into the urine and will increase in the plasma, whereas smaller proteins, although synthesized to excess, will enter the urine and will decrease in the plasma. These variations in plasma proteins

Common Glomerular Diseases Presenting as Nephrotic Syndrome in Adults

Disease	Associations	Serologic Tests
Minimal change disease (MCD)	Allergy, atopy, NSAIDs, Hodgkin disease	None
Focal segmental glomerulosclerosis (FSGS)	African Americans HIV infection Heroin, pamidronate	— HIV antibody —
Membranous nephropathy (MN)	Idiopathic drugs: gold, penicillamine, NSAIDs Infections: hepatitis B and C; malaria Lupus nephritis Malignancy: breast, lung, gastrointestinal tract	Anti-PLA_2R antibody Hepatitis B surface antigen, anti–hepatitis C virus antibody Anti-DNA antibody —
Membranoproliferative glomerulonephritis (MPGN) type I	C4 nephritic factor	C3 ↓, C4 ↓
Dense deposit disease (MPGN type II)	C3 nephritic factor	C3 ↓, C4 normal
Cryoglobulinemic MPGN	Hepatitis C	Anti–hepatitis C virus antibody, rheumatoid factor, C3 ↓, C4 ↓, CH50 ↓
Amyloid disease	Myeloma Rheumatoid arthritis, bronchiectasis, Crohn disease (and other chronic inflammatory conditions), familial Mediterranean fever	Plasma free light chains Serum protein electrophoresis, urine immunoelectrophoresis C-reactive protein
Diabetic nephropathy	Other diabetic microangiopathy	None

Table 15-2 Common glomerular diseases presenting as nephrotic syndrome in adults. *HIV,* Human immunodeficiency virus; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *PLA_2R,* phospholipase A_2 receptor.

Age-related Variations in Nephrotic Syndrome

		Prevalence (%)			
		Young Adult		*Middle and Old Age*	
	Child (<15 years)	*Whites*	*Blacks*	*Whites*	*Blacks*
Minimal change disease (MCD)	78	23	15	21	16
Focal segmental glomerulosclerosis (FSGS)	8	19	55	13	35
Membranous nephropathy (MN)	2	24	26	37	24
Membranoproliferative glomerulonephritis (MPGN)	6	13	0	4	2
Other glomerulonephritides	6	14	2	12	12
Amyloid	0	5	2	13	11

Table 15-3 Age-related variations in nephrotic syndrome. *(Data modified from references 6 and 7.)*

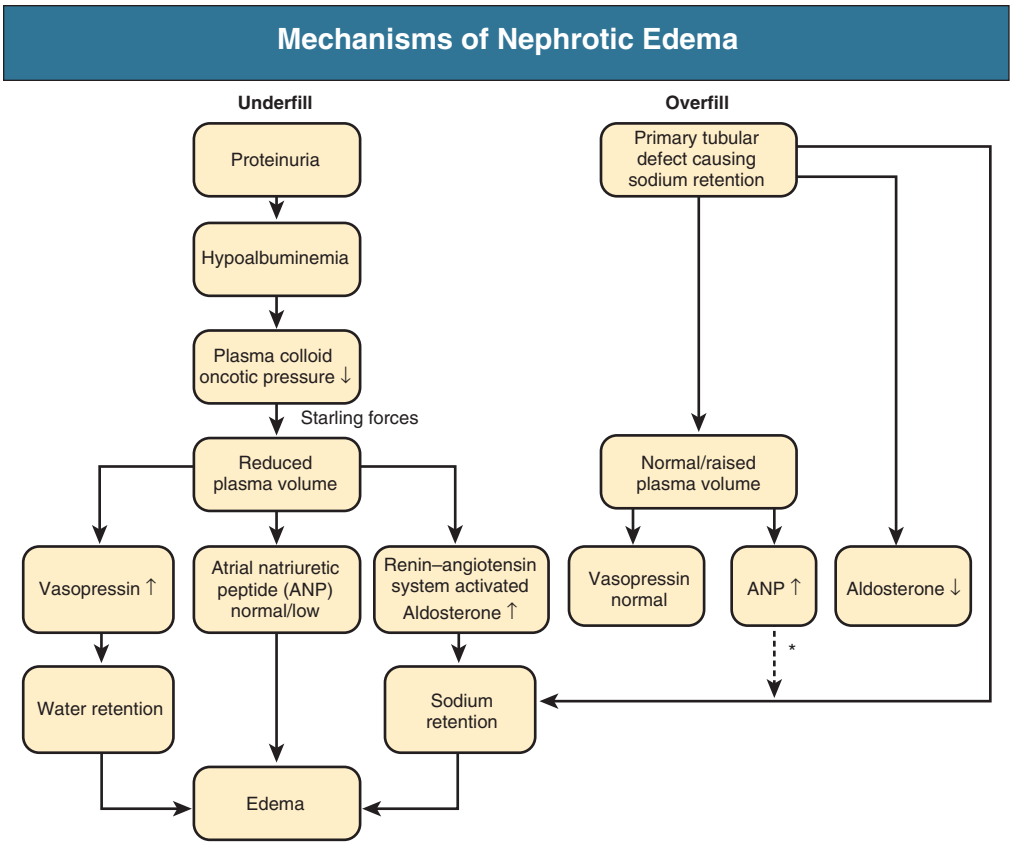

Figure 15-9 Mechanisms of nephrotic edema.* The kidney is relatively resistant to ANP in this setting, so ANP has little effect in countering sodium retention.

are clinically important in two areas, hypercoagulability and hyperlipidemia (see later discussion).

Edema

At least two major mechanisms are involved in the formation of nephrotic edema, underfill and overfill[10] (Fig. 15-9; see Chapter 7). In the first mechanism, which is more common in children with MCD, the edema appears to result from the low serum albumin, producing a decrease in plasma oncotic pressure, which allows increased transudation of fluid from capillary beds into the extracellular space according to the laws of Starling. The consequent decrease in circulating blood volume *(underfill)* produces a secondary stimulation of the renin-angiotensin system (RAS), resulting in aldosterone-induced sodium retention in the distal tubule. This attempt to compensate for hypovolemia merely aggravates edema because the low oncotic pressure alters the balance of forces across the capillary wall in favor of hydrostatic pressure, forcing more fluid into the interstitial space rather than retaining it within the vascular compartment.

Many nephrotic patients, however, appear to have a primary defect in the ability of the distal nephron to excrete sodium, possibly related to activation of the epithelial sodium channel (ENaC) by proteolytic enzymes that enter the tubular lumen in heavy proteinuria.[11] As a result, there is an increased blood volume; suppression of renin, angiotensin, and vasopressin; and a tendency to hypertension rather than to hypotension. The kidney is also relatively resistant to the actions of atrial natriuretic peptide. An elevated blood volume results *(overfill),* which, in association with the low plasma oncotic pressure, provokes transudation of fluid into the extracellular space and edema. The mechanism for the defect in sodium excretion remains unknown, although it has been hypothesized that inflammatory leukocytes in the interstitium, which are found in many glomerular diseases, may impair sodium excretion by producing angiotensin II and oxidants (oxidants inactivate local nitric oxide, which is natriuretic).[12]

Metabolic Consequences of Nephrotic Syndrome

Negative Nitrogen Balance

The heavy proteinuria leads to marked negative nitrogen balance, usually measured in clinical practice by serum albumin. Nephrotic syndrome is a wasting illness, but the degree of muscle loss is masked by edema and is not fully apparent until the patient is rendered edema free. Loss of 10% to 20% of lean body mass can occur. Albumin turnover is increased in response to the tubular catabolism of filtered protein rather than merely to urinary protein loss. Increasing protein intake does not improve albumin metabolism because the hemodynamic response to an increased intake is a rise in glomerular pressure, increasing urine protein losses. A low-protein diet in turn will reduce proteinuria, but also reduces the albumin synthesis rate and in the longer term may increase the risk of a worsening negative nitrogen balance.

Hypercoagulability

Multiple proteins of the coagulation cascade have altered levels in nephrotic syndrome; in addition, platelet aggregation is enhanced.[13] The net effect is a hypercoagulable state that is enhanced further by immobility, coincidental infection, and hemoconcentration if the patient has a contracted plasma volume (Fig. 15-10). Not only is venous thromboembolism common at any site, but spontaneous arterial thrombosis may occur. Arterial thrombosis may occur in adults in the context of atheroma, promoting coronary and

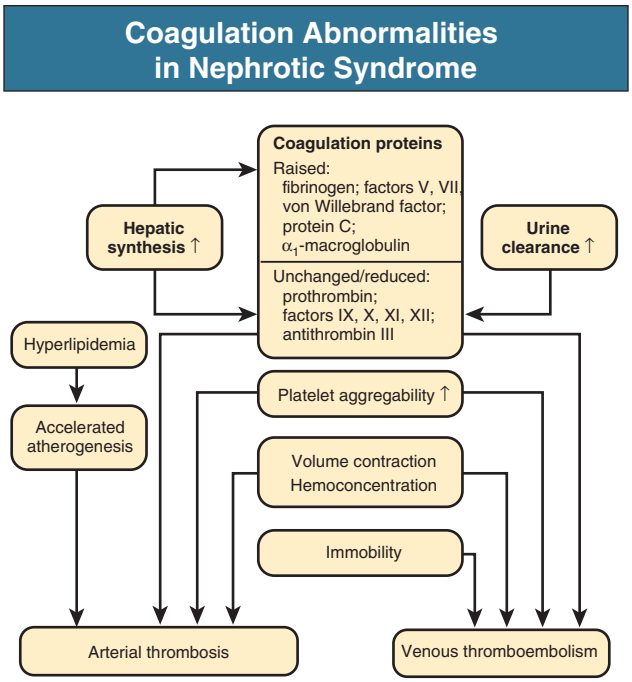

Figure 15-10 **Coagulation abnormalities in nephrotic syndrome.**

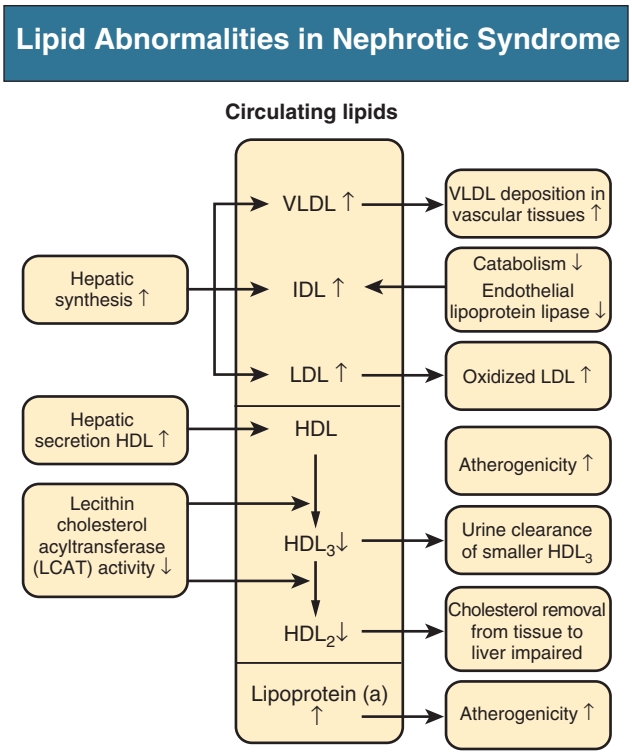

Figure 15-11 **Lipid abnormalities in nephrotic syndrome.** Changes in high-density lipoprotein *(HDL)* are more controversial than those in very-low-density lipoprotein *(VLDL)*. *IDL,* Intermediate-density lipoprotein; *LDL,* low-density lipoprotein.

cerebrovascular events in particular, but it also occurs in nephrotic children, in whom spontaneous thrombosis of major limb arteries is an uncommon but feared complication. Up to 10% of nephrotic adults and 2% of children will have a clinical episode of thromboembolism. For unexplained reasons, the risk appears particularly high in those with membranous nephropathy.[14] Individual levels of coagulation proteins are not helpful in assessing the risk of thromboembolism, and serum albumin is mostly used as a surrogate marker. Thromboembolic events increase greatly if the serum albumin concentration decreases to less than 2 g/dl.

The hypoproteinemia and dysproteinemia produce a marked increase in erythrocyte sedimentation rate, and ESR no longer serves as a marker of an acute-phase response in nephrotic patients.

Renal vein thrombosis is an important complication of nephrotic syndrome (see Chapter 66). Although once considered possible, renal vein thrombosis is no longer thought to cause nephrotic syndrome. Renal vein thrombosis is reported clinically in up to 8% of nephrotic patients; but when sought systematically by ultrasound or contrast venography, the frequency increases to 10% to 50%. Symptoms when the thrombosis is acute may include flank pain and hematuria; rarely, acute kidney injury (AKI) can occur if the thrombosis is bilateral. However, the thrombosis often develops insidiously with minimal symptoms or signs because of the development of collateral blood supply. Pulmonary embolism is an important complication.

Hyperlipidemia and Lipiduria

Hyperlipidemia is such a frequent finding in patients with heavy proteinuria that it is regarded as an integral feature of nephrotic syndrome.[15] Clinical stigmata of hyperlipidemia, such as xanthelasmas, may have a rapid onset (see Fig. 15-5). Serum cholesterol concentration can be above 500 mg/dl (13 mmol/l), although serum triglyceride levels are highly variable. The lipid profile in nephrotic syndrome is known to be highly atherogenic in other populations (Fig. 15-11). The presumption that coronary heart disease is increased in nephrotic syndrome because of the combination of hypercoagulation and hyperlipidemia has been difficult to prove. Many patients who are nephrotic for more than 5 to 10 years will develop additional cardiovascular risk factors, including hypertension and uremia, so it is difficult to separate these influences. However, it is now generally accepted that nephrotic patients do have about a fivefold increased risk of coronary death, except for those with MCD, presumably because the nephrotic state is transient before remission with corticosteroid treatment and does not subject the patient with MCD to prolonged hyperlipidemia.

Experimental evidence shows that hyperlipidemia contributes to progressive renal disease by various mechanisms, with protection afforded by lipid-lowering agents. However, clinical evidence to support a role of statins in slowing CKD progression is inconclusive.[16] Adequate prospective clinical studies on this issue remain to be done, and lipid-lowering drugs are indicated in nephrotic syndrome primarily for cardiovascular reasons.

Several mechanisms account for the lipid abnormalities in nephrotic syndrome. These include increased hepatic synthesis of low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), and lipoprotein(a) secondary to the hypoalbuminemia; defective peripheral lipoprotein lipase activity resulting in increased VLDL; and urinary losses of high-density lipoprotein (HDL; Fig. 15-11).

Lipiduria, the fifth component of the nephrotic syndrome pentad, is manifested by the presence of refractile accumulations of lipid in cellular debris and casts (oval fat bodies and fatty casts; Fig. 15-12). However, the lipiduria appears to be a result of the proteinuria and not of the plasma lipid abnormalities.

Other Metabolic Effects of Nephrotic Syndrome

Vitamin D–binding protein is lost in the urine, resulting in low plasma 25-hydroxyvitamin D levels, but plasma-free vitamin D is usually normal, and overt osteomalacia or uncontrolled hyperparathyroidism is very unusual in nephrotic syndrome in the absence of

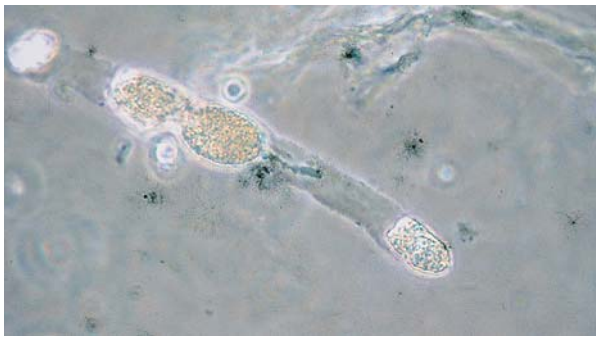

Figure 15-12 Fat in the urine. This hyaline cast contains oval fat bodies, which are tubular epithelial cells full of fat. Oval fat bodies often appear brown.

renal impairment. Thyroid-binding globulin is lost in the urine and total circulating thyroxine reduced, but again free thyroxine and thyroid-stimulating hormone are normal, and there are no clinical alterations in thyroid status. Occasional patients have been described with copper, iron, or zinc deficiency caused by the loss of binding proteins in the urine.

Drug binding may be altered by the decrease in serum albumin. Although most drugs do not require dose modifications, one important exception is clofibrate, which at normal doses produces a severe myopathy in nephrotic patients. Reduced protein binding may also reduce the dose of warfarin (Coumadin) required to achieve adequate anticoagulation or the dose of furosemide required to achieve adequate fluid loss (see later discussion).

Infection

Nephrotic patients are prone to bacterial infection. Before corticosteroids were shown to be effective in childhood nephrotic syndrome, sepsis was the most common cause of death and remains a major problem in the developing world. Primary *peritonitis,* especially that caused by pneumococci, is particularly characteristic of nephrotic children. It is less common with increasing age; by 20 years most adults have antibodies against pneumococcal capsular antigens. Peritonitis caused by both β-hemolytic streptococci and gram-negative organisms occurs, but staphylococcal peritonitis is not reported. Cellulitis, especially in areas of severe edema, is also common, most frequently caused by β-hemolytic streptococci.

The increased risk of infection has several explanations. Large fluid collections are sites for bacteria to grow easily; nephrotic skin is fragile, creating sites of entry; and edema may dilute local humoral immune factors. Loss of IgG and complement factor B (of the alternative pathway) in the urine impairs host ability to eliminate encapsulated organisms such as pneumococci. Zinc and transferrin are lost in the urine, and both are required for normal lymphocyte function. Neutrophil phagocytic function is impaired in patients with nephrotic syndrome, and several forms of *in vitro* T cell dysfunction are described, although their clinical significance is uncertain.

Acute and Chronic Changes in Renal Function

Acute Kidney Injury

Patients with nephrotic syndrome are at risk for the development of AKI,[17] through a variety of mechanisms (Box 15-1). These include volume depletion or sepsis, resulting in either pre-renal AKI or acute tubular necrosis[18]; transformation of the underlying disease, such as development of crescentic nephritis in a patient with membranous

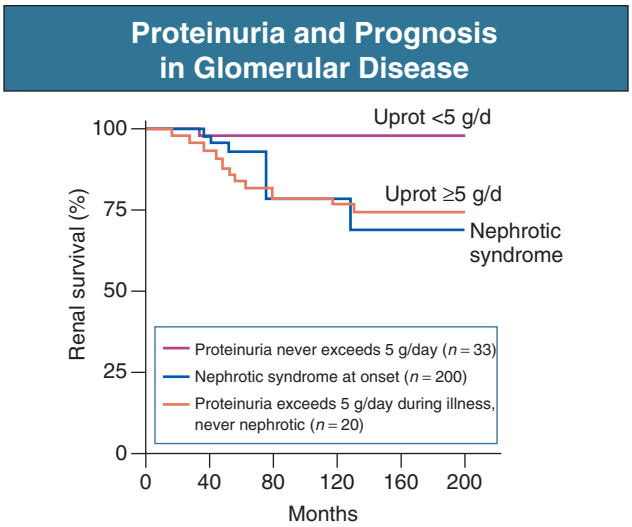

Figure 15-13 Proteinuria and prognosis in glomerular disease. The influence of heavy proteinuria on long-term renal function in 253 patients with primary glomerular disease at Manchester Royal Infirmary, United Kingdom. Heavy proteinuria at any time during long-term follow-up substantially worsens the prognosis even without frank nephrotic syndrome. *(Courtesy Dr. C. D. Short.)*

Acute Kidney Injury in Nephrotic Syndrome

- Pre-renal failure caused by volume depletion
- Acute tubular necrosis caused by volume depletion and/or sepsis
- Intrarenal edema
- Renal vein thrombosis
- Transformation of underlying glomerular disease (e.g., crescentic nephritis superimposed on membranous nephropathy)
- Adverse effects of drug therapy
- Acute allergic interstitial nephritis secondary to various drugs, including diuretics
- Hemodynamic response to nonsteroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)

Box 15-1 Acute kidney injury in nephrotic syndrome. Problems to consider in the evaluation of acute deterioration in renal function in the patient with nephrotic syndrome.

nephropathy; development of bilateral renal vein thrombosis; increased disposition to pre-renal AKI from NSAIDs and ACE inhibitors or ARBs; and increased risk of allergic interstitial nephritis secondary to drugs, including diuretics. Also, some patients may develop AKI from intrarenal edema with compression of tubules and, as with nephrotic patients with pre-renal azotemia, may respond with diuresis to albumin infusions combined with a loop diuretic.

Chronic Kidney Disease

With the exception of MCD, most causes of nephrotic syndrome are associated with some risk for the development of progressive renal failure. In this regard, one of the greatest risk factors for progression is the degree of proteinuria (see Chapter 80). Progression is uncommon if there is sustained proteinuria of less than 2 g/day. The risk increases in proportion to the severity of the proteinuria, with marked risk of progression when protein excretion is more than 5 g/day (Fig. 15-13). This risk may result because proteinuria identifies patients with severe glomerular injury, although experimental and clinical evidence also suggests that proteinuria itself may be toxic, especially to the tubulointerstitium.[19] In experimental models,

Differentiation Between Nephrotic Syndrome and Nephritic Syndrome		
Typical Features	**Nephrotic**	**Nephritic**
Onset	Insidious	Abrupt
Edema	++++	++
Blood pressure	Normal	Raised
Jugular venous pressure	Normal/low	Raised
Proteinuria	++++	++
Hematuria	May/may not occur	+++
Red blood cell casts	Absent	Present
Serum albumin	Low	Normal/slightly reduced

Table 15-4 Differentiation between nephrotic syndrome and nephritic syndrome.

measures that reduce proteinuria (e.g., ACE inhibitors) also prevent tubulointerstitial disease and progressive renal failure.

Common Glomerular Diseases Presenting as Nephritic Syndrome		
Disease	**Associations**	**Serologic Tests**
Poststreptococcal glomerulonephritis	Pharyngitis, impetigo	ASO titer, streptozyme antibody
Other postinfectious disease		
Endocarditis	Cardiac murmur	Blood cultures, C3 ↓
Abscess	—	Blood cultures, C3, C4 normal or increased
Shunt	Treated hydrocephalus	Blood cultures, C3 ↓
IgA nephropathy	Upper respiratory or gastrointestinal infection	Serum IgA ↑
Lupus nephritis	Other multisystem features of lupus	Antinuclear antibody, anti-double-stranded DNA antibody, C3 ↓, C4 ↓

Table 15-5 Common glomerular diseases presenting as nephritic syndrome.

NEPHRITIC SYNDROME

In *nephrotic* syndrome, the glomerular injury is manifested primarily as an increase in permeability of the capillary wall to protein. By contrast, in the *nephritic* syndrome, there is evidence of glomerular inflammation resulting in a reduction in GFR, non-nephrotic proteinuria, edema and hypertension (secondary to sodium retention), and hematuria with RBC casts.

The classic nephritic syndrome presentation is that seen with acute poststreptococcal GN in children. These children usually present with rapid onset of oliguria, weight gain, and generalized edema during a few days. The hematuria results in brown rather than red urine, and clots are not seen. The urine contains protein, RBCs, and RBC casts. Because proteinuria is rarely in the nephrotic range, serum albumin concentration is usually normal. Circulating volume increases with hypertension, and pulmonary edema follows without evidence of primary cardiac disease.

The distinction between typical nephrotic syndrome and nephritic syndrome is usually straightforward on clinical and laboratory grounds (Table 15-4). The use of these clinical descriptions in the approach to patients with suspected GN at first presentation helps to narrow the differential diagnosis. However, the classification systems are imperfect, and patients with certain glomerular disease patterns, such as membranoproliferative GN, may present with either a nephrotic or a nephritic picture.

Etiology

Table 15-5 lists the primary glomerular diseases associated with the nephritic syndrome and the serologic tests helpful in diagnosis. The classification is even more challenging than for nephrotic syndrome, because some diseases are identified by histology (IgA nephropathy), others by serology and histology (ANCA-associated vasculitis and lupus nephritis), and others by etiology (postinfectious GN).

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Rapidly progressive glomerulonephritis (RPGN) describes the clinical situation in which glomerular injury is so acute and severe that renal function deteriorates during days or weeks. The patient may present as a uremic emergency, with nephritic syndrome that is not self-limited but moves on rapidly to renal failure, or with rapidly deteriorating renal function when being investigated for extrarenal disease (many of the patterns of GN associated with RPGN occur as part of a systemic immune illness).

The histologic counterpart of RPGN is crescentic GN. The proliferative cellular response seen outside the glomerular tuft but within Bowman space is known as a "crescent" because of its shape on histologic cross section (see Fig. 16-8). Typically, the glomerular tuft also shows segmental necrosis, or focal segmental necrotizing GN; this is particularly characteristic of the vasculitis syndromes.

The term *rapidly progressive* GN is therefore often used to describe acute deterioration in renal function in association with a crescentic nephritis. Unfortunately, not all patients with a nephritic urine sediment and AKI will fit this syndrome. For example, AKI may also occur in milder forms of glomerular disease if it is complicated by accelerated hypertension, renal vein thrombosis, or acute tubular necrosis. This emphasizes the need to obtain histologic confirmation of the clinical diagnosis.

Etiology

Table 15-6 show the primary glomerular diseases associated with RPGN and helpful serologic tests. As with nephritic syndrome, different assessment methods are useful for different diseases causing RPGN.

PROGRESSIVE CHRONIC KIDNEY DISEASE

In most types of chronic GN, a proportion of patients (often between 25% and 50%) will have slowly progressive renal impairment. If no clinical event early in the course of the disease brings them to medical attention, patients may present late with established hypertension, proteinuria, and renal impairment. In longstanding GN, the kidneys shrink, but remain smooth and symmetric. Renal biopsy at this stage is more hazardous and less likely to provide diagnostic material. Light microscopy often shows nonspecific features of

Common Glomerular Diseases Presenting as Rapidly Progressive Glomerulonephritis

Disease	Associations	Serologic Tests
Goodpasture Syndrome		
	Lung hemorrhage	Anti–glomerular basement membrane antibody (occasionally antineutrophil cytoplasmic antibody [ANCA] present)
Vasculitis		
Wegener granulomatosis	Upper and lower respiratory involvement	Cytoplasmic ANCA
Microscopic polyangiitis	Multisystem involvement	Perinuclear ANCA
Pauci-immune crescentic glomerulonephritis	Renal involvement only	Perinuclear ANCA
Immune Complex Disease		
Systemic lupus erythematosus	Other multisystem features of lupus	Antinuclear antibody, anti-double-stranded DNA antibody, C3 ↓, C4 ↓
Poststreptococcal glomerulonephritis	Pharyngitis, impetigo	ASO titer, streptozyme antibody C3 ↓, C4 normal
IgA nephropathy; Henoch-Schönlein purpura	Characteristic rash ± abdominal pain in HSP	Serum IgA ↑ (30%) C3 and C4 normal
Endocarditis		
	Cardiac murmur; other systemic features of bacteremia	Blood cultures ANCA (occasionally) C3 ↓, C4 normal

Table 15-6 Glomerular diseases presenting as rapidly progressive glomerulonephritis (RPGN). Note the overlap between these diseases and those in Table 15-5. A number of glomerular diseases may present with either nephritic syndrome or RPGN.

end-stage renal disease (ESRD), consisting of focal or global glomerulosclerosis and dense tubulointerstitial fibrosis, and it may not be possible to define with confidence that a glomerular disease was the initiating renal injury, let alone define the pattern further. Immunofluorescence may be more helpful; in particular, mesangial IgA may be present in adequate amounts to allow a diagnosis of IgA nephropathy to be made. However, when renal imaging shows small kidneys, only rarely will biopsy be appropriate. For this reason, chronic GN has often been a presumptive diagnosis in patients presenting late with shrunken kidneys, proteinuria, and renal impairment. This is imprecise and in the past has led to an overestimate of the frequency of GN as a cause of ESRD in registry data. GN should be diagnosed only if there is confirmatory histologic evidence.

TREATMENT OF GLOMERULAR DISEASE

General Principles

Before any therapeutic decisions, it should always be ascertained that glomerular disease is *primary* and that no specific therapy is available. For example, treatment of an underlying infection or tumor may result in remission of GN. In the remaining cases, both general supportive treatment (see Chapter 80) and disease-specific therapy should be considered. Supportive treatment includes measures to treat blood pressure, reduce proteinuria, control edema, and address other metabolic consequences of nephrotic syndrome. If successful, these relatively nontoxic therapies can prevent the need for immunosuppressive drugs, which have multiple potential side effects. Supportive therapy is usually not necessary in corticosteroid-sensitive MCD with rapid remission or in patients with IgA nephropathy, Alport syndrome, or thin basement membrane nephropathy, provided the patient exhibits no proteinuria, loss of GFR, or hypertension.

Hypertension

Hypertension is very common in GN; it is virtually universal as chronic GN progresses toward ESRD and is the key modifiable factor in preserving renal function. Sodium and water overload is an important part of the pathogenetic process, and high-dose diuretics with moderate dietary sodium restriction are usually an essential part of the treatment. As in other chronic renal diseases, the aim of blood pressure control is not only to protect against the cardiovascular risks of hypertension, but also to delay progression of the renal disease. In the Modification of Diet in Renal Disease (MDRD) study, patients with proteinuria (>1 g/day) had a better outcome if their blood pressure was reduced to 125/75 mm Hg rather than to the previous standard of 140/90 mm Hg.[20,21] The recent Kidney Disease: Improving Global Outcomes (KDIGO) CKD guideline recommends a blood pressure target below 130/80 mm Hg in proteinuric patients.[22] There are strong theoretical and experimental reasons for ACE inhibitors and ARBs to be first-choice therapy, and this is now well documented in clinical studies.[23-25] Nondihydropyridine calcium channel blockers may also have a beneficial effect on proteinuria as well as on blood pressure. In contrast, dihydropyridine calcium channel blockers may exacerbate proteinuria because of their ability to dilate the afferent arteriole, but these agents are considered relatively safe to use if the patient is receiving either an ACE inhibitor or an ARB. As in primary hypertension, lifestyle modification (salt restriction, weight normalization, regular exercise, and smoking cessation) should be an integral part of the therapy.[22] If target blood pressure cannot be achieved with these measures, antihypertensive therapy should be stepped up according to current guidelines (see Chapter 36).

Treatment of Proteinuria

Besides hypertension, proteinuria represents the second key modifiable factor to preserve GFR in patients with glomerular disease (see also Chapters 80 and 81). Most studies suggest that the progressive loss of renal function observed in many glomerular diseases can largely be prevented if proteinuria can be reduced to levels below 0.5 mg/day. This may be because many of the measures to reduce protein excretion (e.g., ACE inhibitors, ARBs) also reduce glomerular hypertension, which contributes to progressive renal failure. However, there is also increasing evidence that proteinuria or factors present in proteinuric urine may be toxic to the tubulointerstitium.[19] In nephrotic patients, a reduction of proteinuria to a non-nephrotic range can induce serum proteins to rise, with alleviation of many of the metabolic complications of nephrotic syndrome.

Most of the agents used to reduce urinary protein excretion do so hemodynamically, either by blocking efferent arteriolar constriction (ACE inhibitors or ARBs) or by reducing preglomerular pressure (most other classes of antihypertensive drugs). As mentioned,

dihydropyridine calcium antagonists are the exception because they can increase intraglomerular pressure and thus exacerbate proteinuria. Some of the agents, such as ACE inhibitors and ARBs, may also directly reduce the increased glomerular capillary wall permeability. A consequence of this type of therapy is a reduction in GFR; in general, however, the decrease in GFR is of a lower magnitude than the decrease in protein excretion. The antiproteinuric agents of choice are ACE inhibitors and ARBs, which reduce proteinuria by an average of 40% to 50%, particularly if the patient is on dietary salt restriction. There is little clinical evidence to suggest that ACE inhibitors differ from ARBs in this respect. The combination of the two may result in additive antiproteinuric activity but increases the risk of AKI.[26] Similar concerns relate to the combination of ACE inhibitor or ARB with a direct renin inhibitor.[27] In addition, whereas other classes of antihypertensive agents will reduce proteinuria coincident with a decrease in systemic blood pressure, particularly the nondihydropyridine calcium channel blockers such as diltiazem, both ACE inhibitors and ARBs usually reduce proteinuria independent of blood pressure. If doses are increased slowly to minimize symptomatic hypotension, treatment with ACE inhibitors and ARBs is usually possible in the normotensive proteinuric patient. Increasing the inhibitor or ARB dose may further reduce proteinuria without lowering blood pressure, which may indicate the inefficacy of other antihypertensive drugs in blocking the stimulated intrarenal RAS. Common side effects include hyperkalemia in patients with advanced CKD, which may necessitate a loop diuretic but rarely should lead to cessation of ACE inhibitors and ARBs, and cough ACE inhibitors, in which case ARBs should be used instead. Because both agents lower GFR, a 10% to 30% increase in serum creatinine concentration may be observed. Unless creatinine continues to increase, this moderate increase reflects the therapeutic effect of ACE inhibitors and ARBs and should not prompt their withdrawal.

The NSAIDs lessen proteinuria by reducing intrarenal prostaglandin production and dipyridamole through adenosine-mediated afferent arteriolar vasoconstriction. Given the safety of the therapies discussed previously, as well as the risk of profound decreases in GFR, salt retention, and diuretic resistance with NSAIDs, these are generally contraindicated despite their potential benefit on proteinuria.

A low-protein diet will lessen proteinuria but must be advised with great care because of the risk of malnutrition.[22] Adequate compensation must be made for urine protein losses,[28] and the patient must be carefully monitored for evidence of malnutrition (see Chapter 87). Whether a low-protein diet is still antiproteinuric in patients treated with a full-dose ACE inhibitor or ARB is not established.

Treatment of Hyperlipidemia

Treatment of hyperlipidemia (or hypercholesterolemia) in patients with glomerular disease should usually follow the guidelines that apply to the general population to prevent cardiovascular disease. A statin or statin/ezetimibe combination is recommended in adults older than 50 with CKD stage 3 to 5. Statins alone are also recommended in adults over 50 with earlier-stage CKD. In younger adults, statins should be considered if the patient has significant comorbidity (coronary disease, diabetes mellitus, stroke). Statin therapy may also protect from a decrease in GFR, although this is not firmly established. Dietary restriction alone has only modest effects on hyperlipidemia in glomerular disease, particularly nephrotic syndrome. Side effects of some medications, such as rhabdomyolysis provoked by fibrates, occur more frequently in patients with renal failure. The addition of bile acid sequestrants such as cholestyramine may lower LDL further and increase HDL, but it is usually not tolerated because of GI effects.

Avoidance of Nephrotoxic Substances

Apart from NSAIDs, which may induce AKI, particularly in patients with preexisting renal impairment and dehydration, other nephrotoxic substances, such as radiocontrast agents, some cytotoxic drugs, and antibiotics (e.g., aminoglycoside antibiotics), should also be used with caution in patients with glomerular disease and renal impairment or nephrotic syndrome.

Special Therapeutic Issues in Patients with Nephrotic Syndrome

Treatment of Nephrotic Edema

In contrast to the lack of therapies in the past (Fig. 15-14), the mainstay of current treatment of nephritic edema is diuretic therapy accompanied by moderate dietary sodium restriction (60 to 80 mmol/24 h). Nephrotic patients are diuretic resistant even if GFR is normal. Loop diuretics must reach the renal tubule to be effective, and transport from the peritubular capillary requires protein binding, which is reduced in hypoalbuminemia. When the drug reaches the renal tubule, it will become 70% bound to protein present in the urine and therefore be less effective. Oral diuretics with twice-daily administration are usually preferred, given the longer therapeutic effect compared with intravenous (IV) diuretics. However, in severe nephrosis, GI absorption of the diuretic may be uncertain because of intestinal wall edema, and IV diuretic, by bolus injection or infusion, may be necessary to provoke an effective diuresis. Alternatively, combining a loop diuretic with a thiazide diuretic or with metolazone may overcome diuretic resistance (see Chapter 7). Significant hypovolemia is not often a clinical problem, provided fluid removal is controlled and gradual. Daily weight is the best measurement of progress; ideally it should decrease by no more than 1 to 2 kg/day. Nephrotic children are much more prone to hypovolemic shock than adults. A stepwise approach to diuretic use is required, aiming at

Figure 15-14 Treatment of nephrotic edema before the availability of diuretics. Edema in nephrotic syndrome was very difficult to treat. In 1953, this child with anasarca stands in a bowl while edema fluid drips out through small tubes placed through needles in the skin of the feet. Nevertheless, this was effective treatment. The two pictures of the same child were taken 4 days apart, during which time the child lost 4.5 kg (10 lb), or 18% of body weight. *(Courtesy Dr. Robert Vernier.)*

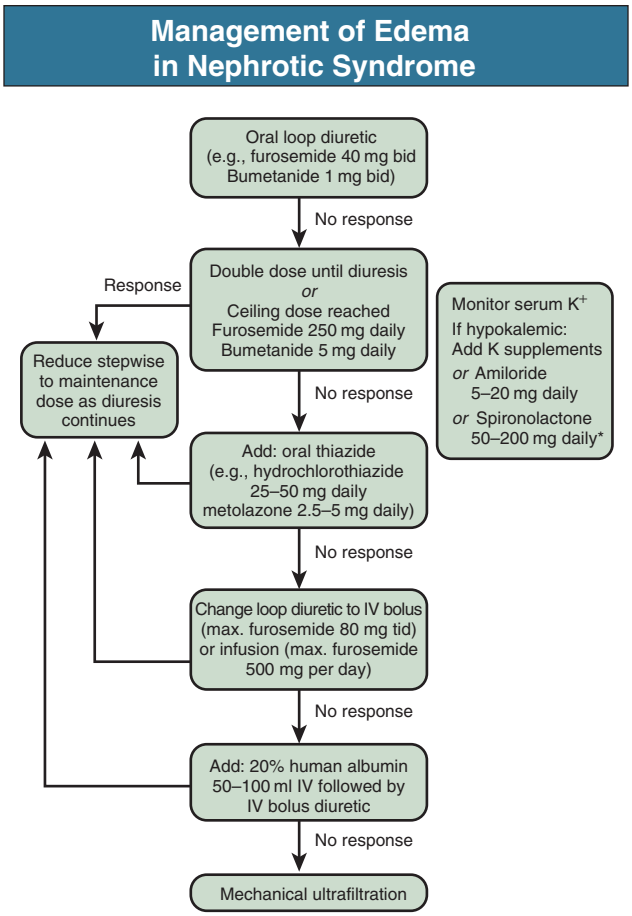

Figure 15-15 Management of edema in the patient with nephrotic syndrome. Edema is often diuretic resistant, but the response is not predictable. Therefore, stepwise escalation of therapy is appropriate until diuresis occurs. Even when there is anasarca, diuresis should not proceed faster than 2 kg/day in adults to minimize the risk of clinically significant hypovolemia; *bid,* twice daily. Mechanical ultrafiltration is rarely required for nephrotic edema unless there is associated renal impairment. *Spironolactone is less effective in nephrotic syndrome than in cirrhosis and is often poorly tolerated because of gastrointestinal side effects. Spironolactone should be used with great caution if the GFR is very low.

fluid removal in adults of no more than 2 kg daily, moving on to the next drug level if this is not achieved (Fig. 15-15).

Correction of Hypoproteinemia

In view of the problems associated with either increased protein administration or dietary protein restriction in nephrotic patients, adequate dietary protein should be ensured (0.8 to 1 g/kg/day) with a high carbohydrate intake to maximize use of that protein. In patients with heavy proteinuria, the amount of urinary protein loss should be added to dietary protein intake.

In the rare setting of proteinuria so severe that the patient is dying of the complications of nephrotic syndrome, the physician may need to resort to nephrectomy to prevent continued protein losses. This may be done as a *medical* nephrectomy: the deliberate use of NSAIDs combined with ACE inhibitors and diuretic to lessen proteinuria by provoking AKI. If medical nephrectomy alone does not adequately reduce proteinuria, bilateral renal artery embolization can be considered. It is a painful procedure and is not always as successful as might be expected (perhaps because of collateral arterial supply to kidneys, which is not blocked by embolization). A final alternative is bilateral nephrectomy, which carries significant mortality in these severely ill hypoproteinemic patients and is rarely used in adults, although it is a conventional part of management of infants with congenital nephrotic syndrome.

Treatment of Hypercoagulability

The risk of thrombotic events becomes progressively more important as serum albumin values decrease to less than 2.5 g/dl. Immobility as a consequence of edema or intercurrent illness further aggravates the risk. Prophylactic low-dose anticoagulation (e.g., heparin 5000 units subcutaneously twice daily) is indicated at times of high risk, such as relative immobilization in the hospital and albumin levels between 2 and 2.5 g/dl. Full-dose anticoagulation with low-molecular-weight heparin or warfarin should be considered if serum albumin decreases to less than 2 g/dl,[13,29] and this is mandatory if a thrombosis or pulmonary embolism is documented. Heparin is used for initial anticoagulation, but an increased dose may be needed because part of the action of heparin depends on antithrombin III, which is often reduced in the plasma in nephrotic patients. Warfarin (target international normalized ratio [INR] 2 to 3) is the long-term treatment of choice but should be adjusted with special care because of altered protein binding, which may require dose reductions.

Management of Infection

A high order of clinical suspicion for infection is vital in nephrotic patients. Especially in nephrotic children, ascitic fluid should be examined microscopically and cultured if there is any suspicion of systemic infection. Bacteremia is common even if clinical signs are localized. ESR is unhelpful, but an elevated C-reactive protein level may be informative. Parenteral antibiotics should be started once culture specimens are taken, and the regimen should include benzylpenicillin (to cover pneumococci). If repeated infections occur, serum immunoglobulins should be measured. If serum IgG is less than 600 mg/dl, evidence in an uncontrolled study showed that infection risk is reduced by monthly administration of intravenous immune globulin (10 to 15 g) to keep the IgG levels above 600 mg/dl.[30]

Disease-Specific Therapies

Specific treatments for glomerular diseases are discussed in the subsequent chapters; the general principles are discussed here. Because most glomerular disease is thought to have an immune pathogenesis, treatment has generally consisted of immunosuppressive therapy aimed at blocking both the systemic and the local effects. In the patient with glomerular disease resulting from ineffectual elimination of a foreign antigen, treatment involves measures to eliminate this antigen whenever possible, such as antibiotics in endocarditis-associated GN or antiviral therapy for cryoglobulinemia resulting from hepatitis C infection.

In general, the more severe and acute the presentation of GN, the more successful is immunosuppressive treatment. Immunosuppression in several patterns of chronic GN has had minimal success. When renal function is declining rapidly, as in RPGN, the toxicity of intensive regimens becomes acceptable for a short period, although it would be unacceptable if prolonged. Furthermore, the nonspecific nature of most immunosuppressive treatments results in widespread interruption of immune and inflammatory events at multiple levels. In the acute situation, this broad-based attack is a virtue; in more indolent disease, more specific treatment is needed but is largely unavailable. Despite great increases in the understanding of immune mechanisms in glomerular disease since the 1970s, most immunosuppressive therapies are not yet much more specific or precise. The mainstays of treatment remain agents that were available in the 1960s: corticosteroids, azathioprine, and cyclophosphamide. Other,

newer immunosuppressive agents developed for use in transplantation, including cyclosporine, tacrolimus, mycophenolate mofetil, sirolimus, and everolimus, or those developed in oncology, including rituximab, have emerging indications in glomerular disease.

The use of immunosuppressive therapies to treat GN patients has certain drawbacks. In many diseases, treatment is based on small series, and good prospective controlled trials are often lacking. Because of both the rarity and the variable natural history of GN, proof of efficacy for a particular therapy often requires a multicenter approach with prolonged follow-up, which is logistically difficult. If sufficient glomerular damage is present, proteinuria and progressive deterioration of renal function may occur by nonimmune pathways that may not be responsive to immunosuppressive therapies. This is particularly relevant in patients in whom the GN has already resulted in advanced CKD. Unfortunately, good noninvasive markers to assess disease activity are missing in most clinical circumstances. Given the frequent uncertainty of the response to immunosuppressive therapy, it becomes mandatory to weigh the potential benefits against the risks of therapy.

Immunosuppression may be associated with reactivation of tuberculosis and hepatitis B infection and can also lead to a hyperinfection syndrome in patients with *Strongyloides* infection. Therefore, high-risk patients should be screened for these diseases before embarking on therapy.

Alkylating agents such as cyclophosphamide and chlorambucil have considerable toxicity. In the short term, leukopenia is common, as is alopecia, although hair will regrow within a few months with discontinuation of therapy. These agents can cause infertility (observed in adults with cumulative doses of cyclophosphamide >200 mg/kg and chlorambucil 10 mg/kg). There is also an increased incidence of leukemias (observed with total doses of cyclophosphamide >80 g and chlorambucil 7 g). Cyclophosphamide is also a bladder irritant, and treatment can result in hemorrhagic cystitis and bladder carcinoma, particularly after therapy lasting more than 6 months.[31] Irritation of the bladder is caused by a metabolite, acrolein. The effect can be minimized in patients receiving IV cyclophosphamide by enforcing a good diuresis and administering mesna. The dose of mesna (mg) should equal the dose of cyclophosphamide (mg); 20% is given intravenously with the IV cyclophosphamide, and the remaining 80% should be given in two equal oral doses at 2 and 6 hours by IV infusion at the same dosage as the cyclophosphamide. Chlorambucil and cyclophosphamide also require dose reduction in the setting of renal impairment. Given all these concerns, oral treatment with these agents should ideally be limited to 12 weeks.

The modes of action and potential adverse effects of corticosteroids, azathioprine, and other immunosuppressive agents occasionally used in glomerular disease are discussed further in Chapter 101.

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CHAPTER 16

Introduction to Glomerular Disease: Histologic Classification and Pathogenesis

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HISTOLOGIC CLASSIFICATION

Glomerular disease may have a wide variety of etiologies and clinical presentations (see Chapter 15). Some glomerular diseases are given the generic title of glomerulonephritis (GN), which implies an immune or inflammatory pathogenesis. Although a specific diagnosis can be made in some patients based on clinical presentation and laboratory tests, in most patients a renal biopsy is useful for both classification and prognosis. Ideally, the renal biopsy should be examined by light microscopy, immunofluorescence, and electron microscopy. Using this approach, a histologic pattern can be diagnosed. Some histologic patterns can be coupled with other laboratory tests to identify a specific etiology, but in many cases the condition is idiopathic. However, because treatments are often developed for specific histologic patterns, this approach is currently favored in the management of patients with glomerular disorders.

HISTOPATHOLOGY

The full assessment of a renal biopsy requires light microscopy, electron microscopy, and examination for deposits of complement and immunoglobulin by immunofluorescence (IF) or immunoperoxidase (IP) techniques.

Light Microscopy

In GN the dominant, but not the only, histologic lesions are in glomeruli (Fig. 16-1). GN is described as *focal* (only some glomeruli are involved) or *diffuse*. In any individual glomerulus, injury may be *segmental* (affecting only part of any glomerulus) or *global*. Sampling error is possible in a renal biopsy; the extent of a focal lesion may be misjudged in a small biopsy specimen, and sections through glomeruli may miss segmental lesions. Lesions may also be hypercellular because of an increase in endogenous endothelial or mesangial cells (termed *proliferative*) and an infiltration of inflammatory leukocytes (termed *exudative*). Severe acute inflammation may produce glomerular necrosis, which is often segmental. The walls of the glomerular capillaries can also be thickened by a number of processes, which include an increase in glomerular basement membrane (GBM) material and immune deposits. Segmental sclerosis and scarring may also occur and are characterized by segmental capillary collapse with the accumulation of hyaline material and mesangial matrix and often with attachment of the capillary wall with Bowman capsule (synechiae or adhesion formation).

The classic stains used in light microscopy include hematoxylin-eosin (HE) and the periodic acid–Schiff (PAS) reaction, which is particularly effective for evaluating cellularity and matrix expansion. More specific stains include methenamine silver, which stains GBM and other matrix black and may reveal a double contour to the GBM because of the interposition of cellular material or may show increased mesangial matrix not easily seen with other techniques. Trichrome staining is also useful to show areas of scarring (blue) and immune deposits (red).

Crescents are inflammatory collections of cells in Bowman space. Crescents develop when severe glomerular injury results in local rupture of the capillary wall or Bowman capsule, allowing plasma proteins and inflammatory material to enter into the Bowman space. Crescents consist of proliferating parietal and visceral epithelial cells, infiltrating fibroblasts, and lymphocytes and monocytes/macrophages, often with local fibrin deposition. They are called "crescents" because of their appearance when the glomerulus is cut in one plane for histology. These cell collections are destructive and rapidly increasing in size and may lead to glomerular tuft occlusion (Fig. 16-1). If the acute injury is stopped, the crescents may either resolve with restitution of normal morphology or heal by fibrosis, causing irreversible loss of renal function. Crescents are most frequently observed with vasculitis, in Goodpasture disease, and in severe acute GN of any etiology.

Tubulointerstitial injury and fibrosis can also accompany GN and may play an important role in the prognosis (see Chapter 79).

Immunofluorescence and Immunoperoxidase Microscopy

Indirect IF and IP staining are both used to identify immune reactants (Fig. 16-2). Examination consists of staining for immunoglobulins (IgG, IgA, and IgM), for components of the complement system (usually C3, C4, and C1q), and for the presence of fibrin, which is typically observed in crescents and in capillaries in thrombotic disorders such as hemolytic uremic syndrome and the antiphospholipid syndrome. Immune deposits may occur along the capillary loops or in the mesangium. They may be continuous (linear) or discontinuous (granular) along the capillary wall or in the mesangium.

Electron Microscopy

Electron microscopy (EM) is valuable for defining the morphology of the basement membranes, which is abnormal in some forms of hereditary nephropathy (e.g., Alport syndrome and thin basement membrane nephropathy; see Chapter 48), and for identifying fibrils (e.g., in amyloidosis) or tubuloreticular intracellular structures (e.g., in lupus nephritis). EM is also useful for localizing the site of immune deposits, which are usually homogeneous and electron dense (Fig. 16-3). Electron-dense deposits are seen in the mesangium or along the capillary wall on the subepithelial or subendothelial side of the

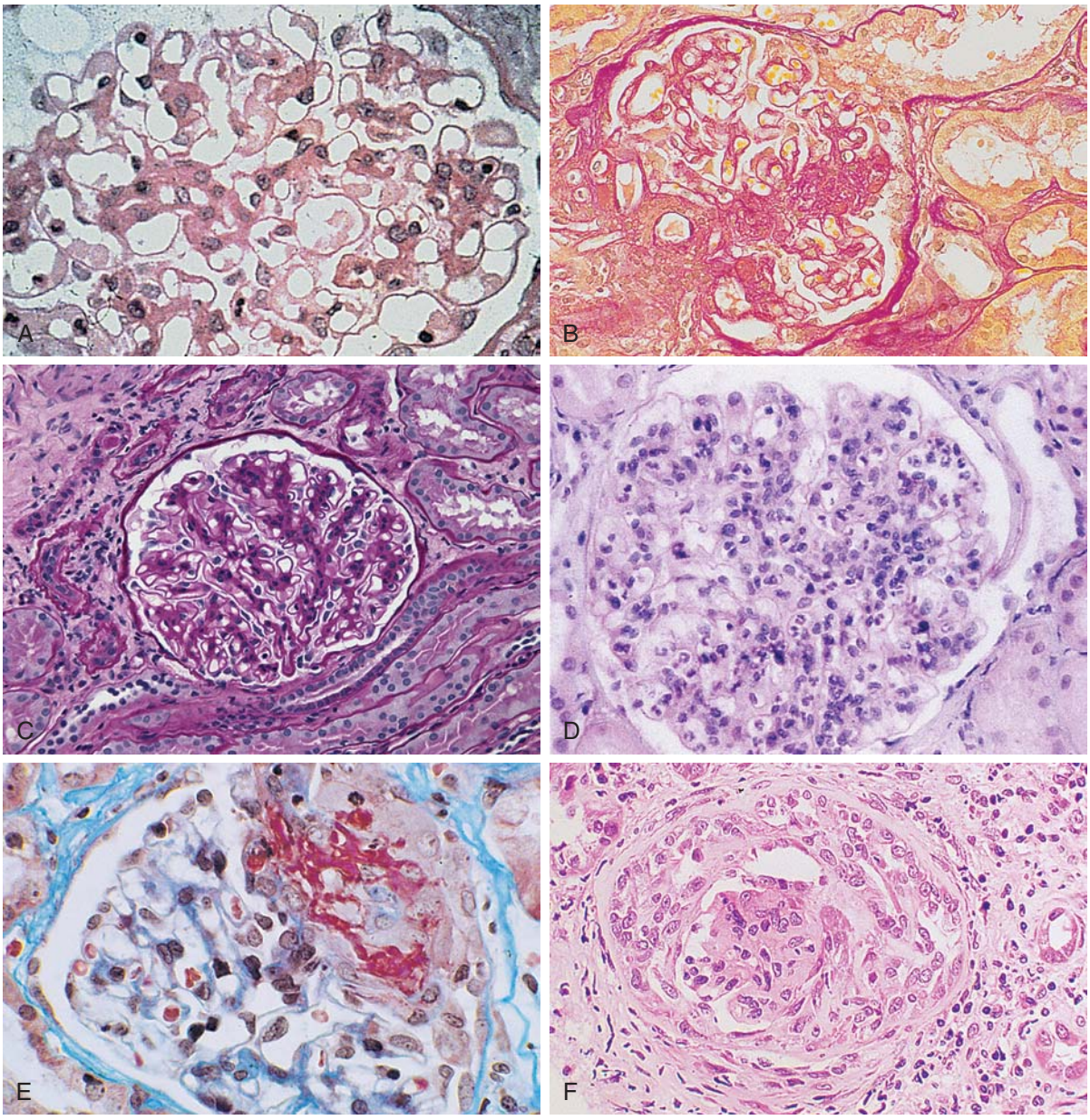

Figure 16-1 Pathology of glomerular disease: light microscopy. Characteristic patterns of glomerular disease illustrating the range of histologic appearances and the descriptive terms used. **A,** Normal glomerulus: minimal change disease. **B,** Segmental sclerosis: focal segmental glomerulosclerosis. **C,** Diffuse mesangial hypercellularity: IgA nephropathy. **D,** Diffuse endocapillary hypercellularity: poststreptococcal glomerulonephritis. **E,** Segmental necrosis: renal vasculitis. **F,** Crescent formation: anti–glomerular basement membrane disease. (**A** and **B,** Hematoxylin-eosin; **C, D,** and **F,** periodic acid–Schiff; **E,** trichrome.)

GBM. Infrequently, the electron-dense material lies linearly within the GBM. The sites of immune deposits are helpful in the classification of the types of GN.

GENERAL MECHANISMS OF GLOMERULAR INJURY

Proteinuria

Proteinuria is the hallmark of glomerular disease. The endothelial glycocalyx and the GBM may repel proteins in part through their highly negative charge (proteins are mostly negatively charged as well) and prevent them from entering Bowman space. A central barrier for protein is the slit diaphragm between the podocyte foot processes[1] (Fig. 16-4). The slit diaphragm consists of several transmembrane proteins that extend from adjacent interdigitating foot processes to form a zipper-like scaffold on the outer side of the GBM (Fig. 16-5).

The importance of the slit diaphragm in proteinuric states has been documented in numerous hereditary types of nephrotic syndrome in which the mutations involve various slit diaphragm proteins (see Chapter 19). These diseases usually present as a type of steroid-resistant minimal change disease or focal segmental glomerulosclerosis (FSGS). Whereas most recessive mutations of slit diaphragm or podocyte proteins manifest in childhood or even prenatally, dominant mutations tend to manifest in early adult life.[2]

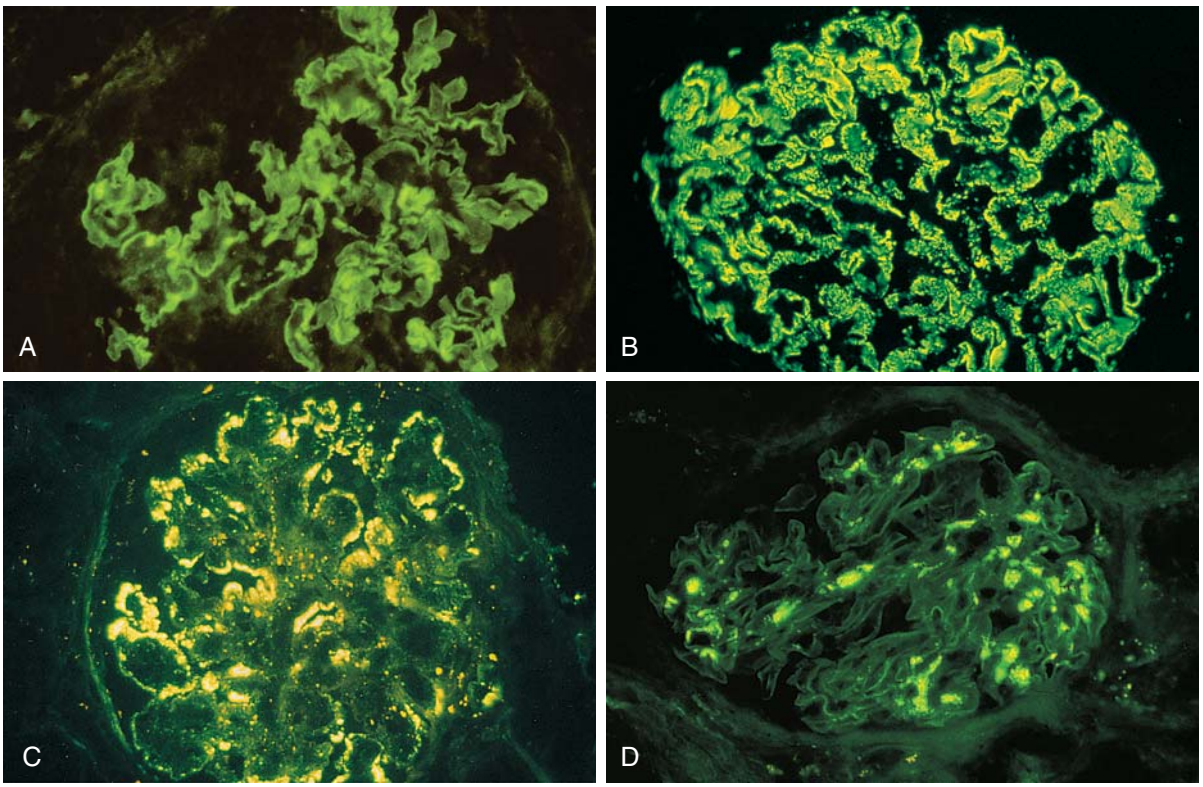

Figure 16-2 Pathology of glomerular disease: immunofluorescence microscopy. Common patterns of glomerular staining found by immunofluorescence. **A,** Linear capillary wall IgG: anti–glomerular basement membrane disease. **B,** Fine granular capillary wall IgG: membranous nephropathy. **C,** Coarse granular capillary wall IgG: membranoproliferative glomerulonephritis type I. **D,** Granular mesangial IgA: IgA nephropathy.

An exception is steroid-resistant autosomal recessive nephrotic syndrome, in which the homozygous mutation in podocin *(NPHS2)* presents in childhood, but the heterozygous mutation, when it coexists with the p.R229Q variant polymorphism, may present clinically in young adulthood (age 20 to 40 years old).[3]

Although it may result from injury or mutation of slit diaphragm proteins, proteinuria may be caused by nonspecific injury to the podocyte in many cases. When the podocyte is injured, it may undergo shape changes with swelling and loss or fusion of the foot processes. Filtration is reduced at sites where the foot processes fuse (possibly accounting for reduction of filtration coefficient K_f seen in nephrotic syndrome), but there are gaps where the podocytes are detached from the GBM. Massive protein filtration may occur at these sites; structurally, the capillary wall defects are likely to correspond to the large pores noted in functional studies[4] (Fig. 16-6). Podocyte immaturity can also result in nephrotic syndrome, perhaps from incomplete differentiation and slit diaphragm development. Congenital nephrotic syndrome with mesangial sclerosis has recently been linked with mutations in phospholipase C epsilon gene *(PLCE1),* which is important in podocyte development.[5]

In addition to podocyte damage, and in particular slit diaphragm defects, evidence also shows that proteinuria can result from changes in the glomerular endothelium, especially its glycocalyx, as well as from changes in the GBM and altered electrical forces across the GBM.

Severe albuminuria reflects a glomerular defect, but some albumin is normally filtered but then endocytosed and metabolized in the proximal tubule or is transcytosed intact through the tubular cell. Proximal tubular dysfunction can therefore result in albuminuria if endocytosis is impaired, although this is generally in the nonnephrotic range.

Antibody and Antigen

Many glomerular diseases are associated with deposition or glomerular trapping of immunoglobulins, often with components of the complement system, and with the presence of electron-dense deposits by EM. These findings likely represent immune complexes. Experimentally, immune complexes can localize in glomeruli by two major mechanisms. In some conditions, such as mesangial proliferative GN, membranoproliferative GN (MPGN), or lupus nephritis, the immune complexes are thought to originate in the circulation and to be passively trapped in the mesangium or subendothelial areas. However, circulating immune complexes cannot readily pass across the GBM. Therefore, the presence of IgG on the subepithelial aspect of the basement membrane, such as occurs in membranous nephropathy, either results from the direct binding of podocyte antigens by antibody or represents binding of an antibody to an antigen that was temporarily "trapped" or bound at this site (*in situ* complex formation).[6] GN may also occur only with complement activation in the glomeruli in the absence of IgG, as occurs in dense deposit disease (DDD), in which ribbon-like deposits replace the basement membrane (see Chapter 22). Some antigens may also deposit in glomeruli and directly activate the alternative pathway of complement in the absence of IgG, as may occur in poststreptococcal GN (PSGN). Antibody with aberrant characteristics may also aggregate in glomeruli and activate complement in the absence of antigen, as occurs in IgA nephropathy with aberrantly glycosylated IgA.[7]

Normally, immune complexes are removed from the circulation by binding of the complex to the C3b receptors on erythrocytes. The immune complexes are then removed and degraded during transit of the erythrocytes in the liver and spleen. If antigenemia persists or clearance of complexes is impaired (e.g., chronic liver disease), immune complexes may deposit in the glomerulus by binding to Fc

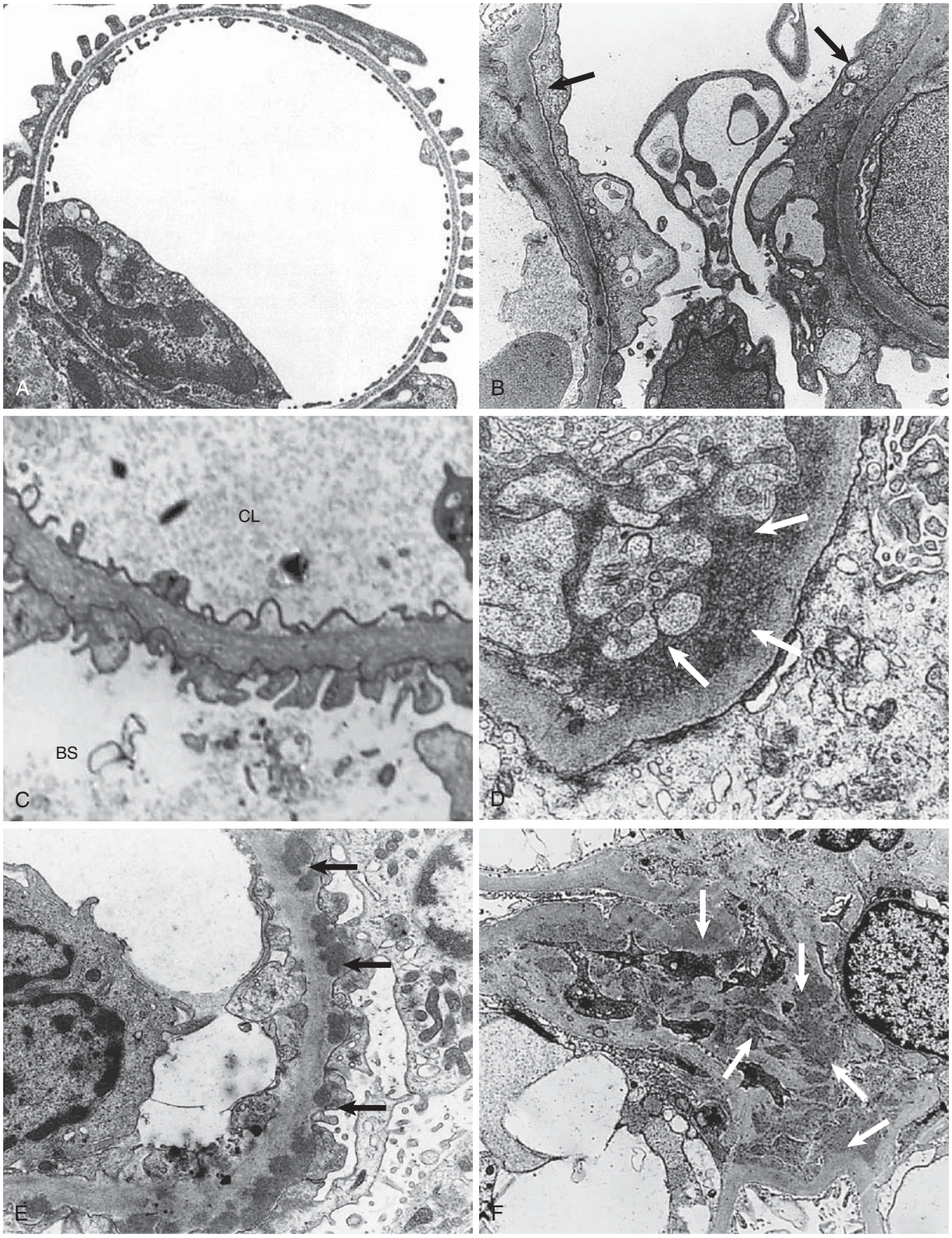

Figure 16-3 Ultrastructural pathology of glomerular disease. Some characteristic patterns of electron-dense deposits and GBM abnormalities seen in glomerular disease. **A,** Normal. **B,** Foot process effacement: minimal change disease *(arrows)*. **C,** GBM thickening and splitting: Alport syndrome. *CL,* Capillary lumen; *BS,* Bowman space. **D,** Subendothelial electron-dense deposits *(arrows):* membranoproliferative glomerulonephritis type I. **E,** Subepithelial electron-dense deposits *(arrows):* membranous nephropathy. **F,** Mesangial electron-dense deposits *(arrows):* IgA nephropathy.

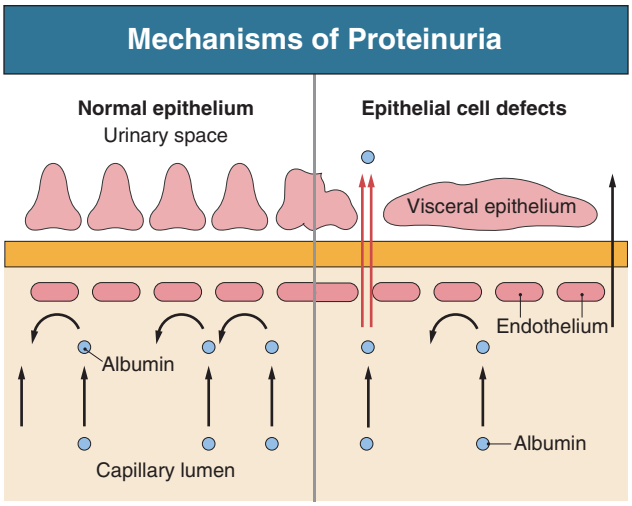

Figure 16-4 Mechanisms of proteinuria. Normally, negatively charged proteins such as albumin *(blue circles)* are repelled by the negatively charged proteins in the endothelium (sialoglycoproteins) and basement membrane (heparan sulfate proteoglycans) as well as by a size barrier in the GBM and at the slit diaphragm so that only small amounts of albumin pass into the urinary space. In most proteinuric states, the podocytes are injured, leading to foot process swelling and injury to the slit diaphragm; in these situations, large amounts of protein (albumin) can pass through the GBM and the gaps between the fused foot processes *(red arrows)*.

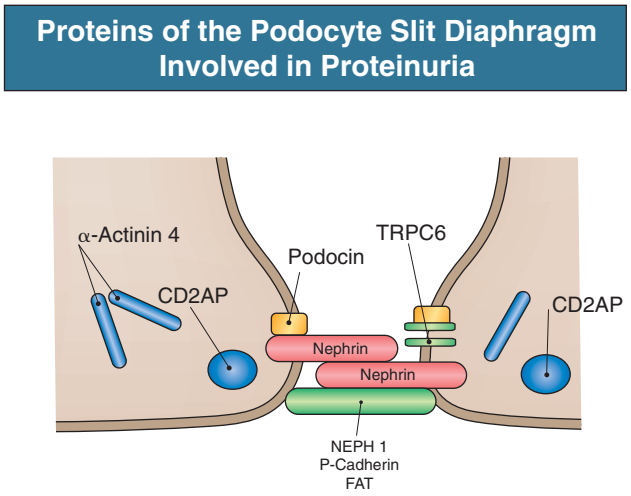

Figure 16-5 Proteins of the podocyte slit diaphragm involved in proteinuria. Several inherited glomerular diseases involve mutations of antigens associated with the slit diaphragm. These include nephrin in congenital nephrotic syndrome of the Finnish type; podocin in autosomal recessive FSGS; and α-actinin and TRPC6 (transient receptor potential cation channel), both associated with autosomal dominant FSGS. In addition, mutation of CD2-associated protein results in nephrotic syndrome in mice. *(Modified from reference 1.)*

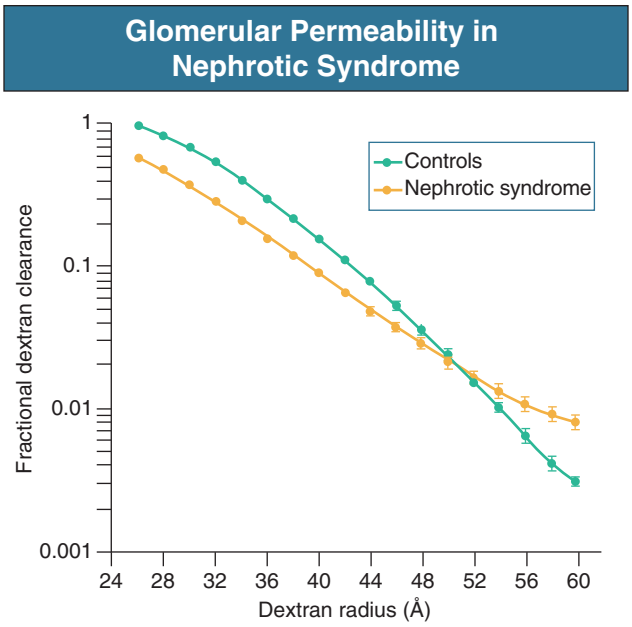

Figure 16-6 Glomerular permeability in nephrotic syndrome. Dextran sieving curve shows the relative glomerular permeability of different-sized dextrans in normal individuals and nephrotic patients with membranous nephropathy and minimal change disease. Nephrotic patients actually have a lower fractional dextran clearance for small dextrans (26 to 48 Å [2.6 to 4.8 nm]) but have an increased clearance for dextrans of larger molecular weight (52 to 60 Å [5.2 to 6.0 nm]). This is consistent with large pores appearing in the GBM. *(Modified from reference 4.)*

Antigens Identified in Glomerulonephritis

Disease	Antigens
Poststreptococcal GN	Streptococcal pyrogenic exotoxin B (SPEB), plasmin receptor
Anti-GBM disease	α3 Type IV collagen (likely induced by molecular mimicry)
IgA nephropathy	Possibly no antigen but rather polymerized polyclonal IgA (?superantigen driven)
Membranous nephropathy	Phospholipase A_2 receptor (idiopathic) Neutral endopeptidase (NEP) in podocyte (congenital) HBeAg (hepatitis associated)
Staphylococcus aureus–associated GN	*Staphylococcus* superantigens induce polyclonal response; not necessarily antigen in glomeruli
Membranoproliferative GN	HCV and HBsAg in hepatitis-associated MPGN
ANCA-associated vasculitis	Endopeptidase (proteinase) 3 (c-ANCA) and myeloperoxidase (p-ANCA) in neutrophils Antibodies to lysosome-associated membrane protein 2 (LAMP-2) on endothelial cells, likely induced by molecular mimicry to fimbriated bacterial antigens

Table 16-1 Antigens identified in glomerulonephritis *(GN).* *ANCA,* Antineutrophil cytoplasmic autoantibody (antibody); *GBM,* glomerular basement membrane; *HCV,* hepatitis C virus; *HBsAg,* hepatitis B surface antigen.

receptors on mesangial cells or by passive deposition in the mesangium or subendothelial space. Physical characteristics of the complexes may also favor deposition, including avidity, charge, and size. However, measurement of circulating immune complexes in patients with GN does not correlate reliably with glomerular events and thus is not typically measured.

In some glomerular diseases, the target antigen has been identified (Table 16-1). In other patients, glomerular disease develops as a result of infection with organisms that release superantigens that cause a polyclonal activation of B cells. The classic organism responsible for superantigen-associated GN is *Staphylococcus aureus*, and the pattern of immune deposits often includes the presence of both IgG and IgA. Some infections initiate an immune response that cross-reacts with endogenous antigens. This type of molecular mimicry may be responsible for Goodpasture disease and certain types of vasculitis[8,9] (Table 16-1). Once an immune response is

initiated, local injury may lead to the release of additional antigens that extend the immune response (epitope spreading). In Goodpasture disease, in which the antigen is α3 chain of type IV collagen, the antigen is present in the lung alveolar basement membrane but is normally sequestered. In tobacco smokers, however, the inhalation results in oxidative injury with exposure of the α3 chain, allowing the binding of antibody.[10] This may explain why lung involvement rarely occurs in nonsmokers with Goodpasture disease.

Complement

The complement system is often activated in glomerular disease (Fig. 16-7). Complement can be activated through three pathways. *Classical pathway* activation involves the binding of C1q to the Fc region of antibody in IgG- and IgM-containing immune complexes and can result in reduced serum C4 and C3. This is common in lupus nephritis, type I MPGN, and cryoglobulinemic MPGN. Complement may also be activated by the *alternative pathway,* which is activated independently of immune complexes and can be triggered by polysaccharide antigens, polymeric IgA, injured cells, bacterial products (e.g., streptococcal antigens), and antibodies to complement pathway components (C3 convertase). The alternative pathway appears to be activated in IgA nephropathy, DDD, and PSGN. Serum complement levels are generally normal in IgA nephropathy; in DDD and PSGN, however, the C3 is typically low but C4 is normal. In DDD the activation of the alternative pathway may not involve an antigen but rather results from continuous activation of the pathway through altered factor H or an IgG autoantibody (nephritic factor) that stabilizes the C3 convertase (see Chapter 22). Complement can also be activated through the *mannose-binding lectin* (MBL) *pathway* initiated by MBL, which has a similar structure to C1q. The role of the MBL pathway in GN is emerging in IgA nephropathy and idiopathic membranous nephropathy. However, despite evidence for intraglomerular complement activation in these conditions, major serum complement components such as C3 and C4 generally remain in the normal range.

Activation of the complement pathway has several consequences. Leukocyte recruitment is facilitated by the chemotactic factor C5a, and C3b binding is important in the binding and opsonization of the immune complexes by the infiltrating leukocytes. The terminal membrane attack complex of the cascade, C5b-9, inserts into cell membranes, where it can kill cells or activate them to secrete cytokines, oxidants, and extracellular matrix. C5b-9 likely has a role in mediating injury to the glomerular epithelial cell in membranous nephropathy, in which immune deposits and complement activation occur in the subepithelial space. Complement can also be activated

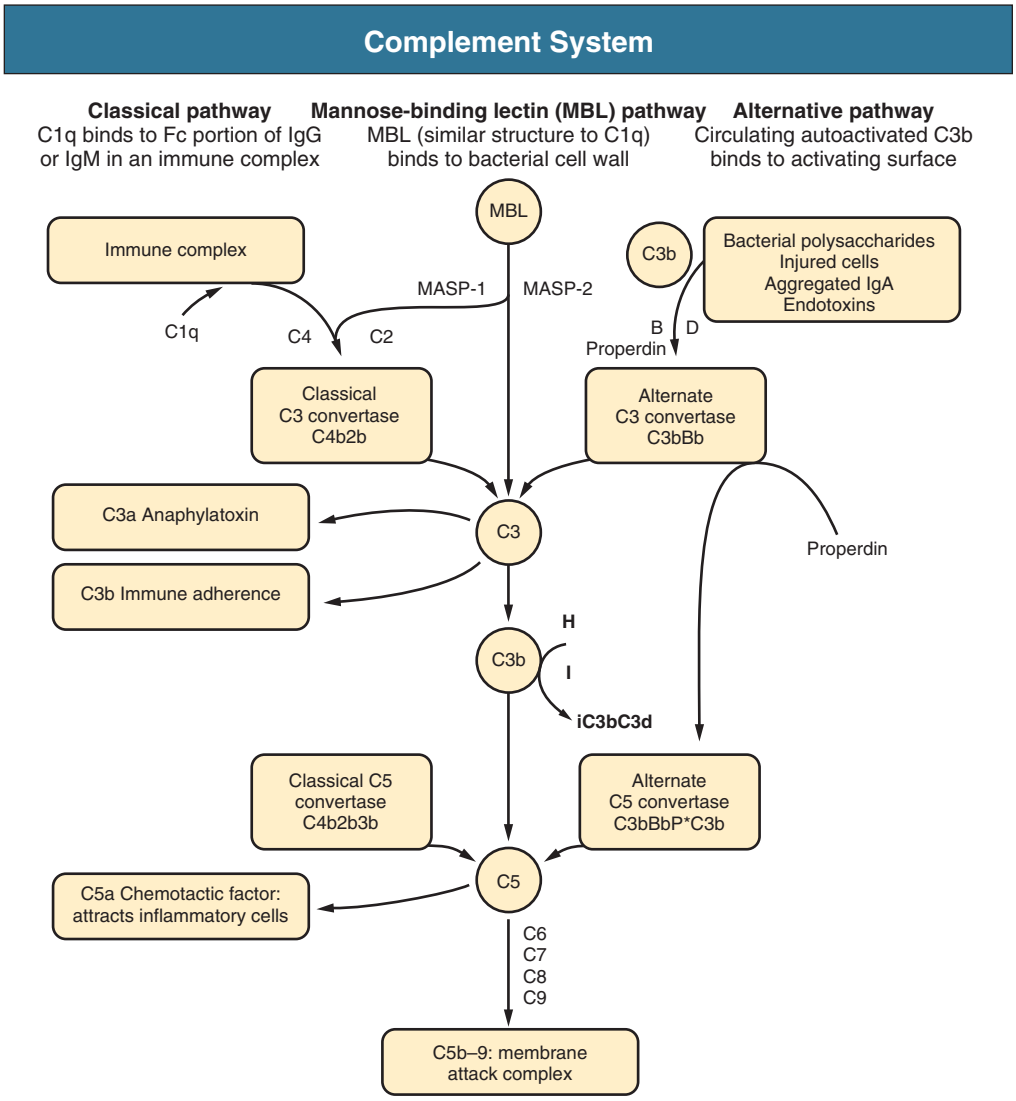

Figure 16-7 Complement system. The complement system is a self-amplifying cascade of proteins that generates a membrane attack complex, which is cytolytic; the cascade promotes inflammation by the activity of the fragments it produces. The amplifying cascades result from activated fragments of the components combining to make convertase enzymes that degrade C3 and C5. The complement cascade is controlled in part by the short active life of many of its components. There are also inhibitory regulatory proteins, most notably factors H and I inhibiting C3b. Activated fragments of any component are designated *b* (e.g., C3b); anaphylatoxic fragments are designated *a* (e.g., C5a). Inflammatory functions of complement components are shown in *green*. *MASP,* MBL-associated serine protease.

in proteinuric urine because of amidation of C3 by ammonia, which may have a role in mediating tubulointerstitial injury even in conditions not associated with immune complex formation. Experimental studies have emphasized the importance of local synthesis of complement components by the tubular cells as a mechanism that may augment this process.[11]

Activation of complement is controlled by complement regulatory proteins (Fig. 16-7). A genetic absence or malfunction of factor H or other regulatory proteins can result in increased susceptibility to glomerular endothelial injury, resulting in hemolytic uremic syndrome (HUS; Chapter 29) or less often in hereditary forms of GN (see Chapter 22).

Mechanisms of Immune Glomerular Injury

Two major mechanisms account for the presence of immune complexes in glomerular diseases. There may be ineffectual clearance of an antigen from an impaired immune response, as in chronic viral infections caused by hepatitis B or hepatitis C virus (HBV or HCV). Despite a strong humoral response, viral infection persists because the cell-mediated response required for elimination of these viruses is impaired. The consequence is a state of persistent antigenemia with circulating antigen-antibody complexes, which predisposes to glomerular injury. Eradication of the virus with antiviral therapy can be associated with remission of the glomerular disease.

More often, glomerular disease results from *autoimmunity*. In health, a tension exists between the normal immune response to foreign antigen and tolerance, which is the cellular process that prevents an immune response to self antigen. Tolerance develops because self-reactive T and B cells are clonally deleted during fetal and neonatal life, although small numbers survive outside the thymus or bone marrow, respectively. Under certain conditions, these peripheral self-reactive cells can be stimulated to generate a cellular and humoral response to a self antigen. Infection or toxins may play a role in initiating the response by releasing antigens from sequestered sites so they have access to dendritic cells (DCs), which carry the antigen to lymph nodes for presentation to T cells, by altering host proteins to make them more immunogenic, or by molecular mimicry, in which antibodies to an exogenous antigen (e.g., those present in infecting organism) cross-react with a native protein. Activation of T cells may be further enhanced by the release of cytokines or endogenous danger-associated molecular patterns, such as Toll-like receptor ligands or inflammasome activators, and the conversion of normally innocuous endogenous renal cells into antigen-presenting cells through the upregulated or *de novo* expression of human leukocyte antigen (HLA) class II molecules and cytokines.

Regulatory T cells ($CD4^+CD25^+$) have a key role in controlling T cell responses and preventing the development of autoimmunity. These cells are decreased in patients with Goodpasture disease at presentation and may play a role in the loss of tolerance. Indeed, in experimental anti-GBM nephritis, the administration of regulatory T cells reduces glomerular damage by blocking T cell–dependent renal injury.[12]

Variations in HLA molecules and the T cell receptor are under strong genetic influence. Close immunogenetic associations, particularly between HLA expression and various patterns of GN, have been described in IgA nephropathy, membranous nephropathy, and other glomerular diseases. For example, whereas HLA-DR2 identifies a powerful relative risk of the development of Goodpasture disease, some individuals can develop the disease without HLA-DR2, and the vast majority with HLA-DR2 never develop this rare disease. HLA associations also differ among various ethnic groups. To date, HLA associations have no practical diagnostic or therapeutic implications, and HLA typing is not needed in the clinical management of GN patients.

Inflammation

The presence of glomerular inflammation is largely determined by the site of immune deposits. Immune deposits with direct access to the circulation (subendothelial and basement membrane locations) are usually associated with leukocyte accumulation. Mesangial deposits elicit an intermediate response, whereas immune deposits in the subepithelial space generally are not associated with inflammatory cells.

In GN associated with subendothelial deposits, such as class IV lupus nephritis or MPGN, leukocyte infiltration is common. With acute injury, the predominant infiltrating cells are neutrophils, platelets, and monocytes, and in chronic injury, the predominant cells are monocyte/macrophages and T cells. The primary mechanism for attracting these cells is the secretion of chemokines and the expression of leukocyte adhesion molecules by local endothelial and resident cells; local release of complement activation fragments (C5a) is also important.

Although neutrophils are common with immune complex disease, cell-mediated immunity is important in some glomerular diseases. For example, T cells likely have a role in crescentic nephritis, becoming sensitized to endogenous or exogenous antigen and then recruiting macrophages that mediate crescent formation.

Proliferation, Apoptosis, and Fibrosis

Intrinsic glomerular cells (epithelial, mesangial, and endothelial) are also activated in various glomerular diseases. Mesangial cells can become myofibroblast-like cells that proliferate and produce excessive extracellular matrix. Endothelial cells produce nitric oxide and other anti-inflammatory proteins, and injury to this cell population can result in the expression of leukocyte adhesion molecules and activation of the coagulation system. Podocytes are terminally differentiated cells; injury may not only result in proteinuria (see earlier) but when associated with apoptosis, may also result in glomerulosclerosis. Important growth factors associated with glomerular injury include transforming growth factor β (TGF-β), which mediates matrix deposition; platelet-derived growth factor (PDGF), which mediates mesangial cell proliferation; and vascular endothelial growth factor (VEGF), required for endothelial health.

Crescent formation represents a severe cellular response and is initiated by cytokine-driven proliferation, particularly of the parietal epithelial cells. Local breaks in the GBM or Bowman capsule, mediated by activated leukocytes, are followed by macrophage infiltration, myofibroblast accumulation, and local fibrin deposition (Fig. 16-8).

Glomerular scarring is characterized by proliferation of mesangial cells with loss (apoptosis) of endothelial cells and podocytes. Tubulointerstitial fibrosis also accompanies progressive glomerular disease and correlates with both renal function and prognosis. Proteinuria has been shown to activate tubular cells and induce toxicity, either directly or through the generation of oxidants (from iron proteins excreted in urine) or from complement activation, which can be shown in proteinuric urine. Tubulointerstitial ischemia after loss of glomerular and peritubular capillaries may also drive fibrosis. Finally, loss of renal function may result from leakage of plasma ultrafiltrate into the peritubular space, resulting in a scarring response (misdirected filtration), or stenosis/occlusion of the opening of the proximal tubule from Bowman space, resulting in nonfunctional (atubular) glomeruli. A detailed discussion of current mechanisms involved in glomerulosclerosis is presented in Chapter 79. Specific

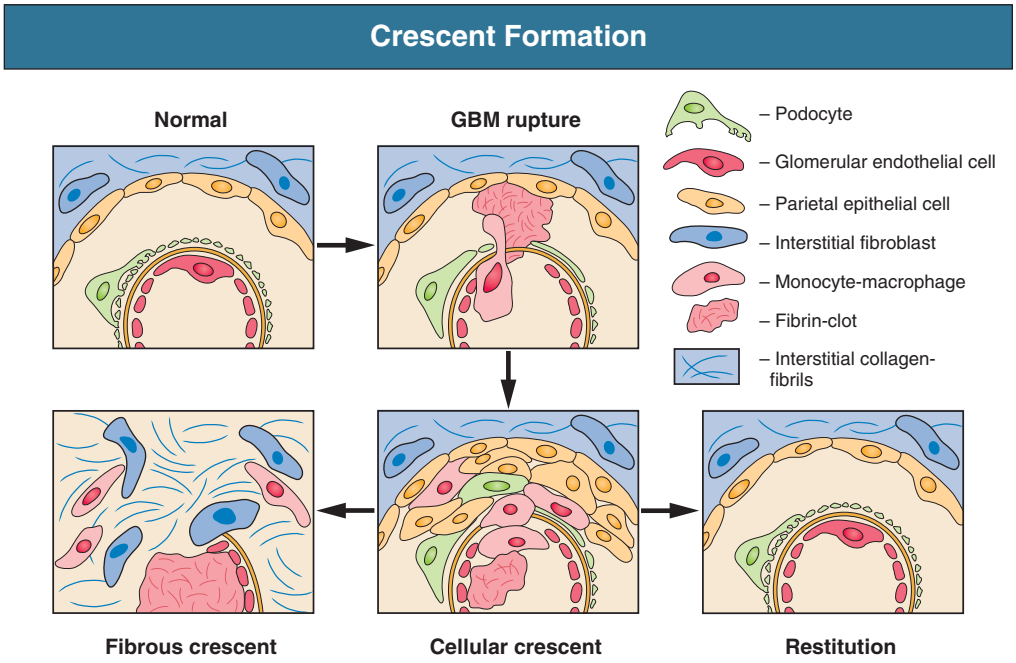

Figure 16-8 Crescent formation. In early crescent formation, cytokines and growth factors cross the glomerular basement membrane *(GBM)* to initiate proliferation of the parietal epithelial cells. Small breaks in the GBM occur secondary to injury from oxidants and proteases from neutrophils and macrophages, thus allowing the macrophage to enter Bowman space, where it can proliferate. Breaks in Bowman capsule secondary to the periglomerular inflammation also occur, allowing the entrance of more inflammatory cells as well as fibroblasts. The proliferation of parietal and visceral epithelial cells and macrophages is associated with fibrin deposition, slowly choking the glomerular tuft until filtration becomes impossible. In the late stages, the crescent becomes fibrotic and the glomerulus end stage. Alternatively, in less severe cases, complete restitution of the glomerular tuft can occur.

pathogenic mechanisms in the different patterns of glomerular disease are discussed in subsequent Section IV chapters.

PATHOGENESIS OF SPECIFIC GLOMERULAR SYNDROMES

Minimal Change Disease

Minimal change disease (MCD) is a steroid-sensitive nephrotic syndrome in which the only structural abnormality is podocyte swelling and fusion of foot processes on EM (see Chapter 17). For many years, the podocyte injury in MCD was thought to be caused by a cytokine released from T cells. T cells are activated in MCD, and T cell hybridomas from these patients secrete a factor that provokes heavy proteinuria in rats.[13] One candidate cytokine is interleukin-13 (IL-13), which is expressed by T cells in MCD patients, and overexpression of IL-13 causes nephrotic syndrome and histologic changes consistent with MCD in rats. However, proteinuria can be induced in immunodeficient mice using CD34-positive hematopoietic bone marrow cells of patients with MCD and recurrent FSGS but not by their T cells.[14] Thus, the role of T cells in this disorder remains to be clarified.

Evidence also suggests that the podocyte injury is associated with overexpression of angiopoietin-like-4, which may be responsible for the proteinuric response.[15] This overexpression can be reduced with corticosteroids and *N*-acetyl-D-mannosamine. In addition, patients with MCD show high levels of CD80 (B7.1) in urine and in podocytes, and the level of urinary CD80 correlates with disease activity. CD80 is an antigen that is normally expressed by DCs and B cells, and hence the observation that the podocyte can express CD80 suggests that the podocyte can acquire some DC-like characteristics.

Focal Segmental Glomerulosclerosis

Focal segmental glomerulosclerosis is a type of nephrotic syndrome that also occurs without immune deposits, but as with MCD, there is a generalized capillary wall defect with foot process fusion (also termed *effacement*) on EM (see Chapter 18). However, unlike MCD, there is segmental scarring (sclerosis) in some glomeruli with FSGS.

Idiopathic FSGS is also thought to be caused by a circulating factor, and recent studies suggest that some cases may be mediated by circulating soluble urokinase receptor (suPAR) that activates the β_3 integrin on podocytes, leading to podocyte activation and proteinuria.[16] The mechanism responsible for stimulating suPAR is unknown, and it is still too early to know if measuring suPAR will reliably discriminate FSGS from other glomerular diseases or even guide therapy. Other proteins, such as cardiotrophin-like cytokine 1, are also being investigated as potential circulating factors that may mediate FSGS.

A variant of FSGS is *collapsing* FSGS, in which there is proliferation of the normally quiescent podocyte, leading to collapse of the glomerular tuft, often in association with massive proteinuria. The pathogenesis may involve production by the podocyte of growth factors such as VEGF or local inhibition of cell cycle proteins that normally maintain the podocyte in a nonproliferative state.[17]

Focal sclerosing lesions in the absence of nephrotic syndrome can also occur in a wide variety of renal lesions, including GN, chronic hypertension, and progressive renal disease of any etiology. These lesions are particularly common in African Americans; recent findings suggest this susceptibility relates to increased frequency of a genetic polymorphism in *APOL1*, a gene coding for a circulating lipoprotein.

Membranous Nephropathy

In membranous nephropathy (MN), immune deposits are localized to the subepithelial space, where they had long been considered to represent autoantibody binding to an intrinsic podocyte antigen (see Chapter 20). This antigen has now been identified as the M-type phospholipase A_2 receptor (PLA_2R) in as many as 70% of cases of idiopathic MN.[18] Antibodies to PLA_2R are specific for MN and are available as a diagnostic test in Europe, although the test is not yet available in the United States or elsewhere. Circulating anti-PLA_2R reflects the immunologic activity of the disease and may be useful to monitor the clinical course, including patient response to treatment. Other autoantibodies have also been found. In neonatal MN, in which the mother genetically lacks neutral endopeptidase (NEP), the maternal transfer of antibody to NEP may occur, resulting in MN in

the child. Another antigen that may cause some forms of childhood MN is bovine serum albumin (BSA); cationic forms of BSA may first localize to the subepithelial space, followed by autoantibody binding.[19] Some cases of MN may also be caused by low-avidity immune complexes, which may dissociate and then re-form at the subepithelial space; this may be a mechanism for some MN caused by viruses such as HBV.

Interestingly, most cases of idiopathic MN caused by anti-PLA_2 antibodies are associated with IgG4 deposition, which is an isoform of IgG that does not activate the classical complement pathway. However, there is new evidence that the IgG4-PLA_2 complex can activate complement through the MBL complement pathway, resulting in local generation of the membrane attack complex (C5b-9), which may insert into the podocyte to cause activation, injury, and proteinuria.

Membranoproliferative Glomerulonephritis

In MPGN type I, the immune deposits localize both to the mesangium and the subendothelial space (see Chapter 21). A similar pattern is observed in cryoglobulinemic GN, in which the immune complexes contain a monoclonal IgM or polyclonal IgM that acts as a rheumatoid factor by binding to the IgG in the immune complex. In both cases, the disease is thought to occur by passive deposition from the circulation, and the antigen is often a component of the HCV virus, especially in adults. When this pattern is seen in lupus nephritis, it may be facilitated by the binding of nucleosomes to the complexes. *Nucleosomes* are cationic nuclear proteins that can interact with the negatively charged proteins within the glomerulus.

Studies in experimental models suggest that the intraglomerular immune complexes cause local complement activation with the generation of chemotactic factors, including C5a, chemokines, and leukotrienes. Leukocyte adhesion molecules on endothelial cells are upregulated (intracellular adhesion molecule 1) or expressed *de novo* (E- and P-selectin). Proinflammatory cytokines (IL-1 and tumor necrosis factor α) are generated locally and augment the inflammatory response. Neutrophils, platelets, and monocytes/macrophages then localize in the glomerulus and release oxidants, particularly hypohalous acids generated by neutrophil myeloperoxidase, and proteases (elastase, cathepsin G, metalloproteinases) that cause local cellular injury and GBM degradation.

Dense Deposit Disease

In contrast to MPGN type I, immune complexes are absent in glomeruli of patients with DDD, also called MPGN type II. Initiation results from spontaneous intraglomerular activation of the alternative complement pathway. The most common cause is nephritic factor, an autoantibody that activates the alternative pathway. Some cases may also be caused by mutations of the complement regulatory factor H, in which case the location of the mutation within the gene determines whether the disease manifests as DDD or atypical HUS.[20]

Mesangial Proliferative Glomerulonephritis

A mesangial proliferative GN, IgA nephropathy is the most common type of glomerulonephritis (see Chapter 23). Production of an abnormally glycosylated IgA, possibly by a bacterial superantigen,[21] or from generalized mucosal hyperreactivity, may lead to IgA polymers that deposit in the mesangium; the glomerular capillary wall is relatively spared. Marked proteinuria is a common feature of the clinical presentation. Mesangial cell injury may be mediated by binding of the IgA-containing immune complexes to Fcα or other IgA receptors on the mesangial cell, resulting in the release of chemokines and growth factors that provokes leukocyte infiltration as well as mesangial cell proliferation and mesangial matrix production.

Poststreptococcal Glomerulonephritis

Poststreptococcal GN has long been considered the human equivalent of acute serum sickness in rabbits (see Chapter 57). It is observed only in patients infected with specific (nephritogenic strains) of group A streptococci. One antigen responsible for some cases of PSGN, streptococcal pyrogenic exotoxin B (SPEB), enters the circulation and localizes to glomeruli, resulting in a brisk inflammatory reaction with local endothelial and mesangial cell proliferation and manifestations of nephritic syndrome. Complement activation occurs through the alternative pathway and may result from direct activation of the pathway by streptococcal antigens. Some deposits ("humps") also form in the subepithelial space and may represent the translocation of immune complexes across the GBM.

Goodpasture Disease

Goodpasture disease (anti-GBM disease) is caused by an autoantibody to the α3 chain of type IV collagen present in the GBM and alveolar basement membrane (see Chapter 24). The autoantibody develops in genetically susceptible individuals because of molecular mimicry between the type IV collagen antigens and certain bacterial antigens.[8] Binding of antibody results in complement activation with the infiltration of inflammatory cells, causing local capillary wall damage and proteinuria. Crescent formation also usually occurs and may be mediated by both T cells and macrophages.

ANCA-Associated Vasculitis

A severe form of segmental necrotizing glomerular injury, often in association with crescents, can be observed with various types of vasculitis (see Chapter 25). The two most common types of vasculitis causing this type of injury are Wegener granulomatosis and microscopic polyangiitis (MPA). Both are associated with circulating antibodies against neutrophil cytoplasmic antigens (ANCAs), with antibodies to endopeptidase (proteinase) 3, which give a cytoplasmic pattern by staining (c-ANCA) in most patients with Wegener granulomatosis, and antibodies to myeloperoxidase, which give a perinuclear staining pattern (p-ANCA) in subjects with MPA. Although experimental evidence suggests that ANCAs are pathogenic by activating neutrophils within the vasculature, pathogenic autoantibodies to lysosome-associated membrane protein 2 (LAMP-2) may have a role in some types of vasculitis.[9] LAMP antibodies appear to develop from molecular mimicry with various bacteria and viruses and when injected into rats results in crescentic nephritis. The clinical value of measuring LAMP autoantibodies is not yet clear.

There is further discussion of specific pathogenic mechanisms in the different patterns of glomerular disease in Chapters 17 to 29.

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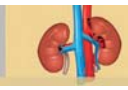
CHAPTER 17



Minimal Change Nephrotic Syndrome

Philip D. Mason and Peter F. Hoyer

DEFINITION

Minimal change disease (MCD) is the cause of nephrotic syndrome in about 90% of children younger than 10 years, about 50% to 70% of older children, and 10% to 15% of adults. MCD is defined by the absence of histologic glomerular abnormalities, other than ultrastructural evidence of fusion of epithelial cell foot process, in a patient presenting with nephrotic syndrome who is typically corticosteroid responsive. *Corticosteroid-sensitive nephrotic syndrome* is the term used to describe the disease occurring in children with nephrotic syndrome who respond to corticosteroids but who have not had a renal biopsy to provide the histologic proof of MCD. The presence of nephrotic syndrome is important because similar histologic findings may be seen in patients with proteinuria in the absence of nephrotic syndrome. Such patients may have different conditions with different prognoses and requirements for management.

Whereas MCD is classically associated with normal-appearing glomeruli and corticosteroid responsiveness, MCD appears to overlap with a variety of histologic variants that have a tendency to be less corticosteroid responsive. These conditions include focal segmental glomerulosclerosis (FSGS; see Chapter 18) and IgM nephropathy (see later discussion). It is possible that both MCD and FSGS have similar initial histologic appearances, but that FSGS is less corticosteroid responsive and thus develops secondary sclerosing lesions over time. Whether this represents a continuum of the same disease, in which some patients are corticosteroid sensitive and others are not, or whether these represent two distinct etiologies remains debatable.

ETIOLOGY AND PATHOGENESIS

In children age 2 to 12 years, MCD is the most common cause of nephrotic syndrome. However, it is also relatively common in adults. Many patients have a history of allergy, including atopy, asthma, or eczema (Box 17-1). Most cases are idiopathic, but MCD has also been associated with certain cancers, especially Hodgkin disease, in which it may be the presenting symptom. MCD is further associated with certain medications, such as interferon alfa and nonsteroidal anti-inflammatory drugs (NSAIDs).

The primary abnormality in MCD is a defect in the glomerular filtration barrier to protein. In normal glomeruli, the barrier to protein filtration is provided by the glomerular basement membrane (GBM) and the slit diaphragm that extends between the podocyte foot processes. Size barriers and charge selectivity of GBM exclude neutral molecules larger than 4 to 4.5 nm from filtration; albumin molecules smaller than this are excluded because they are anionic and are repelled by the negative charge on the epithelial cells and GBM.

In MCD, FSGS, and other causes of nephrotic syndrome, the clearance of proteins becomes greatly enhanced, whereas the filtration of small molecules is actually reduced. Some authorities have attributed the reduction in small molecular clearance to the diffuse foot process fusion, which reduces overall slit diaphragm area and thereby may account for the reduction in the ultrafiltration coefficient (K_f, see Chapter 2) typically observed. In contrast, the albuminuria is thought to result from specific areas ("large pores") where the protein escapes into the urine.

Studies in nephrotic syndrome have implicated injury to the podocyte, and particularly the slit diaphragm, as the key factor leading to proteinuria. The importance of the slit diaphragm for nephrosis was first shown with the congenital nephrotic syndrome of the "Finnish type," in which the primary defect is a mutation in nephrin, a key protein in the slit diaphragm. In particular, this nephrotic syndrome can histologically and clinically appear identical to MCD, except that it typically begins shortly after birth and is corticosteroid resistant (see Chapter 19). Since the discovery of the etiology of this nephrotic syndrome, numerous other genetic causes of nephrotic syndrome have been identified. All have mutations in genes involved in the development, structure, and function of podocytes (*NPHS2, NPHS3, WT1, LAMB2, LMXI2, ACTN4, CD2AP, TRPC6,* and *INF2*) and mitochondrial proteins (e.g., *COQ2, PDSS2, GMS1*).

As evidence for involvement of a primary podocyte abnormality, MCD is associated with expression of CD80 (B7.1) on the podocyte, and shed CD80 can be found in the urine of patients with MCD.[1] CD80 expression by podocytes is associated with shape change and development of proteinuria. Reduced levels of dystroglycans (adhesion molecules believed to anchor podocytes to GBM) have also been reported in MCD but not in FSGS, with normalization after corticosteroid treatment.[2] Podocyte overexpression of angiopoetin-like-4 *(ANGPTL4)* has been shown to bind to the GBM, with loss of charge and associated with nephrotic-range proteinuria. Furthermore, supplementation with *N*-acetyl-D-mannosamine may improve proteinuria, suggesting that hyposialysated *ANGPTL4* may be responsible for inducing proteinuria and may be a therapeutic target.[3]

Others have proposed that the permeability defect is caused by alterations in the GBM, particularly a loss of negative charge. In this case, podocyte changes could be secondary to the proteinuria. This would be consistent with observations of preserved foot processes in the early phase of some highly proteinuric states (e.g., recurrent FSGS after renal transplantation) and of podocyte foot process fusion in children with severe hypoalbuminemia, but not proteinuria, dying of kwashiorkor.[4]

Evidence also suggests that a circulating factor may be responsible for inducing the alteration in the capillary wall. *Hemopexin,* an acute-phase reactant extracted from human plasma, is capable of inducing proteinuria in rats,[5] and in one small study, plasma hemopexin activity was increased in MCD patients in relapse, with evidence of an altered isoform.[6] Evidence of a circulating factor in humans is also supported by the observation that proteinuria resolved within days after transplantation from a cadaveric donor

Minimal Change Disease: Factors Associated with Onset of Nephrotic Syndrome

Drugs
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Interferon alfa
Lithium: rare (usually causes chronic interstitial nephritis)
Gold: rare (usually causes membranous nephropathy)

Allergy
Pollens
House dust
Insect stings
Immunizations

Malignancy
Hodgkin disease
Mycosis fungoides
Chronic lymphocytic leukemia: uncommon (usually associated with membranoproliferative glomerulonephritis)

Box 17-1 Factors associated with onset of nephrotic syndrome in patients with minimal change disease.

Frequency of Types of Nephrotic Syndrome in Children and Adults

Histology	Children	Adults	Zimbabwe	Durban
MCD	76	20	9.2	14
FSGS	8	15	15.1	28
MN	7	40	15.1	41*
MPGN	4	7	33.6	9
Other	5	18	17.0	5

Table 17-1 Frequency of various types of nephrotic syndrome. In annual incidence per 1 million population, in children and adults, from Europe, the United States, and Africa. *MCD,* Minimal change disease; *FSGS,* focal segmental glomerulosclerosis; *MN,* membranous nephropathy; *MPGN,* membranoproliferative glomerulosclerosis. *35 with hepatitis B virus infection. *(Data from references 13, 14, and 15.)*

with MCD.[7] Evidence for a T cell abnormality includes the absence of immune deposits, the remarkable sensitivity of the disease to corticosteroids and cyclosporine, the relationship with Hodgkin disease, and the reports that active measles infection (which depresses cell-mediated immunity) can rapidly induce remission. Studies have shown that T regulatory cells are abnormal in MCD patients, and that generalized activation of T cells occurs during active disease.

Some studies have also implicated interleukin-13 (IL-13) released from T cells in causing the proteinuria, because T cell production of IL-13 is elevated, and overexpression of IL-13 can induce nephrotic syndrome in rats.[8] Interestingly, the mechanism involved the induction of CD80 in the podocyte. IL-13 is also a cytokine associated with allergic states, and MCD can be triggered by vaccination[9] or exposure to an allergen in sensitive individuals. As a result, patients with identified food allergies have been managed with exclusion diets, with reported complete or partial remission and with relapse after reintroduction of the offending food. However, even if a relationship exists, the allergic events may merely trigger relapse, as may infections. B cell involvement was based on some patients' response to rituximab, which binds to CD20 found on B cells. Recently, however, CD20 expression has been demonstrated on podocytes and may be upregulated in abnormal circumstances, and rituximab may also interact with podocyte sphingomyelin phosphodiesterase–like 3 protein.[10] Bisphosphonate therapy may lead to proteinuria, possibly through interference with the podocyte cytoskeleton.

Although steroids are first-line treatment for patients with MCD, the mechanism is unclear, and the optimal dose has never been formally tested. Previous studies describe an association between risk of relapse and suppression of the hypophyseal-adrenal axis.[11] Recent studies report melanocortin-1 receptors on podocytes and, interestingly, a significant reduction of proteinuria with adrenocorticotropic hormone (ACTH) therapy.[12]

EPIDEMIOLOGY

Most frequently presenting between 2 and 7 years of age, MCD affects 2 to 7 per 100,000 children per year, with a prevalence of 15 per 100,000. MCD is also an important cause of nephrotic syndrome in adults of all ages, although the incidence varies geographically. MCD is reported to be as low as 1 per million of the population in the United Kingdom and up to 27 per million in the United States. It is more common in South Asians and Native Americans but is much rarer in African Americans, in whom nephrotic syndrome is much more likely to be caused by FSGS and to be corticosteroid resistant. MCD is also relatively rare in developing countries, such as most countries in Africa and South America[13-15] (Table 17-1). Boys are twice as likely to be affected as girls, but the gender incidence is comparable in adolescents and adults. Data also suggest that MCD has become less common in adults.[16]

CLINICAL MANIFESTATIONS

Patients with MCD typically present with edema that develops during days to weeks, with fluid retention that often exceeds more than 3% of the body weight. Up to two thirds of initial presentations and relapses follow an infection, most often of the upper respiratory tract, but whether these are of causative significance is uncertain.

The clinical signs and symptoms of MCD are the same as for nephrotic syndrome of any cause (see Chapter 15), although nephrotic syndrome is often of rapid onset, increasing the risk of hypovolemia, particularly in children. Ascites is common, particularly in children with MCD, who may present with abdominal pain, a symptom that may suggest peritonitis or herald hypovolemia. Pleural effusions may also occur but are less common. In rare patients, pericardial effusions may occur, but even more rarely cause significant complications. Pulmonary edema is uncommon, except after excessive treatment with albumin or with coexisting cardiac disease. Hepatomegaly is common in children but may be overlooked in the presence of ascites. The distribution of edema is gravitational, but facial puffiness is common, and genital swelling may be extremely uncomfortable, especially in men. Gross edema may predispose to ulceration and infection of dependent skin; striae often appear even without corticosteroids, and lacerations or needlestick punctures weep fluid profusely. Edema of the bowel wall may cause diarrhea, rarely with significant albumin loss from the gut. Other clinical features include white nails, sometimes in bands (Muehrcke lines) correlating with periods of clinical relapse (see Fig. 15-4). In adults, xanthomas may occasionally result in association with gross hyperlipidemia.

Microscopic hematuria is rare in MCD. Although not typical in children, hypertension has been observed at presentation in 30% of 89 adults in one UK study.[17] Higher-than-normal blood pressure has also been described in 14% to 21% of children, compared with appropriate age- and gender-matched blood pressure reference ranges. Hypertension usually resolves during remission, especially in children. Hypertension is sometimes associated with expansion of the intravascular volume but may paradoxically be related to hypovolemia and stimulation of the renin-angiotensin system (RAS).

Before the introduction of corticosteroids, the morbidity and mortality of patients with MCD were high because of complications of nephrotic syndrome, particularly infection. Infection continues to be a serious problem, particularly in those presenting late.[18] Six of 389 children with MCD described by the International Study of Kidney Disease in Children (ISKDC) in 1984 died of sepsis.[19] Peritonitis remains a major cause of mortality in the developing world, mainly in children. *Streptococcus pneumoniae, Haemophilus influenzae,* and other encapsulated bacteria are implicated. Children with frequently relapsing nephrotic syndrome should be immunized against *S. pneumoniae* and *H. influenzae* during remission and given prophylactic oral penicillin in relapse.[20] Peritonitis is rare in adults, who usually have protective antibodies against these bacteria, and prophylactic antibiotics are not indicated.

The risk of thromboembolism is increased in MCD, as in all patients with nephrotic syndrome (see Chapter 15). Venous thromboembolism may occur in the lower extremities, renal veins, and other sites. Pulmonary embolism may be overlooked in children because of a lack of suspicion, even with pulmonary symptoms, and children may compensate better than adults. Nephrotic children occasionally have other catastrophic events, such as intracerebral venous or sinus venous thrombosis. Arterial thrombosis is a rare but feared complication, described in children almost exclusively, and may even result in loss of limbs.

Renal function is generally preserved. Serum creatinine concentrations are usually low in children but can be slightly elevated in adults. Acute kidney injury is a complication particularly seen in adults. AKI may follow hypovolemia, which should be avoided especially during intensive diuretic treatment, but it may also rarely occur in volume-replete patients.

Secondary MCD may mimic idiopathic MCD and may result from drugs or with cancer. The classic drugs associated with MCD are NSAIDs and particularly fenoprofen. This is an idiosyncratic reaction and is usually associated with chronic NSAID use that has occurred for several weeks or months. Unlike classic MCD, this syndrome is usually associated with massive nephrotic syndrome with impaired renal function, and renal biopsy shows MCD with features of an acute interstitial nephritis with T cell infiltration. Other causes of secondary MCD, such as the use of interferon alfa or interferon beta, or MCD observed in Hodgkin disease, may appear clinically identical to idiopathic MCD.

PATHOLOGY

Classically, MCD is associated with normal-appearing glomeruli by light microscopy and is negative for immunoglobulins and complement by immunofluorescence or other methodologies. Podocyte (epithelial cell) foot process effacement is observed with electron microscopy (Fig. 17-1) and is the only abnormality, but this is a nonspecific finding. The tubulointerstitium will show an absence of inflammation. Hyaline casts obstructing tubules, rare foam cells, and occasionally appearances consistent with acute tubular necrosis may be seen, especially if acute kidney injury is present at the time of biopsy.

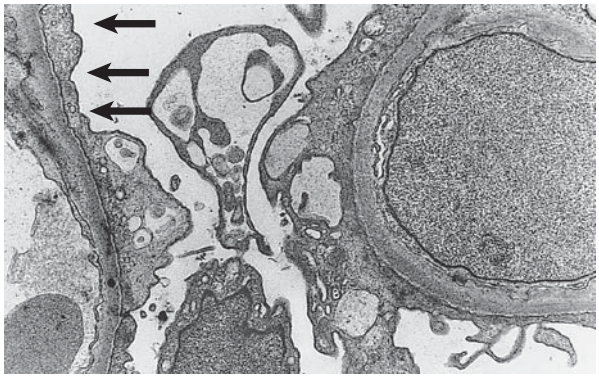


Figure 17-1 Podocyte foot process fusion in minimal change disease. The epithelial cells *(arrows)* are completely effaced along the glomerular basement membranes. (Electron micrograph; magnification ×6000.) The normal appearance of epithelial cell foot processes is shown in Figures 1-6 and 1-7 (see Chapter 1).

Variants

Mild mesangial hypercellularity is an infrequent finding in MCD patients (3% to 5%), and small amounts of mesangial IgG, complement C3, and occasionally IgA may be observed in patients whose clinical course is indistinguishable from classic MCD.

The *glomerular tip lesion* describes structural segmental changes adjacent to the tubular pole of Bowman capsule, with protrusion into the tubular lumen. This lesion is observed more frequently in adults than children, but whether it is a variant of MCD or a type of FSGS remains controversial. Generally considered a benign lesion, it may also be rarely observed in membranoproliferative glomerulonephritis, IgA nephropathy, and renal allografts. The most important reason to recognize the glomerular tip lesion is to prevent a misdiagnosis of a proliferative glomerulonephritis.

The presence of *mesangial hypercellularity* in MCD may correlate with increased resistance to corticosteroid therapy.[21] Some consider mesangial hypercellularity to be an intermediate step in cases of evolution (progression) of MCD to FSGS (see Chapter 18).

IgM Nephropathy

Some patients presenting with nephrotic syndrome have mesangial deposits of IgM, often with a minor degree of mesangial hypercellularity. Patients are more likely to have microscopic (and occasionally macroscopic) hematuria and are also less likely to respond to corticosteroids (50% versus 90% for minimal change nephrotic syndrome).[22] Whether this represents a distinct entity or is part of the spectrum observed with MCD and FSGS remains uncertain (see also Chapter 18).

Focal Segmental Glomerulosclerosis

Some patients who are considered to have MCD by renal biopsy may not respond to corticosteroids and on repeated biopsy are found to have FSGS. Others who initially are responsive to corticosteroids eventually become resistant and are discovered to have FSGS on a subsequent biopsy. This has led some to suggest that MCD and FSGS are part of a spectrum of the same disease process. However, the initial biopsies may have missed the sclerotic lesions of FSGS because they are focal.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The clinical diagnosis of nephrotic syndrome is straightforward, with edema in the presence of heavy proteinuria, usually without microscopic hematuria on urine dipstick testing. Urine microscopy reveals hyaline casts and sometimes lipid casts. There is hypoalbuminemia (<2.5 g/dl) and nephrotic-range proteinuria (>3.5 g/24 h in adults or >1 g/m^2/24 h [>40 mg/m^2/h] in children) or a protein/creatinine ratio of more than 0.25 g/mmol (>2 mg protein/mg creatinine) on a spot urine sample. Hyperlipidemia is also a common laboratory finding. Hyponatremia and hemoconcentration may be seen, even before treatment. Elevated urea and creatinine concentrations occur more often in adults. Typically, serum IgG levels are low and IgM is increased. Serum complement levels are normal.

In children, corticosteroid-sensitive MCD is usually associated with selective proteinuria of smaller molecules, including albumin and transferrin, but not of larger molecules, such as immunoglobulins and ferritin. A selectivity index is usually derived from the ratio of IgG clearance to albumin clearance, as follows:

$$\text{Selectivity index} = [(\text{IgG})_u(\text{albumin})_s]/[(\text{IgG})_s(\text{albumin})_u]$$

where subscript *u* is concentration in urine and *s* is that in serum. If the selectivity index is less than 0.1, the proteinuria is highly selective, and if more than 0.2, is nonselective. This is of limited clinical value because highly selective proteinuria is less common in adult MCD and does not influence the decision to treat with corticosteroids. However, highly selective proteinuria, when present, does indicate that MCD is more likely to be the diagnosis, and some argue that such patients should be given a trial of corticosteroids without a renal biopsy, especially if the risk of biopsy complications is high.

In children from the Northern Hemisphere age 2 to 12 years, renal biopsy is unnecessary unless the patient does not respond to a standard prednisone treatment of 60 mg/m^2/day within 4 weeks. In Africa and South America, the prevalence is lower. In this setting, a trial of corticosteroids might depend on the frequency of MCD in this region and should also consider the higher risk of infections.

In adults, in whom there is a wide differential diagnosis for nephrotic syndrome and corticosteroid responsiveness is less likely, a renal biopsy is required to establish the diagnosis.

On occasion, a renal biopsy may histologically appear like MCD, but there is another cause. In patients with nephrotic syndrome, this may be caused by FSGS in which the sclerotic glomeruli are not sampled. In young children, it could result from a hereditary nephrotic syndrome resembling MCD (see Chapter 19). Rarely, early membranous nephropathy will have a light microscopy appearance of normal glomeruli, but immunofluorescence will reveal immune deposits. Early amyloidosis may also mimic MCD histologically in the adult. In non-nephrotic subjects, diseases such as thin basement membrane disease can appear histologically normal but can be diagnosed by demonstration of the thin GBM on electron microscopy.

Natural History

Patients with MCD tend to run a relapsing-remitting course, which is more common in children. Those presenting at a younger age are more likely to have more relapses and a longer disease course (Fig. 17-2).[23] Relapse is common, affecting more than two thirds of children, and about 50% will relapse more than four times, usually after corticosteroid cessation or reduction. If relapse occurs during corticosteroid reduction, the patient is described as "corticosteroid dependent." Long-term remission can be expected in 75% of initial responders who do not relapse within 6 months; those who do relapse become nonrelapsing after an average of 3 years, and 84% are in long-term remission after 10 years.[24] Indeed, it is reassuring that less than 5% of children with MCD enter adulthood still having relapses, although the younger the age at onset of the first attack, the longer the child is likely to continue having relapses.[23,25] In general, increasing time since last relapse reduces the risk of further relapse, but adults occasionally have a relapse after an interval of 10 years or more.

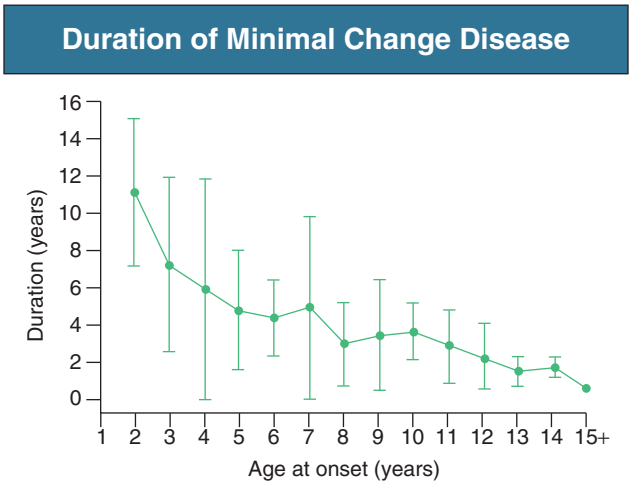


Figure 17-2 Long-term outcome in childhood-onset minimal change disease. The duration of disease is inversely related to the age at presentation. *(Modified from reference 23.)*

Minimal change disease does not progress to renal failure. However, a number of adult patients, but fewer children, with an initial diagnosis of MCD are found to have FSGS on subsequent biopsies and may develop progressive renal failure. It is still unclear whether the focal nature of the disease caused the correct diagnosis to be missed on the initial biopsy, or whether evolution from MCD to FSGS occurs in some individuals.

TREATMENT

Definitions that Guide Treatment

Table 17-2 provides key definitions related to the clinical response of MCD to treatment that are used to guide therapy.[26] For example, patients who relapse more than three times within 1 year are considered *frequently relapsing,* whereas those who respond to corticosteroids but relapse before discontinuation are considered *corticosteroid dependent.* Patients who remain proteinuric despite a course of corticosteroids are considered *corticosteroid resistant.* Stratification of patients into their category can help in management (see later discussion). Our recommendations are consistent with those published by the recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines,[27] although most of these are based on rather low levels and grades of evidence.

Initial Treatment of Minimal Change Disease

Initial management of MCD includes standard management of nephrotic syndrome as discussed in Chapter 15, including low-sodium diet to control edema. Bed rest should be avoided because of the increased risk for thrombosis. Diuretics are infrequently used in children because of potential further volume depletion, but

Nephrotic Syndrome: Definitions		
	Definitions	
Term	***Adult***	***Pediatric***[17,18]
Relapse	Proteinuria ≥3.5 g/day occurring after complete remission obtained for >1 month	Albu-stix 3+ or proteinuria >40 mg/m²/h occurring on 3 days within 1 week
Frequently relapsing Complete remission	2+ relapses within 6 months Reduction of proteinuria to ≤0.20 g/day and serum albumin >35 g/l	2+ relapses within 6 months <4 mg/m²/h on at least 3 occasions within 7 days; serum albumin >35 g/l
Partial remission	Reduction of proteinuria to between 0.21 g/day and 3.4 g/day ± decrease in proteinuria of ≥50% from baseline	Disappearance of edema; increase in serum albumin >35 g/l and persisting proteinuria >4 mg/m²/h or >100 mg/m²/h
Steroid resistant	Persistence of proteinuria despite prednisone therapy, 1 mg/kg/day × 4 months	Persistence of proteinuria despite prednisone therapy, 60 mg/m² × 4 weeks*
Steroid dependent: nephrotic syndrome recurs when therapy stopped or decreased	Two consecutive relapses occurring during therapy or within 14 days of completing corticosteroid therapy[19]	Two relapses of proteinuria within 14 days after stopping or during alternate-day corticosteroid therapy

Table 17-2 Definition of terms used in idiopathic nephrotic syndrome in adults and children. The definitions were generated by a consensus of the International Society for Kidney Diseases in Children and the German Pediatric Nephrology Society. *(Data from reference 26.)* *Or persistence of proteinuria despite prednisone therapy (60 mg m^{-2} × 4 weeks) and three methylprednisolone pulses.

diuretics are often used to control extracellular fluid volume in adults, in whom hypovolemia before treatment is less common. In patients with prolonged nephrotic syndrome, treatment of hyperlipidemia with statins and thrombosis prophylaxis should be considered.

Childhood Minimal Change Disease

Treatment of First Episode

Corticosteroids are the initial treatment of choice (see algorithm, Fig. 17-3), although never formally tested in a trial setting, with experiences based on the empiric regime introduced by ISKDC consensus. Accordingly, children age 2 to 12 years with a first episode of nephrotic syndrome should be treated with oral prednisone (or prednisolone), 60 mg/m²/day (maximum dose 80 mg/day), in three divided doses (calculated on basis of estimated dry weight). With this regimen, about 75% respond within 2 weeks, and almost all who are corticosteroid sensitive respond within 4 weeks[28] (Fig. 17-4). Patients who do not respond within the period are regarded as *nonresponders.*[22] Whereas the ISKDC recommended continuing the daily dose for 4 weeks, later studies recommend 6 weeks.[29] This daily dose should be followed by an alternate-day dose of 40 mg/m²/48 h for an additional 4 weeks (ISKDC) or 6 weeks.[30] A meta-analysis showed that extending the duration of corticosteroid treatment to at least 3 months reduces the 1- to 2-year risk of relapse (Fig. 17-5).[31] However, a recent randomized controlled trial compared an initial treatment period of 3 months with 6 months with both groups receiving the same cumulative dose of steroid. There was no difference in the relapse rate, so the benefit of an extended duration of steroid therapy previously reported is likely to be explained by an increased cumulative dose.[32]

The German Society for Pediatric Nephrology recommends stopping corticosteroid treatment for the first episode after 12 weeks; others recommend tapering (e.g., reducing every 2 weeks by 15 mg/m² on alternate days). Although these two regimens have never been compared, we do not recommend tapering because of concerns about chronic corticosteroid use affecting growth.

Treatment of Relapses

The urine should be tested daily (usually by a parent) during and after treatment. The rationale is that relapses should be treated on the basis of proteinuria (usually requiring at least three or more positive dipstick measurements for 3 consecutive days) to initiate a further course of corticosteroids. The aim is to treat relapse early to avoid nephrosis-associated complications. The intensity of corticosteroid treatment for relapses has not been shown to influence the probability of further relapses.

Our recommendation is oral prednisone, 60 mg/m²/day (maximum dose 80 mg/day) in three divided doses, until the urine is protein free for 3 days, followed by a course of alternate-day prednisone, 40 mg/m²/48 h for 4 weeks, then stop. An alternative recommendation is to taper the alternate dose during weeks to months to define a relapse threshold. However, the acceptability of this approach depends on the corticosteroid threshold, and there is risk of unnecessarily prolonged treatment with more corticosteroid toxicity.

Frequently Relapsing and Corticosteroid-Dependent Nephrotic Syndrome

For both frequently relapsing and corticosteroid-dependent nephrotic syndrome, second-line therapy is required. The second-line drugs most frequently used to avoid corticosteroid toxicity are alkylating agents (cyclophosphamide and chlorambucil), levamisole, and cyclosporine. The decision to use second-line therapy for chronically relapsing patients will depend on how quickly corticosteroid-induced remission occurs and how corticosteroids are tolerated. However, corticosteroid dependency is a clear indication for second-line treatment, which should be started before severe corticosteroid toxicity is apparent. The patient or parents usually are involved in the decision after the potential side effects of the second-line treatment are considered.

The alkylating agent *cyclophosphamide* is the recommended first choice of second-line therapy. Oral cyclophosphamide, 2 to 2.5 mg/kg/day, is given for 12 weeks, on the basis of a study suggesting a lower 2-year remission rate compared with an 8-week course,[33] although these results have not been supported by all published data.[34] Cyclophosphamide can be associated with serious side effects, initially infection and alopecia, and subsequently sterility,[35] hemorrhagic cystitis, bladder cancer, and hematologic malignant neoplasia. However, if therapy is limited to 12 weeks with 2 mg/kg/day, or a total dose of 200 mg/kg, the risk of these complications is low. Others suggest that cyclophosphamide should not be used in younger children (<5.5 years), in whom it is associated with a reduced duration

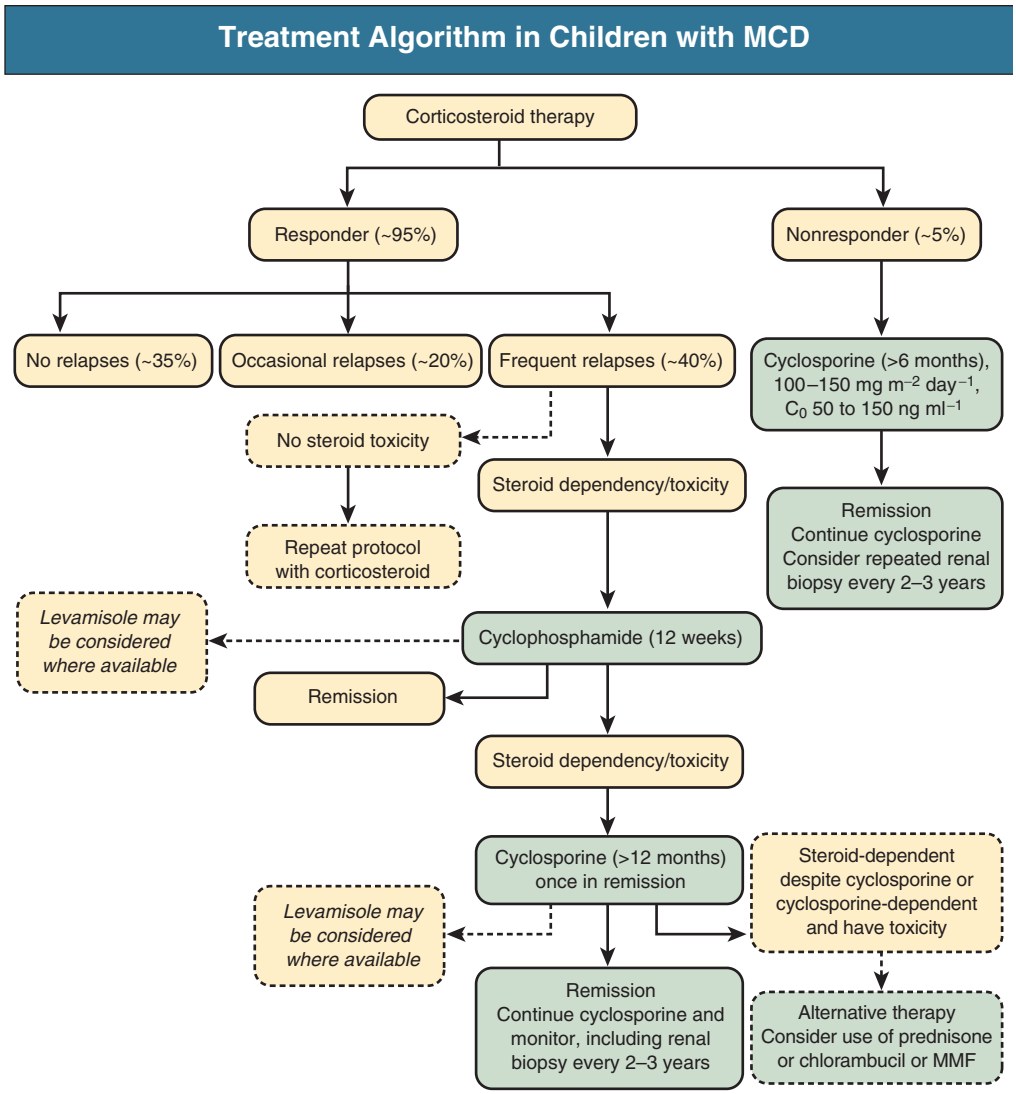


Figure 17-3 Algorithm for treatment of childhood minimal change disease (minimal change nephrotic syndrome). For definitions, see Table 17-2. The patient or parents should be involved in the decision after the potential side effects of the second-line treatment are considered (boxes with interrupted lines show alternative options). In the rare patient who is a nonresponder to standard corticosteroid therapy and by definition "corticosteroid resistant," a trial with cyclosporine may be considered. *MMF,* Mycophenolate mofetil.

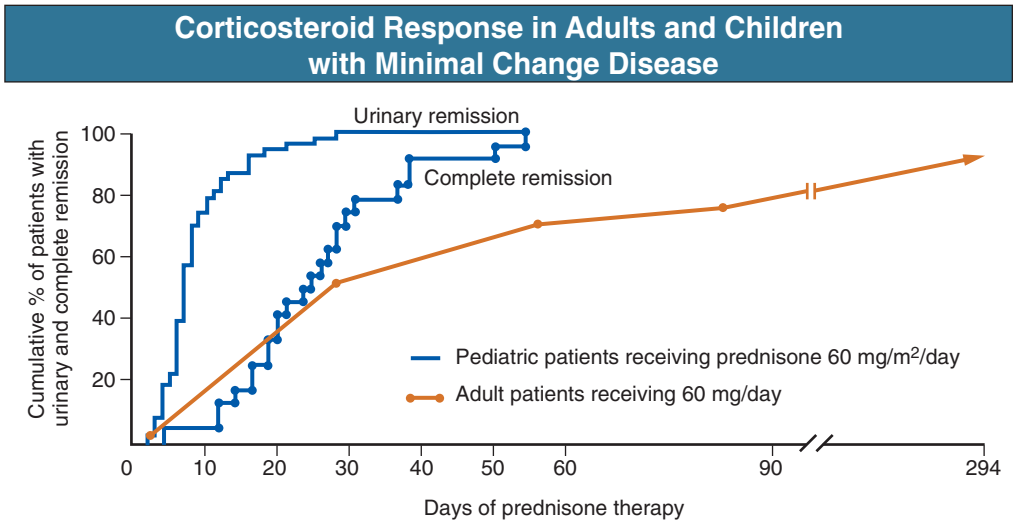


Figure 17-4 Corticosteroid response in adults and children with minimal change disease. Adults with the nephrotic syndrome and MCD take longer to respond than children and are less likely to remit. *Orange line* shows the cumulative percentage of adults with complete remission (i.e., reduction of proteinuria ≤0.2 g/day and serum albumin concentration >35 g/l). *Blue lines* show the cumulative percentage of pediatric patients with urinary remission and with complete remission. Urinary remission is defined by urine on dipstick negative or trace or proteinuria less than 4 mg/m^2/day on at least 3 days; the definition of complete remission requires, in addition to that, a serum albumin concentration above 3.5 g/dl. *(Redrawn from data from references 17 and 28.)*

of remission[36,37] (Fig. 17-6). However, the decision to recommend cyclophosphamide before alternatives may consider the benefits of long-term remission, even if the probability is low.

Chlorambucil, 0.2 mg/kg/day for 2 months, appears to be similar to cyclophosphamide in efficacy but has a greater frequency of adverse effects, including seizures, and therefore is not a preferable substitute.[38]

In general, frequently relapsing children tend to respond better than corticosteroid-dependent children. Second courses of alkylating agents are not recommended because cumulative toxicity occurs.

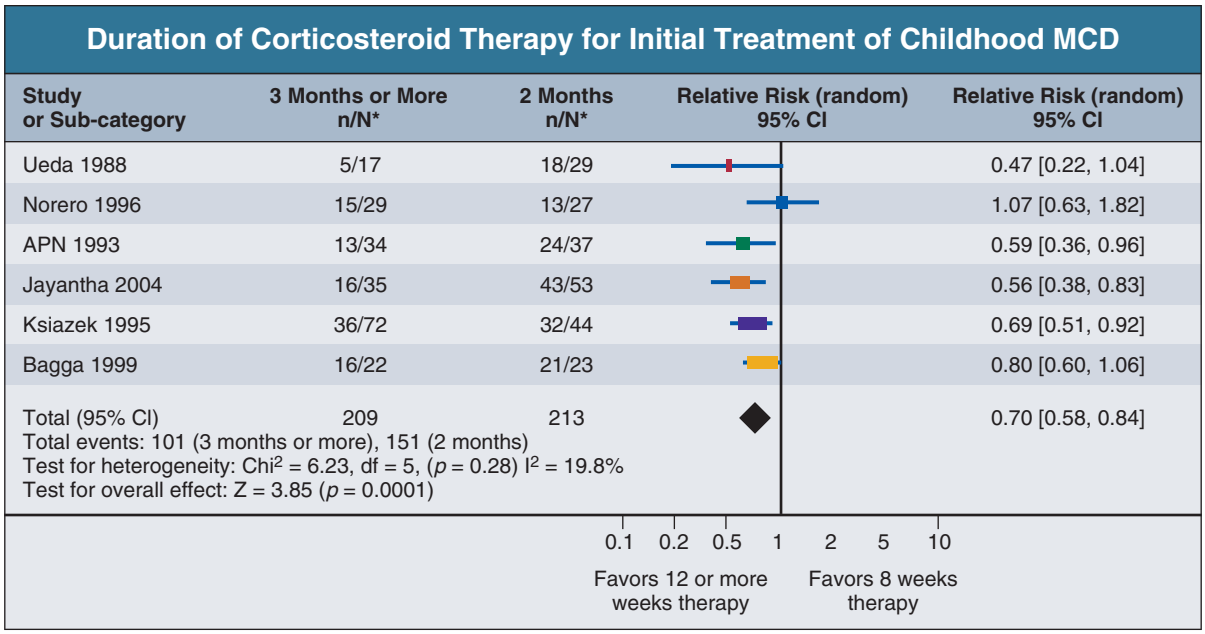


Figure 17-5 Duration of corticosteroid therapy for initial treatment of childhood minimal change disease. Cochrane meta-analysis of studies supports a 12-week or longer course of corticosteroid therapy compared with 8 weeks in the first episode of corticosteroid-sensitive nephrotic syndrome, to induce remission. Summary suggests a 30% better remission rate in patients receiving 12 weeks or more of therapy. **n/N,* Number of children relapsing per total number of children receiving that treatment. *(From reference 31.)*

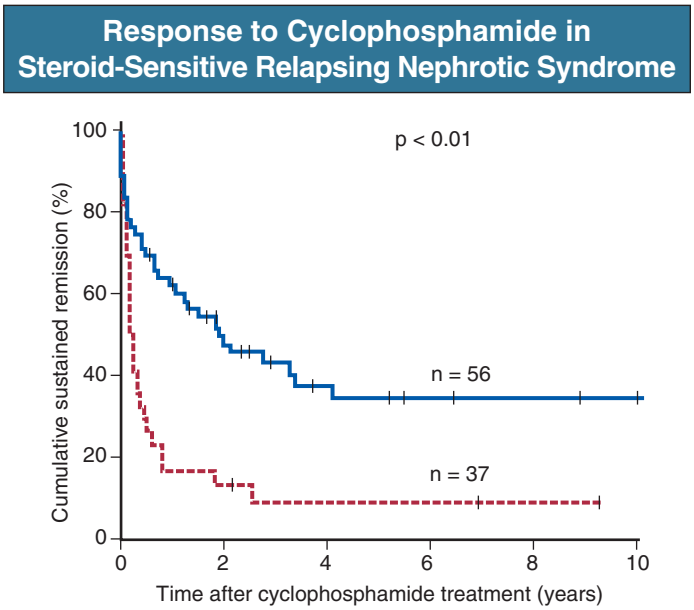


Figure 17-6 Response to cyclophosphamide dependent on age. Sustained remission is higher in children older than 5.5 years *(solid blue line)* than in younger children *(dotted red line)* with steroid-sensitive relapsing nephrotic syndrome. *(From reference 37.)*

During treatment with cyclophosphamide or chlorambucil, blood counts should be checked weekly and dose reductions made if necessary. Primary varicella infection carries a particular risk for nonimmune children receiving immunosuppressive therapy. These children should receive hyperimmune immunoglobulin and probably an antiherpes agent such as valaciclovir if there is an unavoidable contact with active chickenpox or shingles infection.

An alternative medication to alkylating agents is cyclosporine. Cyclosporine, up to 150 mg/m^2 or 3 to 4 mg/kg/day (with whole-blood trough levels of 50 to 150 ng/ml), is usually effective in children with both corticosteroid-dependent and frequently relapsing nephrotic syndrome.[36] However, relapse is almost invariable within 3 months of stopping treatment, and unfortunately, reintroduction of cyclosporine is often less effective once it has been interrupted. Therefore, cyclosporine is often used as long-term therapy. If there is no response, increasing the dose of cyclosporine is sometimes effective, but there is a risk of cyclosporine nephrotoxicity even with low-dose regimens, and careful monitoring of blood levels, glomerular filtration rate (GFR), and blood pressure is required. The aim of therapy is to maintain remission without corticosteroids until the underlying disease remits. The optimal duration of cyclosporine therapy is not established, but early withdrawal is discouraged for children. Besides careful monitoring of renal function, kidney biopsies every 2 to 3 years are recommended to ensure safety of the therapy. Although cyclosporine-associated nephrotoxicity during long-term treatment has been reported, one study with careful follow-up suggested that despite an initial drop in GFR, no further decrease occurred during the subsequent 5 to 10 years. More long-term studies are needed.

Many studies have now reported that tacrolimus is as effective as cyclosporine. Tacrolimus, with its superior cosmetic side effect profile, especially without hypertrichosis and gingival hypertrophy, may be an effective alternative that can improve drug adherence, especially in adolescents. Optimal dosing and drug levels are not fully established, but levels of 4 to 8 ng/l are often targeted. High doses must be avoided because initial experiences in the 1990s reported increased rates of lymphoma with high doses. Drug associated nephrotoxicity with long-term use is not well studied, but the same caution should be exercised with tacrolimus as with cyclosporine.

The antihelmintic levamisole, 2.5 mg/kg on alternate days for 3 months, has also been used successfully as a nontoxic alternative to corticosteroids.[39,40] However, most patients relapse within 3 months of stopping levamisole. It is used in the United States, Japan, and United Kingdom, although it has been withdrawn from the rest of Europe. A clinical trial using levamisole in MCD is ongoing and may provide better insight if there is utility in this disease.

Azathioprine has no proven role in the management of children with MCD and was ineffective in a randomized trial.

Newer Agents

The disadvantages of long-term calcineurin inhibitor (CNI) therapy, particularly the nephrotoxicity, has led to the widespread use of mycophenolic acid (mycophenolate mofetil, MMF), which is not nephrotoxic, in children with corticosteroid-dependent nephrotic syndrome. Many uncontrolled case series have reported MMF as effective in preventing relapses in frequently relapsing or corticosteroid-dependent patients. A small randomized trial with 12 patients in each arm suggested some efficacy with MMF but less than with cyclosporine.[41] A larger randomized crossover trial in 60 frequently relapsing children reported that after 24 months, 84% of cyclosporine-treated patients were relapse free, compared with 64% of the MMF arm. A small subgroup analysis suggested that MMF AUC-adjusted dosing may improve efficacy.[42]

There have been many reports that rituximab is effective in various forms of corticosteroid-dependent nephrotic syndrome refractory to other treatment. Unfortunately, all are uncontrolled case series, and no formal trials have yet been reported. In the largest reported multicenter series, 22 patients age 6 to 22 years with severe corticosteroid- or cyclosporine-dependent nephrotic syndrome had a remission after rituximab treatment, with one or more immunosuppressive drugs withdrawn in 85% of patients.[43] Relapses occurred with reappearance of B cells. However, 45% reported adverse effects, including one death from respiratory infection. The reported experience with rituximab suggests that it may be useful for preventing relapses and, if confirmed, will prevent drug dependency and toxicity. However, the potential role for rituximab in the management of these difficult patients is currently uncertain, and well-designed controlled trials are urgently needed to establish its efficacy, optimal dosing, and long-term safety.

Adult Minimal Change Disease

Studies comparing different corticosteroid regimens in adults with MCD are limited, and the treatment recommendations given here, in line with KDIGO guidelines,[27] are extrapolated from successful approaches in children, although often with slightly lower doses of oral prednisolone (1 mg/kg/day, up to maximum 80 mg/day) (Fig. 17-7). There is no good evidence that alternate-day corticosteroids offer any clinical advantages over daily dosing. Corticosteroids should be combined with gastric protection (H_2 blocker or proton pump inhibitor) and bone protection with a bisphosphonate.

Response is often delayed in comparison with children, and 25% fail to remit after 3 to 4 months[17,27,44] (see Fig. 17-4). Although unclear, the reason may be that many adults are often given a smaller dose of corticosteroids, or that a greater proportion of adults have focal segmental glomerulosclerosis (FSGS), missed on the original biopsy, which is more likely to be corticosteroid resistant.

There are no helpful studies to inform the optimal length of full-dose prednisolone after remission has been induced (absence of protein on urine dipstick). Based on meta-analysis of pediatric patients, however, the recommendation for total length of corticosteroid treatment is at least 3 to 4 months (KDIGO recommends up to 6 months, but based on grade 2D evidence). Full-dose corticosteroids should be continued for at least 2 weeks after full remission is achieved, but for a minimum of 4 weeks if remission occurs early, before tapering the dose. The rate of dose tapering and total length of treatment of the initial episode may need to be foreshortened in individual patients if the steroid toxicity is thought to be a significant factor (e.g., uncontrolled diabetes, psychiatric complications, patient with severe osteoporosis).

If the patient has not responded after 12 to 16 weeks, consideration should be given to concordance (compliance) with corticosteroid treatment or failure of absorption. The latter is unusual unless the patient is vomiting or has diarrhea, in which case some recommend intravenous methylprednisolone, with anecdotal success, although initial treatment with pulse methylprednisolone and lower doses of oral corticosteroid does not seem to be beneficial. A repeat biopsy should be considered in patients failing to respond.

Infrequent relapses should be treated in the same way as the initial presentation, but there is even less evidence that a prolonged course of corticosteroids is beneficial in reducing the frequency of subsequent relapse. Therefore, steroid tapering can start a week after remission, with a taper to finish over 4 to 6 weeks, although this is not evidence based.

Frequently Relapsing and Corticosteroid-Dependent Nephrotic Syndrome

Frequently relapsing nephrotic syndrome usually means two or more relapses within 6 months or four or more within 1 year of initial remission induction. Adults relapse less often than children (30% to 50%). Relapse may also occur in 40% of adults who had MCD in childhood.[45] As in children, some adults have transient non-nephrotic relapses, so it is important to establish that a full relapse has developed with persistent heavy proteinuria, a low albumin level, and fluid retention before recommencing steroids. Frequently relapsing and corticosteroid-dependent patients should receive second-line therapy with cyclophosphamide or cyclosporine, but the timing of this decision will vary between physician and patient. Many factors will influence the decision to abandon repeated corticosteroid courses, including steroid toxicity and tolerance and level of steroid dependence; 5 to 10 mg/day may be acceptable for several months, but more than 20 mg/day would not. The patient should be involved in the decision after explanation of the relative risks with further courses of corticosteroids and the alternative treatments.

Initial second-line management is with a 12-week course of oral cyclophosphamide (2-2.5 mg/kg/day), which induces a permanent remission more often in adults than children (75% and 66% at 2 and 5 years, respectively).[17] Although there are no satisfactory studies comparing 8-week and 12-week courses in adults, the 12-week course is logical on the basis of the pediatric experience. If this treatment is selected, the opportunity for banking sperm or retrieval of eggs should be considered before treatment. Intravenous cyclophosphamide has been recommended to limit the cumulative dose, and two small trials compared outcome with tacrolimus treatment, but the small numbers and trial design limit their value in informing management.

For patients who relapse after cyclophosphamide treatment, cyclosporine, 4 to 6 mg/kg/day, aiming for trough whole-blood levels of 50 to 150 ng/ml for at least 12 months, is also effective, but relapse usually follows dose reduction or withdrawal. Cyclosporine is worth considering as a short-term to medium-term management strategy because evidence suggests that remission eventually occurs in 50% to 75% of patients even without treatment.[16] However, careful monitoring is required because nephrotoxicity is common after more than 1 year of therapy.[46]

Some nephrologists prefer to offer cyclosporine before cyclophosphamide, especially in younger adults and those who want to maximize future fertility, although the risks of the total dose used in MCD are unlikely to cause permanent infertility.

Tacrolimus appears to have similar effectiveness as cyclosporine and may have a more favorable side effect profile. Initial target levels

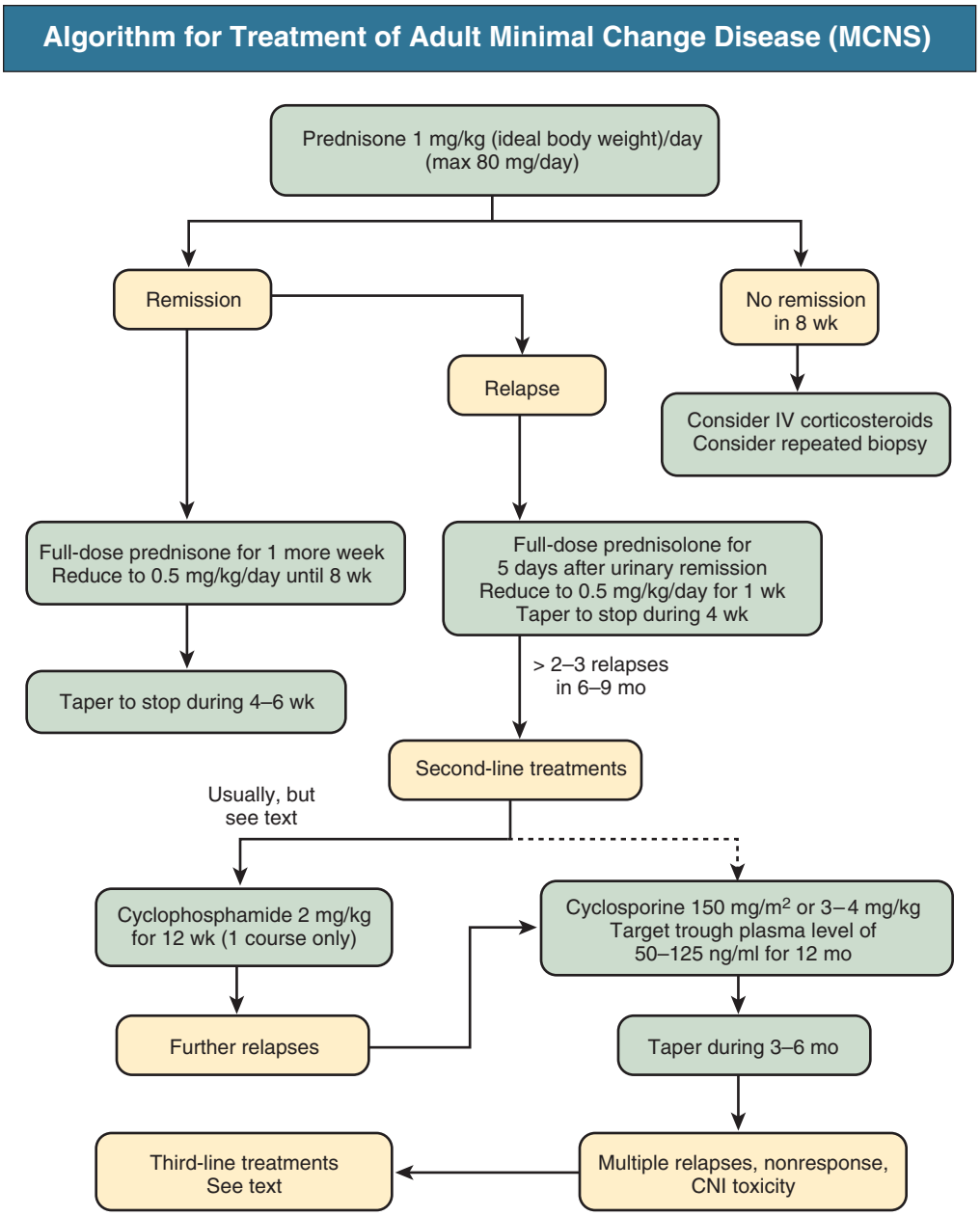


Figure 17-7 Algorithm for treatment of adult minimal change disease (minimal change nephrotic syndrome). *CNI,* Calcineurin inhibitor.

are generally 4 to 8 ng/ml, but higher levels may be required to maintain remission.

Newer Agents

Several uncontrolled reports suggest that MMF may also have a place in management of corticosteroid- and cyclosporine-dependent patients,[47-49] but more data on efficacy, dosage, and duration of treatment are needed before these could be widely recommended. As reported in children, there are many publications suggesting that rituximab results in remission in adults with frequently relapsing disease unresponsive to other treatments. The largest study in adults with corticosteroid-responsive MCD suggests that the safety and efficacy of rituximab are similar to those reported in children, with more than a 10-fold reduction in annual relapse rate.[50] This retrospective study also suggested that response was much better in patients given rituximab during remission. However, as in children, randomized controlled trials are needed to establish efficacy, safety, and optimal dosing schedule.

Minimal Change Disease with Non-nephrotic Proteinuria

In patients with well-documented MCD who have the rare relapse in which the proteinuria is non-nephrotic, treatment does not require corticosteroids but rather can include angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy. If there is any question as to diagnosis, repeated biopsy may be indicated because other conditions can mimic MCD (see Diagnosis and Differential Diagnosis).

Treatment of Secondary Minimal Change Disease

The MCD secondary to NSAIDs requires discontinuation of the offending medication. Many patients are treated with a course of corticosteroids for MCD (higher dose) or for acute interstitial nephritis (see Chapter 62), but evidence of therapeutic benefit is uncertain. Secondary MCD from Hodgkin disease usually responds

to treatment of the lymphoma. Some patients will also receive a drug regimen for MCD as adjunctive therapy in addition to the chemotherapy directed at the tumor.

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CHAPTER 18

Primary and Secondary (Non-Genetic) Causes of Focal and Segmental Glomerulosclerosis

Gerald B. Appel and Vivette D. D'Agati

DEFINITION

Focal segmental glomerulosclerosis (FSGS), a histologic pattern of glomerular injury, defines a number of clinicopathologic syndromes that may be primary (idiopathic) or secondary to diverse etiologies[1-5] (see also Chapter 19). Early in the disease process, the pattern of glomerulosclerosis is focal, involving a minority of glomeruli, and segmental, involving a portion of the glomerular tuft.[4,5] Alterations of podocyte cytoarchitecture identified on electron microscopy are relatively diffuse, underscoring the pathogenetic importance of podocyte injury. As the disease progresses, more diffuse and global glomerulosclerosis evolves. Although it accounts for only a small percentage of cases of idiopathic nephrotic syndrome in young children, FSGS represents as many as 35% of cases in adults.[1] It is a major cause of progressive renal disease and end-stage renal disease (ESRD) in certain populations.[6]

Diverse pathogenetic mechanisms have been identified and often manifest as particular histologic subtypes of disease. Through podocyte depletion and dysregulation, structural deterioration of the glomerular tuft leads to FSGS as a final common pathway.[5] Although primary (idiopathic) FSGS is potentially treatable and curable in many patients, the optimal type and duration of immunosuppressive as well as adjunctive therapy remain controversial. For secondary FSGS, effective therapies exist to slow or to modify the disease course (see Chapter 80).

ETIOLOGY AND PATHOGENESIS

Focal segmental glomerulosclerosis represents a common phenotypic expression of diverse clinicopathologic syndromes with distinct etiologies (Box 18-1). Causes include genetic mutations in podocyte components (see Chapter 19), circulating permeability factors, viral infections, drug toxicities, maladaptive responses to reduced number of functioning nephrons, and hemodynamic stress placed on an initially normal nephron population. In all these forms of FSGS, injury directed to or inherent within the podocyte is a central pathogenetic mediator.[2,5,7,8] These injuries promote altered cell signaling, reorganization of the actin cytoskeleton, and resulting foot process effacement. Critical levels of injury cause podocyte depletion through detachment or apoptosis. Stress placed on the remaining podocytes may lead to local propagation of damage (see Chapter 79). Injury to podocytes may spread to adjacent podocytes by reduction in supportive factors such as nephrin signaling or increased toxic factors such as angiotensin II (Ang II) or mechanical strain on remnant podocytes.[9] Cell-to-cell spread of podocyte injury until the entire glomerular lobule is captured could explain the characteristic segmental nature of the sclerosing lesions.[10]

Minimal Change Disease Versus Focal Segmental Glomerulosclerosis

By definition, the etiology of idiopathic or primary FSGS is unknown. Some clinical data support etiologic factors similar to those at work in minimal change disease (MCD; see Chapter 17).[1] Certain corticosteroid-responsive FSGS patients who exhibit MCD on initial biopsy subsequently relapse and display FSGS on repeated biopsy. In some, this may simply represent a sampling error in the initial biopsy. In others with well-documented repeated relapses of nephrotic syndrome and multiple biopsies over years, FSGS truly appears to have evolved from an initial MCD pattern. The relatedness of these two diseases is further supported by the observation that pathologic changes in the nonsclerotic glomeruli of idiopathic FSGS resemble glomeruli of MCD.[5] In addition, sequential biopsies of recurrent FSGS in the allograft show it passes through an early stage that mimics MCD.[11] Thus, MCD and FSGS are often considered together under the rubric of "podocytopathies".

Both MCD and primary FSGS are thought to be mediated by circulating *permeability factors.*[12] Recent studies suggest that the permeability factors in FSGS and MCD differ and that the diseases can be distinguished using biomarkers. Elevated CD80, a costimulatory factor expressed on podocytes and B cells, is found in the urine of corticosteroid-sensitive MCD[13] but not in FSGS. Angiopoietin-like-4, a podocyte-secreted glycoprotein, is upregulated in podocytes and is elevated in the serum of animal models and patients with MCD.[14] In animal models, induction of urokinase plasminogen activator receptor (uPAR) in podocytes produces effacement, proteinuria, and FSGS by promoting a migratory podocyte phenotype through activation of β_3 integrin.[15,16] Patients with primary FSGS have higher levels of circulating soluble uPAR (suPAR) than equally proteinuric patients with MCD or membranous nephropathy.[16] Elevated suPAR levels have been found in 55% of the European PodoNet cohort of FSGS patients and 84% of the American FSGS-CT cohort, and there was an association between treatment-induced reduction in proteinuria and reduction in suPAR levels.[17] Patients with recurrent FSGS in the allograft also have high circulating suPAR levels, which are reduced by plasma exchange in parallel with reduction in proteinuria. However, some studies have found that patients with secondary FSGS and others with reduced GFR also have high circulating levels of suPAR.[18] Thus the pathogenetic role of suPAR and its diagnostic value presently remain uncertain.

Loss of the glomerular filtration barrier allows negatively charged albumin to leak into Bowman space. The alterations in glomerular capillary wall permeability may occur in response to circulating "humoral" substances that act on the podocyte to promote foot process effacement. Circulating permeability factors that enhance *in vitro* permeability of glomeruli to albumin have been found in the

Etiologic Classification of Focal Segmental Glomerulosclerosis

Primary (Idiopathic) FSGS
Probably mediated by circulating/permeability factor(s)

Secondary FSGS

1. Familial/Genetic*
- Mutations in nephrin *(NPHS1)*
- Mutations in podocin *(NPHS2)*
- Mutations in α-actinin 4 *(ACTN4)*
- Mutations in transient receptor potential cation channel *(TRPC6)*
- Mutations in Wilms tumor suppressor *(WT1)*
- Mutations in inverted formin-2 *(INF2)*
- Mutations in phospholipase C epsilon 1 *(PLCE1)*
- Risk alleles for apolipoprotein L1 *(APOL1)*

2. Virus Associated
- HIV-1 ("HIV-associated nephropathy")
- Parvovirus B19
- Simian virus 40 (SV40)
- Cytomegalovirus (CMV)

3. Drug Induced
- Heroin ("heroin-nephropathy")
- Interferon
- Lithium
- Pamidronate
- Sirolimus
- Anabolic steroids

4. Mediated by Adaptive Structural-Functional Responses

Reduced renal mass
- Oligomeganephronia
- Very low birth weight
- Unilateral renal agenesis
- Renal dysplasia
- Reflux nephropathy
- Sequela to cortical necrosis
- Surgical renal ablation
- Chronic allograft nephropathy
- Any advanced renal disease with reduction in functioning nephrons

Initially normal renal mass
- Hypertension
- Atheroemboli or other acute vaso-occlusive processes
- Obesity
- Increased lean body mass
- Cyanotic congenital heart disease
- Sickle cell anemia

Box 18-1 Etiologic classification of focal segmental glomerulosclerosis (FSGS). *For complete list of genetic causes see Chapter 19. *HIV,* Human immunodeficiency virus.

plasma of some FSGS patients. The presence of such permeability factors has been used to predict the recurrence of FSGS in transplanted FSGS patients.[12] Some FSGS patients with recurrence of nephrotic syndrome after transplantation achieve remissions of nephrotic syndrome after plasma exchange or use of a protein A adsorption column, supporting the role of a circulating factor[12,19,20] (see Chapter 108). As described above, one candidate is suPAR.[16] Another candidate factor is cardiotrophin-like cytokine 1 (CLC1), a member of the IL-6 family of interleukins. Receptors for this cytokine are present on podocytes and are upregulated in human recurrent FSGS.[21] The origin of the factor may be $CD34^+$ stem cells.[22] Induction of T regulatory cells attenuates the proteinuria in experimental FSGS, suggesting the capacity to block or to suppress the pathogenic cells.[23]

In contrast to MCD, the proteinuria in FSGS is usually nonselective, including albumin and higher-molecular-weight macromolecules. In human FSGS and toxin-induced animal models of FSGS, such as puromycin or doxorubicin (Adriamycin) nephrosis, nonselective proteinuria develops in conjunction with detachment of podocyte foot processes from the GBM, a finding not seen in MCD.[5] The susceptibility gene to doxorubicin toxicity in Balb/c mice has been identified as *PRKDC,* required for double-stranded DNA break repair.[24] Animals deficient in this DNA repair machinery develop mitochondrial DNA depletion following doxorubicin exposure, leading to podocyte cell death and FSGS. This mechanism illustrates how long-lived cells such as podocytes, which lack the ability to repair themselves by cell division, are especially vulnerable to genotoxic stress. In humans, repeated and diverse stresses to the podocyte could explain the development of FSGS pattern of injury in age-related nephrosclerosis and glomerular senescence.

Glomerular hypertrophy (or glomerulomegaly) may identify children with MCD at risk for development of FSGS. In early idiopathic FSGS and in many secondary forms of FSGS, such as obesity related, there is initially glomerular hypertrophy and a high glomerular filtration rate (GFR), supporting roles for hyperfiltration and increased intracapillary glomerular pressures (glomerular hypertension).[25] Similarly, in secondary forms of FSGS with reduced nephron numbers, maladaptive hemodynamic alterations may be associated with glomerular hyperfiltration and increased intraglomerular capillary pressures. Other factors, such as intraglomerular coagulation and abnormalities of lipid metabolism, may contribute to glomerulosclerosis in these patients (see Chapter 79).

Genetic Variants of Focal Segmental Glomerulosclerosis

Genetic and familial forms of FSGS are covered in detail in Chapter 19. Many cases of apparently primary FSGS may harbor unidentified mutations or polymorphisms in podocyte genes that go unrecognized because of lack of genetic testing and the absence of a heralding presentation with young-onset corticosteroid-resistant disease or familial inheritance. In primary FSGS, a genetic predisposition may underlie the susceptibility to a "second hit," whereby viral factors or other immune stimuli lead to the initiation of disease. Mutations in podocyte genes may also predispose to FSGS induced by such secondary causes as obesity, systemic hypertension, and infectious agents, allowing multifactorial podocyte stress. For example, mutations in myosin heavy chain 9 *(MYH9)* were initially identified as a major risk factor for FSGS in patients of African ancestry.[26] Subsequent genetic mining of populations at risk for FSGS identified *APOL1* gene, rather than *MYH9*, as the major risk gene for FSGS and chronic hypertensive arterionephrosclerosis among patients of African descent.[27] *APOL1* encodes for apolipoprotein L-1. The gene is located along the same stretch of chromosome 22 and is in linkage disequilibrium with *MYH9.* G1 and G2 mutations in *APOL1* are protective against infection by *Trypanosoma brucei*, the parasite that

causes African sleeping sickness. Similar to the gene for sickle cell disease, which confers selective advantage against malaria, this genetic mutation became prevalent in a population because it was protective against an infectious pathogen. Although *APOL1* is present in preglomerular arterioles and podocytes,[28] it remains unclear how sequence variations in *APOL1* mechanistically cause glomerulosclerosis.

Viral Induction of Focal Segmental Glomerulosclerosis

Although a number of studies have noted a relationship between prior viral infection with parvovirus or other viruses and FSGS, in particular collapsing FSGS, the data have been far from consistent.[29] By contrast, the role of human immunodeficiency virus (HIV) infection in the pathogenesis is well established (see Chapter 58).

Drug-Induced Focal Segmental Glomerulosclerosis

A number of drugs and medications have been associated with the FSGS phenotype, including heroin, lithium, pamidronate, sirolimus, and interferons alpha, beta, and gamma[30] (see Box 18-1). Heroin has been associated with the nephrotic syndrome and FSGS (heroin nephropathy), although its incidence is decreasing in the modern era.[31] Pamidronate, a bisphosphonate used to prevent bone resorption in myeloma and metastatic tumors, has been associated with both collapsing FSGS and MCD.[32] Stabilization of renal function and resolution of nephrotic syndrome may follow withdrawal of the offending medication (e.g., interferon, heroin, pamidronate). Long-term anabolic steroid abuse among bodybuilders has been associated with the development of FSGS. Many of these individuals also consume high-protein diets and potentially injurious supplements, including growth hormone. Mechanisms of glomerular injury include potential direct toxic effects of anabolic steroids on glomerular cells and adaptive responses to elevated lean body mass.[33]

Structural Maladaptation Leading to Focal Segmental Glomerulosclerosis

Many secondary forms of FSGS are mediated by adaptive structural-functional responses.[1,5,7] These adaptive forms include patients with congenital reduction in the number of functioning nephrons and acquired reduction of nephron numbers, whereas other secondary forms are associated with hemodynamic stress placed on an initially normal nephron population (see Box 18-1). *Obesity-related glomerulopathy* (ORG) is increasingly common worldwide and may be associated with metabolic syndrome, including hypertension, diabetes, and hyperlipidemia. ORG usually lacks full nephrotic syndrome and has a low risk of progression to ESRD.[25] Secondary FSGS resembling ORG has been reported in nonobese, highly muscular patients with elevated body mass index due to bodybuilding.[34] Low birth weight associated with prematurity and reduced nephron endowment may also lead to glomerular hypertrophy, with secondary FSGS developing in adolescence or adulthood.[35] Biopsy specimens with secondary adaptive FSGS typically show glomerulomegaly and perihilar lesions of segmental sclerosis and hyalinosis. These conditions resemble experimental models of renal ablation in which the surgical reduction in renal mass causes functional hypertrophy of remnant nephrons with increased glomerular plasma flows and pressures. Whereas these changes are initially "adaptive," the resultant hyperfiltration and increased glomerular pressure become "maladaptive" and serve as mechanisms for progressive glomerular damage.[7,8]

Pathogenesis of Progressive Renal Failure in Focal Segmental Glomerulosclerosis

Although much attention has been focused on the pathogenetic basis for proteinuria in FSGS, the segmental and eventual global glomerulosclerosis in association with interstitial fibrosis and tubular atrophy clearly underlie the progression to renal failure. The etiology of glomerulosclerosis and its progressive nature are discussed in Chapter 79. Podocytes in some forms of FSGS, such as the collapsing variant, display a dysregulated phenotype with dedifferentiation, proliferation, and apoptosis.[36] Such biopsy samples have altered podocyte expression of cell cycle–related proteins.[37] In renal biopsy specimens of patients with FSGS, the expression levels of transforming growth factor (TGF) β1, thrombospondin-1, and TGF-β2 receptor proteins and messenger RNAs are all increased, as are podocyte markers of the phosphorylated Smad2/Smad3 signaling pathway.[38] Thus, pathways that promote podocyte depletion and overproduction of extracellular matrix converge to produce a sclerosing phenotype.

EPIDEMIOLOGY

Studies of patients who have had a kidney biopsy show an increasing prevalence of FSGS in both adults and children in a number of countries on different continents.[39] In some countries, such as Brazil, FSGS is currently the most common primary renal disease.[40] An analysis of the prevalence of ESRD in the United States caused by FSGS during a 21-year period shows an increase from 0.2% in 1980 to 2.3% in 2000, and FSGS is the most common primary glomerular disease leading to ESRD.[5,6] Although some of this change in prevalence may relate to changes in biopsy practice or disease classification, a real increase is likely in the frequency of FSGS.

Primary FSGS is slightly more common in males than in females, and the incidence of ESRD due to FSGS in males of all races is 1.5 to 2 times higher than in females. The incidence in both children and adults is higher in blacks than in Caucasians.[1] In the United States, FSGS is the most common cause of idiopathic nephrotic syndrome in adult African Americans.[6] African Americans had a fourfold greater risk of ESRD from FSGS than Caucasians did. Even in an almost entirely Caucasian U.S. population, a clear major increase in the incidence of FSGS has been documented over a 30-year period,[41] whereas this has not been the case in some Caucasian populations in Europe.[42]

CLINICAL MANIFESTATIONS

Patients with primary FSGS present with asymptomatic proteinuria or full nephrotic syndrome.[1-3] In children, 10% to 30% of patients with asymptomatic proteinuria are detected on routine checkups and sports physical examinations; in adults, asymptomatic detection occurs at military induction examinations, obstetric checkups, and insurance or employment physical examinations. The incidence of nephrotic-range proteinuria at onset in children is 70% to 90%, whereas only 50% to 70% of adults with FSGS present with nephrotic syndrome. Secondary forms of FSGS associated with hyperfiltration, such as remnant kidney and ORG, typically have lower levels of proteinuria, and many such patients have subnephrotic proteinuria and a normal serum albumin concentration.[25,34]

Hypertension is found in 30% to 50% of children and adults with FSGS at diagnosis. Microhematuria is found in 25% to 75% of these patients, and a decreased GFR is noted at presentation in 20% to

30%.[1-3] Daily urinary protein excretion ranges from less than 1 to more than 30 g/day. Proteinuria is typically nonselective. Complement levels and other serologic test results are normal. Occasional patients will have glycosuria, aminoaciduria, phosphaturia, or a concentrating defect indicating functional tubular damage as well as glomerular injury.

Different histologic patterns of FSGS may display different clinical features. When patients with the tip variant of FSGS were compared to those with MCD or FSGS not otherwise specified (NOS), their clinical features were more similar to those of MCD.[43] Those with tip variant typically manifested abrupt clinical onset of full nephrotic syndrome (almost 90%), shorter time course from onset to renal biopsy, more severe proteinuria, and less chronic tubulointerstitial disease than in FSGS NOS. The cellular variant also typically presents with greater proteinuria and higher incidence of nephrotic syndrome than FSGS NOS. Compared with FSGS NOS, the collapsing variant usually presents with greater proteinuria, more full-blown nephrotic syndrome, and lower GFR.[44,45]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Before biopsy, patients with FSGS may be confused with any patient who has glomerular disease or nephrotic syndrome with negative serologic test results. Tests for permeability factors are not available in routine clinical practice. In children with FSGS, most of whom present with nephrotic syndrome, the major differential will be between MCD and other variants of corticosteroid-resistant nephrotic syndrome. In adults with subnephrotic proteinuria, the differential includes almost all glomerular diseases without positive serologic results. In adults with nephrotic syndrome, membranous nephropathy (MN) and MCD may present in an identical manner, and only a renal biopsy will clarify the diagnosis. Focal sclerosing lesions caused by other glomerulopathies (e.g., segmental scarring from chronic glomerulonephritis) must be excluded pathologically. Moreover, because the defining glomerular lesion of FSGS is focal and may be confined to deeper juxtamedullary glomeruli early in the disease, it may not be sampled on renal biopsy. A large glomerular sample of more than 20 glomeruli for light microscopy increases the likelihood of identifying the diagnostic segmental lesions.

Even after the diagnosis of FSGS is established, the primary (idiopathic) form must be distinguished from secondary forms by careful clinicopathologic correlation (see Box 18-1). In general, many forms of adaptive FSGS have lower levels of proteinuria than primary FSGS, a lower incidence of hypoalbuminemia, and on biopsy, lesser degrees of foot process effacement. In patients younger than 25 years and in those with a family history of FSGS, genetic screening for mutations in podocin, nephrin, or other podocyte genes may be useful (see Chapter 19).

PATHOLOGY

The pathologic manifestations of FSGS are heterogeneous, both qualitatively and with respect to the location of lesions within the glomerular tuft. A classification of FSGS by histologic variants (Box 18-2)[46] can be applied to both primary and secondary forms of FSGS (Box 18-1). Subtypes include *classic,* or NOS; *perihilar* variant, in which more than 50% of glomeruli with segmental lesions display hyalinosis and sclerosis involving the vascular pole region; *cellular* variant, manifesting endocapillary hypercellularity; *collapsing* variant, in which at least one glomerulus has global collapse and overlying visceral cell hypertrophy and hyperplasia; and *tip* variant, with segmental lesions involving the tubular pole. This working classification has been applied successfully to retrospective and prospective series of renal biopsies. Other, more controversial histologic variants of FSGS include FSGS with diffuse mesangial hypercellularity and C1q nephropathy (see Chapter 28). Some believe that these are distinct disease entities with unique clinicopathologic features; others believe these are merely subgroups of FSGS.[47,48]

Morphologic Variants of Focal Segmental Glomerulosclerosis

1. FSGS, not otherwise specified (NOS; also known as classic FSGS)
2. FSGS, perihilar variant
3. FSGS, cellular variant
4. FSGS, collapsing variant (also known as collapsing glomerulopathy)
5. FSGS, tip variant

Box 18-2 Morphologic variants of focal segmental glomerulosclerosis (FSGS).

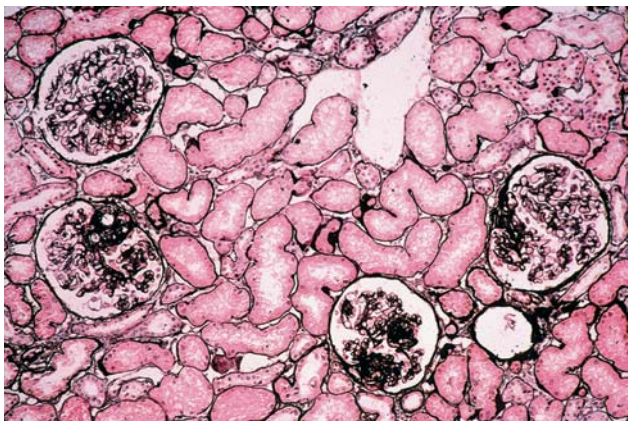

Figure 18-1 Focal segmental glomerulosclerosis, not otherwise specified (FSGS NOS). A low-power view shows four glomeruli with discrete lesions of segmental sclerosis involving a portion of the tuft. The adjacent nonsclerotic capillaries are unremarkable. In this example, there is no evidence of tubulointerstitial injury. (Jones methenamine silver stain; magnification ×100.)

Classic Focal Segmental Glomerulosclerosis (FSGS Not Otherwise Specified)

Classic FSGS, also called FSGS NOS, is the common generic form of the disease. FSGS NOS requires exclusion of the other, more specific subtypes described later. It is defined by accumulations of extracellular matrix (ECM) that occlude glomerular capillaries, forming discrete segmental solidifications (Fig. 18-1).[46] There may be hyalinosis (plasmatic insudation of amorphous glassy material beneath the GBM), endocapillary foam cells, and wrinkling of the GBM (Fig. 18-2). Adhesions or synechiae to Bowman capsule are common, and overlying visceral epithelial cells often appear swollen and form a cellular "cap" over the sclerosing segment. Glomerular lobules unaffected by segmental sclerosis appear normal on light microscopy, except for mild podocyte swelling. Tubular atrophy and interstitial fibrosis are commensurate with the degree of glomerulosclerosis. Immunofluorescence (IF) typically reveals focal and segmental granular deposition of IgM, C3, and more variably C1 in the distribution

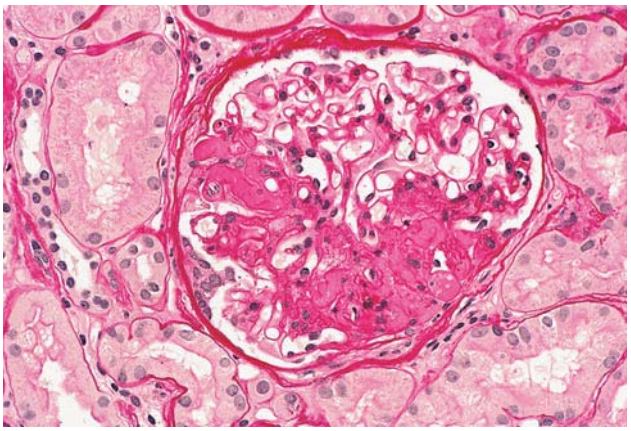

Figure 18-2 Focal segmental glomerulosclerosis, not otherwise specified. The lesions of segmental sclerosis display increased extracellular matrix and hyalinosis. There is adhesion to Bowman capsule without significant podocyte hypertrophy. The nonsclerotic capillaries have glomerular basement membranes of normal thickness and mild podocyte swelling. (Periodic acid–Schiff [PAS] reaction; ×400.)

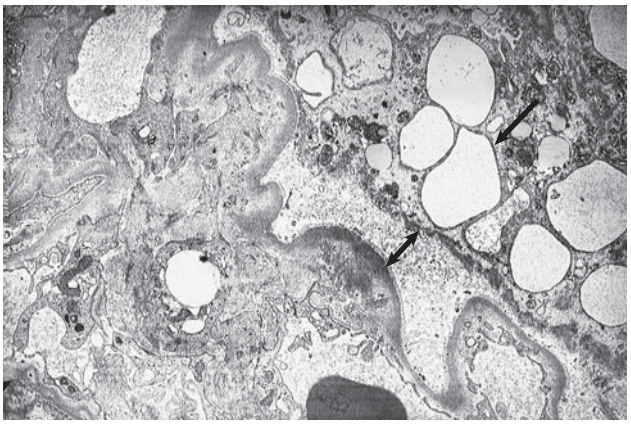

Figure 18-4 Focal segmental glomerulosclerosis, not otherwise specified. Electron micrograph illustrates the lesion of segmental sclerosis with obliteration of the glomerular capillaries by increased extracellular matrix with wrinkled and retracted glomerular basement membranes. The overlying podocytes are detached, with complete effacement of foot processes *(double-headed arrow)* and numerous electron-lucent intracellular transport vesicles *(arrow)*. (×2500.)

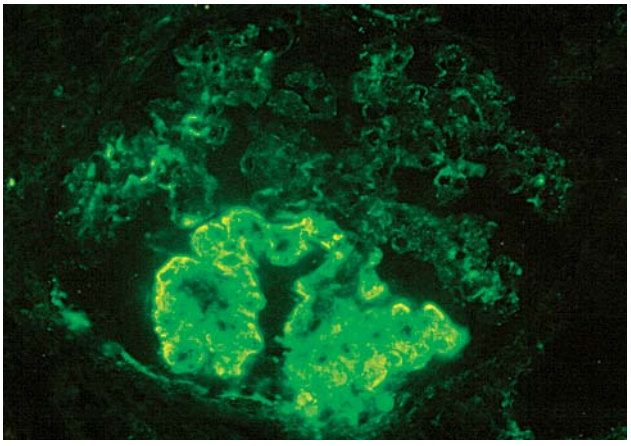

Figure 18-3 Focal segmental glomerulosclerosis, not otherwise specified. The lesions of segmental sclerosis contain deposits of IgM corresponding to areas of increased matrix and hyalinosis. Weaker staining for IgM is also seen in the adjacent mesangium. (Immunofluorescence micrograph; ×400.)

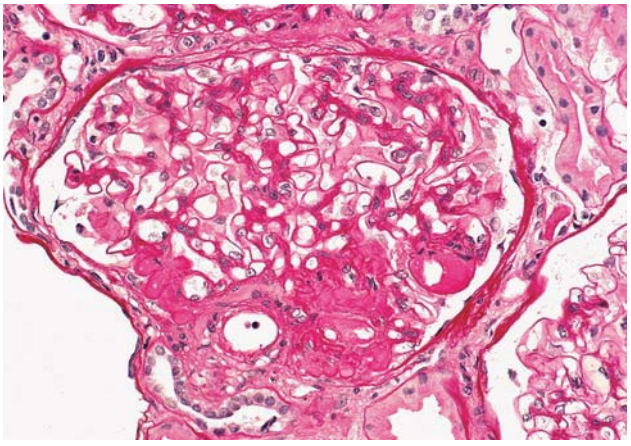

Figure 18-5 Focal segmental glomerulosclerosis (FSGS), perihilar variant. A discrete lesion of segmental sclerosis and hyalinosis is located at the glomerular vascular pole (i.e., perihilar). The glomerulus is hypertrophied. The patient had secondary FSGS in the setting of solitary kidney as a result of contralateral renal agenesis. (PAS; ×250.)

of the segmental glomerular sclerosis (Fig. 18-3). Nonsclerotic glomeruli may have weak mesangial staining for IgM and C3. On electron microscopy (EM), segmental sclerotic lesions exhibit increased ECM, wrinkling and retraction of the GBM, accumulation of inframembranous hyaline, and resulting narrowing or occlusion of the glomerular capillary lumina (Fig. 18-4). No immune-type electron-dense deposits are found. Overlying the segmental sclerosis, there is often podocyte detachment with parietal cell coverage. The adjacent nonsclerotic glomerular capillaries show foot process effacement with variable microvillous transformation (slender projections resembling villi along the surface of podocytes). This is the most frequent variant and may occur in primary or secondary forms of FSGS, including genetic forms.

Perihilar Variant of Focal Segmental Glomerulosclerosis

The perihilar variant is defined as perihilar hyalinosis and sclerosis involving more than 50% of glomeruli with segmental lesions.[34] This category requires exclusion of the cellular, tip, and collapsing variants. Podocyte hyperplasia is uncommon. Although the perihilar variant may occur in primary FSGS, it is particularly frequent in secondary forms of FSGS mediated by adaptive structural-functional responses, where it is typically accompanied by glomerular hypertrophy (glomerulomegaly) and has relatively mild foot process effacement (Fig. 18-5). In this setting, reflex dilation of the afferent arteriole and the greater filtration pressures at the proximal end of the glomerular capillary bed may favor the development of lesions at the vascular pole.[5,7]

Cellular Variant of Focal Segmental Glomerulosclerosis

The cellular variant is characterized by focal and segmental endocapillary hypercellularity that may mimic a form of focal proliferative glomerulonephritis.[49] Glomerular capillaries are segmentally occluded by endocapillary hypercellularity, including foam cells, infiltrating leukocytes, karyorrhectic debris, and hyaline (Fig. 18-6).

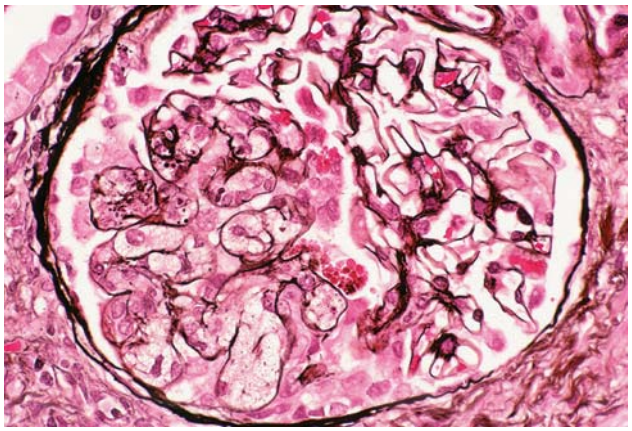

Figure 18-6 Focal segmental glomerulosclerosis, cellular variant. The glomerular capillary lumina are segmentally occluded by endocapillary cells, including foam cells, infiltrating mononuclear leukocytes, and pyknotic debris. The findings mimic a proliferative glomerulonephritis because of the hypercellularity and absence of extracellular matrix material. There are hypertrophy and hyperplasia of the overlying visceral epithelial cells, some of which contain protein resorption droplets. (Jones methenamine silver; ×400.)

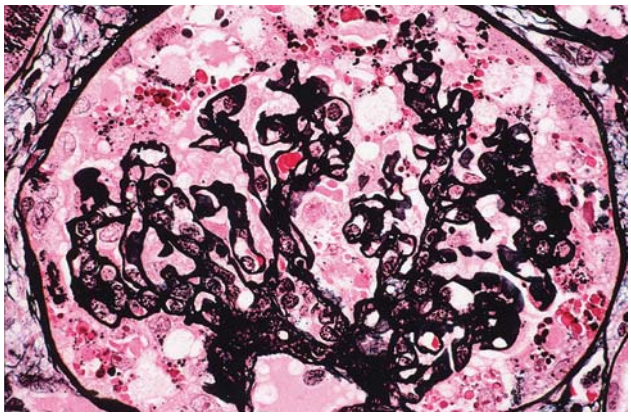

Figure 18-8 Focal segmental glomerulosclerosis, collapsing variant. In this example, exuberant proliferation of glomerular epithelial cells forms a pseudocrescent that obliterates the urinary space. The pseudocrescent lacks the spindle cell morphology, ruptures of Bowman capsule, or pericellular matrix typically seen in true inflammatory crescents of parietal epithelial origin. (Jones methenamine silver; ×400.)

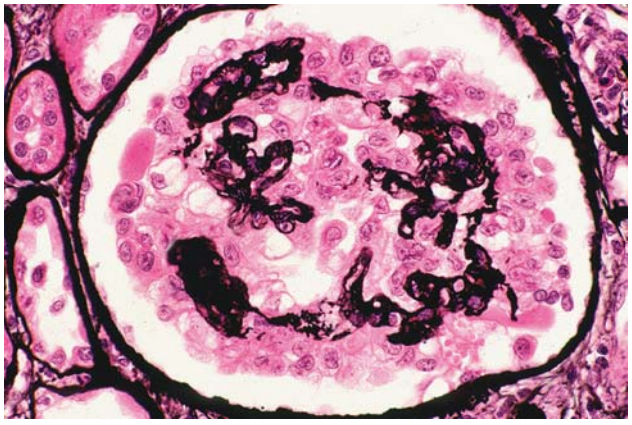

Figure 18-7 Focal segmental glomerulosclerosis, collapsing variant. There is global implosive collapse of the glomerular tuft with obliteration of capillary lumina. The overlying visceral epithelial cells appear hypertrophied and hyperplastic with enlarged nuclei and nucleoli. There are no adhesions to Bowman capsule. (Jones methenamine silver; ×400.)

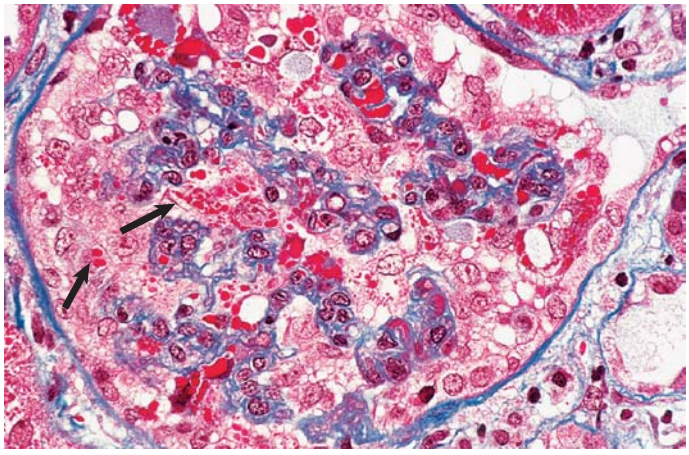

Figure 18-9 Focal segmental glomerulosclerosis, collapsing variant. The crescent-like proliferation of glomerular epithelial cells contains numerous intracytoplasmic vacuoles and trichrome-red protein resorption droplets (*arrows*). (Masson trichrome; ×400.)

There is often hyperplasia of the visceral epithelial cells, which may appear swollen and crowded, sometimes forming pseudocrescents. Foot process effacement is typically severe. This variant requires that tip lesions and collapsing lesions be excluded. Cellular FSGS is thought to represent an early stage in the development of segmental lesions and is usually primary.

Collapsing Variant of Focal Segmental Glomerulosclerosis

The collapsing variant is defined by at least one glomerulus with segmental or global collapse and overlying hypertrophy and hyperplasia of visceral epithelial cells (Fig. 18-7). In these areas, there is occlusion of glomerular capillary lumina by implosive wrinkling and GBM collapse.[44,45] The collapsing lesion is more often global than segmental. Overlying visceral epithelial cells display striking hypertrophy and hyperplasia and express proliferation markers. Glomerular epithelial cells often contain prominent intracytoplasmic protein resorption droplets and may fill Bowman space, forming pseudocrescents (Figs. 18-8 and 18-9). Although visceral cell hyperplasia is found in both the collapsing and the cellular variant of FSGS, collapsing glomerulopathy is distinguished by the absence of endocapillary hypercellularity. Studies suggest that dysregulated podocytes,[36] activated parietal cells (expressing claudin and CD44),[50,51] and progenitor cells (expressing stem cell markers CD133 and CD24)[52,53] that line Bowman capsule contribute to the glomerular epithelial cell hyperplasia. *In vivo* microscopy also has illustrated the ability of parietal cells to rapidly plug sites of podocyte denudation and depletion in FSGS.[54] A major unanswered question is whether cells of Bowman capsular origin have the capacity to differentiate into and replenish mature podocytes.

In collapsing FSGS, there is prominent tubulointerstitial disease, including tubular atrophy, interstitial fibrosis, interstitial edema, and inflammation. A distinctive feature is the presence of dilated tubules forming microcysts that contain loose proteinaceous casts. On EM, there is typically severe foot process effacement affecting both collapsed and noncollapsed glomeruli (Fig. 18-10). Collapsing glomerulopathy may occur as a primary form of FSGS.[44,45] This pattern is also frequently observed in secondary FSGS caused by HIV infection, parvovirus B19 infection, interferon therapy, or pamidronate

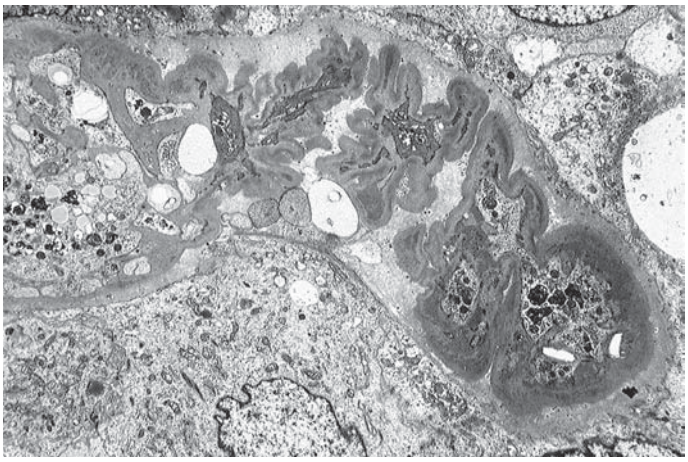

Figure 18-10 Focal segmental glomerulosclerosis, collapsing variant. On electron microscopy, there is tight collapse of the glomerular capillaries with corrugated glomerular basement membrane. The overlying podocytes appear detached and hypertrophied, with complete loss of foot processes. (×2500.)

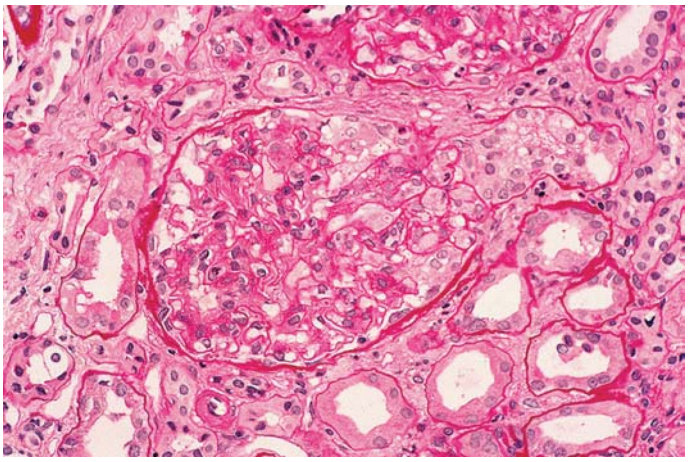

Figure 18-12 Focal segmental glomerulosclerosis, tip lesion variant. A cellular tip lesion displays engorgement of glomerular capillaries by foam cells and adhesion of the involved segment to the origin of the proximal tubule (tubular pole). (PAS; ×250.)

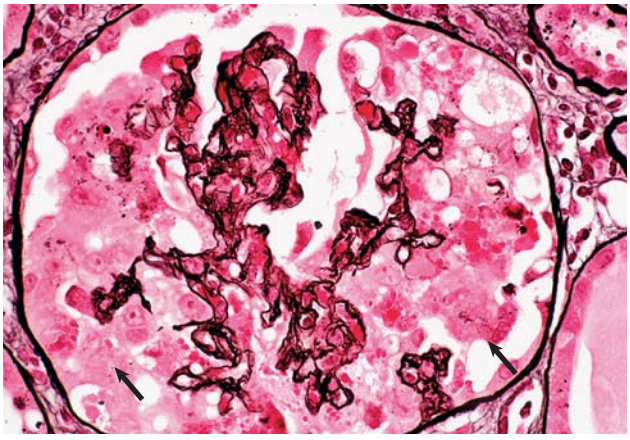

Figure 18-11 Focal segmental glomerulosclerosis, collapsing variant, from pamidronate toxicity. The glomerular tuft is retracted, without appreciable increase in matrix material. The overlying visceral epithelial cells are enlarged and hyperplastic *(arrows),* with numerous intracytoplasmic vacuoles and protein resorption droplets. (Jones methenamine silver; ×400.)

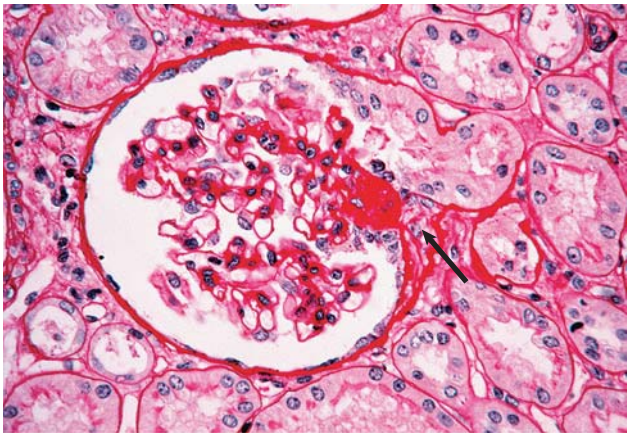

Figure 18-13 Focal segmental glomerulosclerosis, tip lesion variant. A sclerosing tip lesion forms an adhesion to the tubular pole *(arrow)*. (PAS; ×250.)

toxicity[5] (Fig. 18-11). The presence of endothelial tubuloreticular inclusions is helpful to identify collapsing glomerulopathy secondary to HIV-associated nephropathy or interferon therapy.

Tip Variant of Focal Segmental Glomerulosclerosis

The tip variant is defined by the presence of at least one segmental lesion involving the tip domain, or the outer 25% of the tuft next to the origin of the proximal tubule.[43] There is either adhesion between the tuft and Bowman capsule or confluence of swollen podocytes with parietal or tubular epithelial cells at the tubular lumen or neck. The segmental lesions may be cellular or sclerosing (Figs. 18-12 and 18-13). These lesions may evolve more centrally. The presence of perihilar sclerosis or collapsing sclerosis rules out the tip variant. In one study of FSGS tip lesions, biopsy specimens had glomerular tip lesions alone in 26% and glomerular tip lesions plus other peripheral FSGS lesions in the other 74%.[43] The degree of foot process effacement is usually severe. Most cases are primary and resemble MCD in the abrupt onset of nephrotic syndrome, suggesting they may share a similar permeability factor. Higher shear stress and tuft prolapse at the tubular pole are likely to play a role in the morphogenesis of this lesion.[7]

Other Variants of Focal Segmental Glomerulosclerosis

Two histologic variants often included within the FSGS spectrum are FSGS with diffuse mesangial hypercellularity and C1q nephropathy (see also Chapter 28).[5,47,48] FSGS with *diffuse mesangial hypercellularity* has lesions of FSGS on a background of generalized hypercellularity. By IF, there is diffuse mesangial positivity for IgM, with more variable mesangial staining for C3; EM reveals extensive foot process effacement without glomerular electron-dense deposits. This variant occurs almost exclusively in young children.

An idiopathic glomerulopathy, *C1q nephropathy* is defined by dominant or codominant IF staining for C1q, mesangial electron-dense deposits, and light microscopic findings resembling FSGS or MCD with variable mesangial hypercellularity. In one study, 17 patients had a light microscopic appearance of FSGS (including six collapsing and two cellular) and three of MCD.[47] In addition to C1q staining, biopsy specimens may show deposition of other immunoglobulins (particularly IgG) and complement components (C3),

making exclusion of other clinical disease entities important, including lupus nephritis and membranoproliferative glomerulonephritis (MPGN). In C1q nephropathy, electron-dense deposits are typically located predominantly in the paramesangial region subjacent to the GBM reflection. There is variable foot process effacement. The largest series of C1q nephropathy supports that many cases represent a subgroup of primary FSGS or MCD, whereas others are an idiopathic immune complex–mediated glomerulonephritis.[48]

Distinguishing Pathologic Features of Secondary FSGS

Although the pathology of some secondary forms of FSGS resembles closely that of primary FSGS, there are several noteworthy differences. Whereas the light microscopic findings in HIV-associated nephropathy are similar to those of primary collapsing FSGS (Fig. 18-14), tubular microcysts are particularly common (Fig. 18-15).[55] On EM, a major difference is the abundance of tubuloreticular inclusions in the glomerular endothelial cells of HIV-associated nephropathy. These "interferon footprints" consist of 24-nm interanastomosing tubular structures located within dilated cisternae of endoplasmic reticulum (Fig. 18-16). Tubuloreticular inclusions have become less frequent in patients treated with highly active antiretroviral therapy.[55]

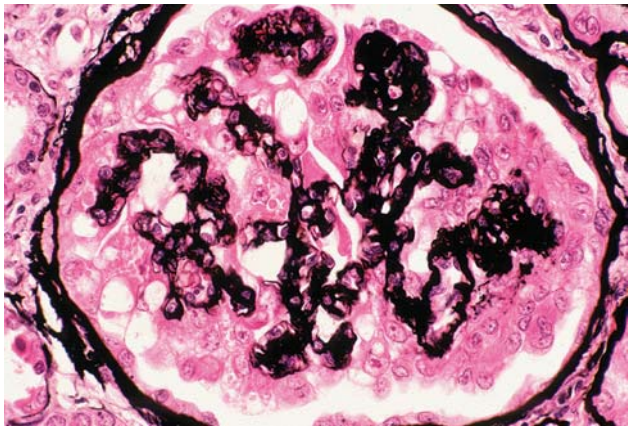

Figure 18-14 Human immunodeficiency virus (HIV)–associated nephropathy. A globally collapsed glomerulus shows marked visceral cell hypertrophy and hyperplasia. (Jones methenamine silver; ×400.)

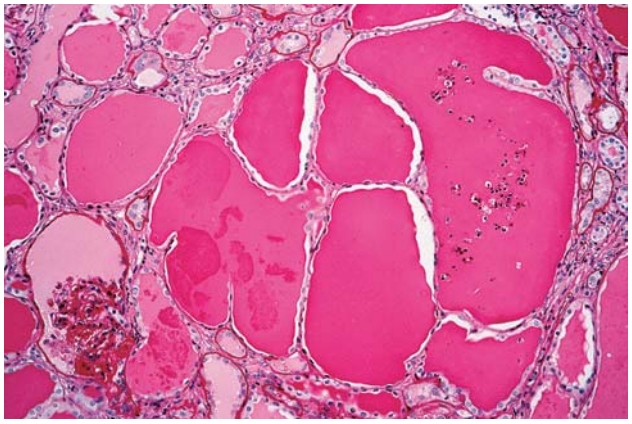

Figure 18-15 HIV-associated nephropathy. At low power, the renal parenchyma contains abundant tubular microcysts with proteinaceous casts. The glomerulus is collapsed with dilated urinary space. (PAS; ×80.)

In secondary adaptive forms of FSGS, renal biopsy typically shows glomerulomegaly and predominantly perihilar lesions of segmental sclerosis and hyalinosis. In secondary FSGS resulting from loss of renal mass, such as from reflux nephropathy or hypertensive arterionephrosclerosis, FSGS is usually seen on a background of extensive global glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriosclerosis. In secondary FSGS related to sickle cell disease, glomerular hypertrophy and sclerosis are associated with capillary congestion by sickled erythrocytes and double contours of the GBM resembling those seen in chronic thrombotic microangiopathy. Importantly, in adaptive forms of FSGS, the degree of foot process effacement tends to be relatively mild, affecting less than 50% of the total glomerular capillary surface area, with correspondingly shorter foot process width (Fig. 18-17). In one study, a cutoff of more than 1500 nm for mean foot process width was able to distinguish primary from adaptive FSGS with high sensitivity and specificity.[56]

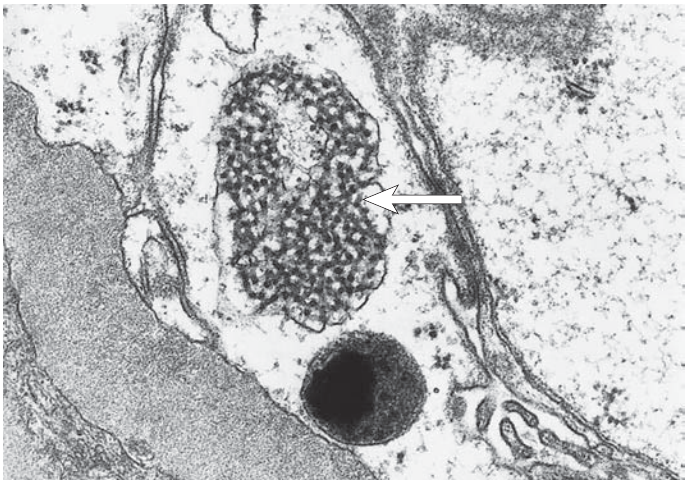

Figure 18-16 HIV-associated nephropathy. The glomerular endothelial cell pictured here contains a large intracytoplasmic tubuloreticular inclusion ("interferon footprint"; *arrow*) composed of interanastomosing tubular structures within a dilated cisterna of endoplasmic reticulum. (Electron micrograph; ×15,000.)

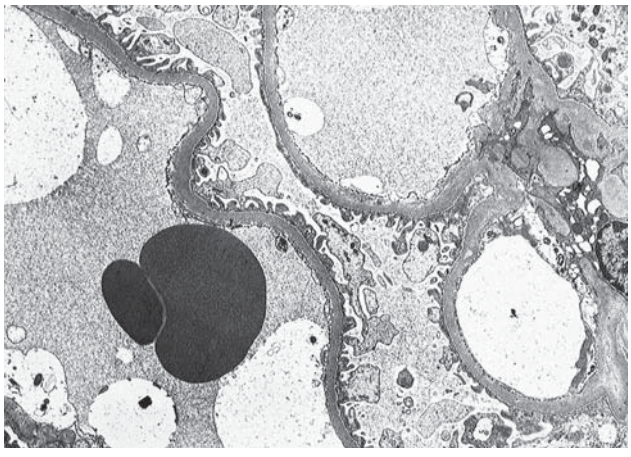

Figure 18-17 Secondary focal segmental glomerulosclerosis (FSGS) from obesity. This patient with morbid obesity had glomerular hypertrophy and predominantly perihilar lesions of segmental sclerosis and hyalinosis on light microscopy. The foot processes show mild effacement involving approximately 20% of the glomerular capillary surface area despite the presence of nephrotic-range proteinuria. This mild degree of foot process effacement is less than that usually seen in primary FSGS. (Electron micrograph; ×2500.)

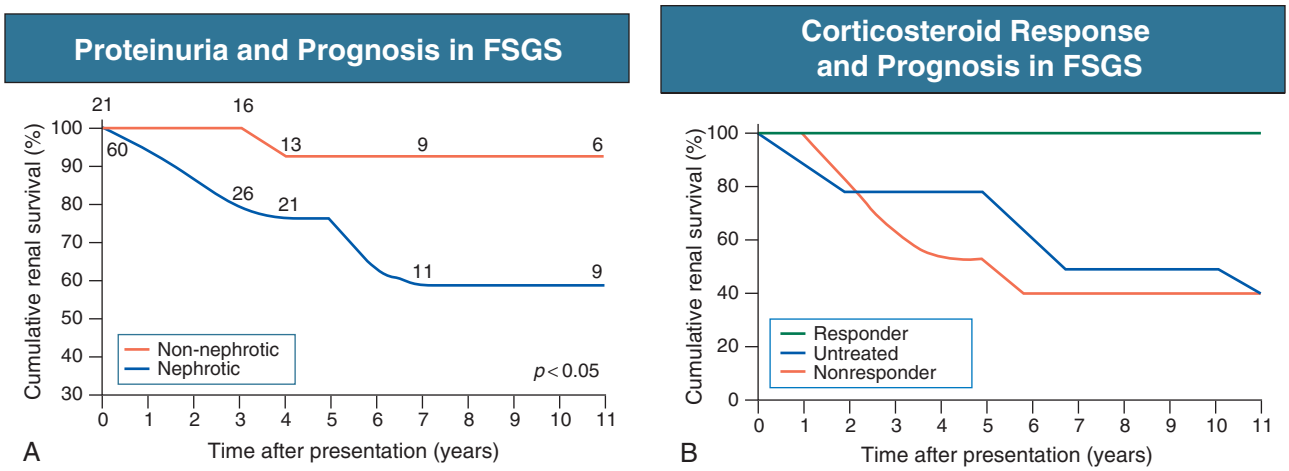

Figure 18-18 Prognosis in primary focal segmental glomerulosclerosis (FSGS). A, The risk for development of renal failure is related to the extent of proteinuria. Those with nephrotic-range proteinuria are much more likely to develop renal failure than those with low-grade proteinuria. The figures indicate the number of at-risk patients at different time points. **B,** Corticosteroid-responsive patients are significantly less likely to develop renal failure than nonresponders and untreated patients. *(Modified from reference 87.)*

Risk Factors for Progressive Renal Disease in Focal Segmental Glomerulosclerosis

Clinical Features at Biopsy
Severity of nephrotic-range proteinuria
Elevated serum creatinine
Black race

Histopathologic Features at Biopsy
Collapsing variant
Tubulointerstitial fibrosis

Clinical Features During Disease Course
Failure to achieve partial or complete remission

Box 18-3 Risk factors for progressive renal disease in FSGS.

NATURAL HISTORY AND PROGNOSIS

The natural history of FSGS is varied.[1-3] Without therapy or response to therapy, the majority of patients with primary FSGS will experience a progressive increase in proteinuria and progression to renal failure. Only 5% to 25% of patients undergo a spontaneous remission of proteinuria.[57] Both unresponsive children and adults have a similar course; most develop ESRD 5 to 20 years from presentation, with approximately 50% of such patients reaching ESRD by 10 years (Fig. 18-18).

Certain epidemiologic, clinical, and histologic findings at diagnosis help predict the long-term course of FSGS patients[1-5] (Box 18-3). African Americans, even when controlled for degree of proteinuria, hypertension, and other features, experience a more rapid progression to renal failure. At biopsy, reduced GFR, greater degrees of proteinuria, and greater degrees of interstitial fibrosis predict a more progressive course.[1] The degree of glomerulosclerosis has been much less consistent as a prognostic finding.[1-5] Patients who experience a remission of proteinuria and the nephrotic syndrome have much better renal survival than those who do not.[1,3,58,59] Even patients with a partial remission of nephrotic syndrome have a lower rate of long-term renal failure.[60]

There is a consensus that outcomes are best for tip variant and worst for collapsing variant of primary FSGS, with intermediate outcome in FSGS NOS.[49,61,62] These differences held true even in a cohort of children and young adults with initially corticosteroid-resistant FSGS.[63] In a comparative series, the percentage of complete and partial remission was greatest for tip lesion (76%), lowest for collapsing variant (13%), and intermediate for cellular (44%), compared with 39% for FSGS NOS. There was a strong inverse correlation between remission rates and progression to ESRD among these subgroups. Accordingly, the percentage ESRD was greatest for collapsing variant (65%), lowest for tip lesion (6%), and intermediate for cellular variant (28%), compared with 35% for FSGS NOS.[49]

TREATMENT

There is still considerable debate about the appropriate treatment of patients with primary FSGS[1-3,5,59] (Fig. 18-19). In part, this relates to confusion between primary and secondary forms of the disease, including unrecognized genetic variants. For example, even after biopsy, it is not always clear whether an obese person with glomerulomegaly, FSGS, and nephrotic-range proteinuria has secondary or primary disease.[18] Moreover, the course of the disease is variable, and only recently have clear prognostic features been defined. Finally, although FSGS is common in adults, there are many therapeutic options with few randomized controlled trials (RCTs) on which to base judgment.

In early studies of FSGS, only 10% to 30% of those treated with corticosteroids for relatively short periods or with other immunosuppressive agents experienced a remission of proteinuria, and the relapse rate was high.[1,59] Thus, many nephrologists considered FSGS to be a resistant disease and did not advocate immunosuppressive treatment. A classic study documented that in Toronto, almost all children with FSGS were treated with immunosuppressives and that 44% experienced a remission.[58] Although the response rate for treated adults was similar (39%), most of the adults never received immunosuppressive therapy.

Use of Corticosteroids

In trials using longer (>6 months) courses of corticosteroids in primary FSGS, the results have been much more rewarding. In adults, therapy is usually with prednisone or prednisolone, 1 mg/kg/day, or 1.5 to 2 mg/kg every other day, for an initial period of 4 to 8 weeks, with subsequent tapering of the dose.[1,3,59] Initial response

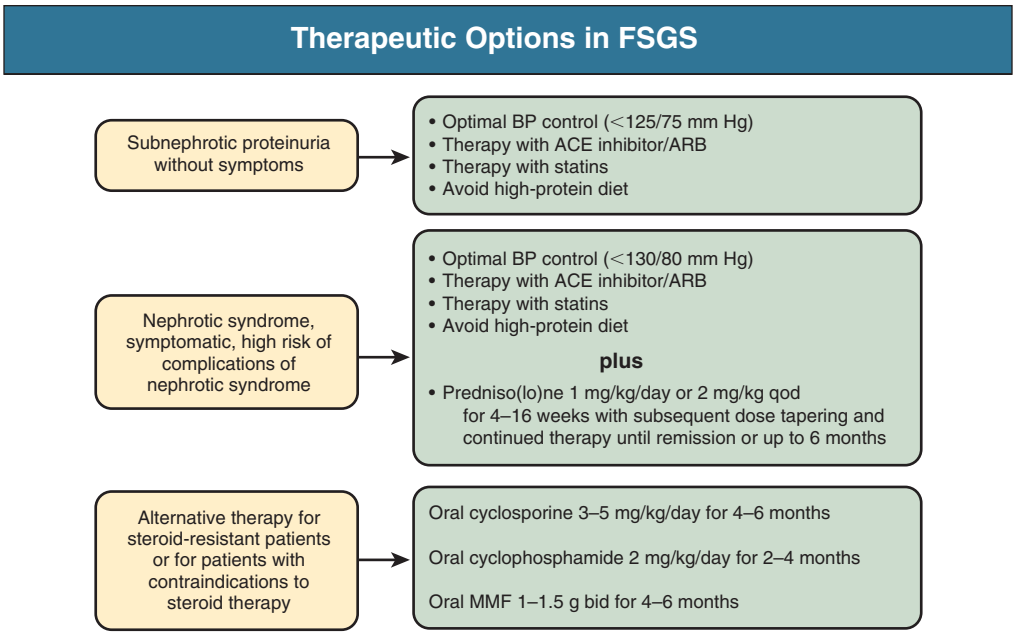

Figure 18-19 Therapeutic options in focal segmental glomerulosclerosis. Treatment of secondary FSGS should be directed at the underlying cause whenever possible. For HIV-associated nephropathy, treatment with highly active antiretroviral therapy (HAART); for pamidronate nephrotoxicity, discontinue the medication; and for obesity-related glomerulopathy, weight loss. *ACE,* Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *MMF,* mycophenolate mofetil.

rates range from 40% to 80%. Nephrotic children typically receive an empiric 4- to 6-week course of prednisone (60 mg/m^2 body surface area) before a renal biopsy is performed, in an attempt to effect remissions in those with MCD. In children with biopsy-documented FSGS, 20% to 25% will achieve a complete remission with a short course of corticosteroids, but as many as 50% will remit with more intensive therapy. In adults, although no large RCTs are available, more prolonged use of corticosteroids has led to much higher remission rates of nephrotic syndrome than in earlier studies.[1,3,59,64,65] The median duration of corticosteroid treatment for complete remission to be achieved is 3 to 4 months; most patients respond by 6 months. Most clinicians would treat all nephrotic primary FSGS patients and those at risk of progressive disease with a prolonged course (6 to 9 months) of daily or every-other-day corticosteroid therapy or other immunosuppressive medication in the hope of inducing a remission of nephrotic syndrome and preventing eventual ESRD.[65] Kidney Disease: Improving Global Outcomes (KDIGO) study guidelines recommend initial prednisone therapy in nephrotic patients with primary FSGS, with the high dose to be continued for a minimum of 4 weeks and a maximum of 16 weeks, with a slow taper over 6 months after achieving complete remission.[66]

Other Immunosuppressive Agents

For many years, either chlorambucil or cyclophosphamide combined with corticosteroids was the treatment of choice for corticosteroid-resistant FSGS.[1,67] One uncontrolled trial in children using combined intravenous pulse corticosteroids and long-term immunosuppression with corticosteroids and cytotoxics found a 60% complete remission rate and a 16% partial remission rate of the nephrotic syndrome and a low rate of progression to renal failure.[68] However, recent KDIGO guidelines specifically suggest that cyclophosphamide not be given to children with corticosteroid-resistant nephrotic syndrome, and to use alternative medicines such as calcineurin inhibitors (CNIs) or mycophenolate.[66] In adults with FSGS treated with oral cyclophosphamide or chlorambucil, pooled data show a high response rate for patients with corticosteroid dependence or intolerance, but a remission rate of less than 20% for corticosteroid-resistant patients.[59]

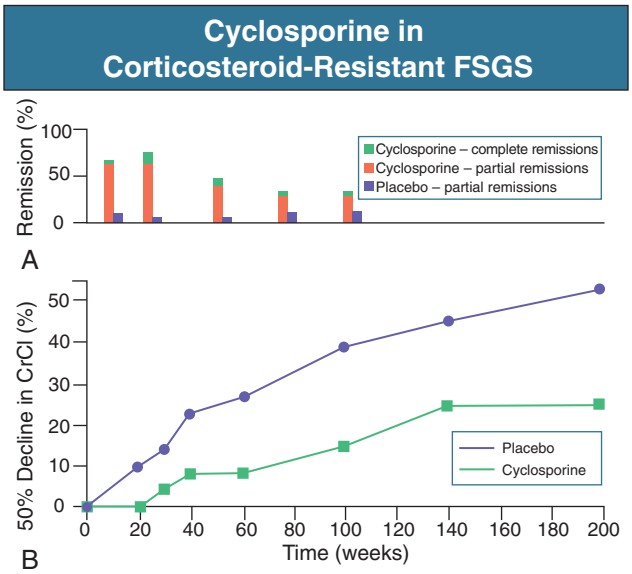

Figure 18-20 Cyclosporine in corticosteroid-resistant focal segmental glomerulosclerosis (FSGS). Randomized controlled trial of 6 months of treatment with prednisolone and either cyclosporine or placebo. **A,** Cyclosporine induces a partial or complete remission significantly more often than placebo. **B,** Cyclosporine treatment results in a lower rate of decline in renal function than with placebo, even after 4 years; *CrCl,* creatinine clearance. *(Modified from reference 70.)*

A number of studies have used low-dose cyclosporine, 3 to 6 mg/kg/day for 2 to 6 months, to treat corticosteroid-resistant FSGS[69,70] (Fig. 18-20). Complete plus partial remission rates of 60% to 70% have been achieved versus only 17% to 33% in the placebo groups. In North America, steroid-resistant adult FSGS patients randomized

to either cyclosporine with low-dose corticosteroids or the same low dose of corticosteroids alone for a 6-month period exhibited a much higher remission rate (12% complete and >70% complete or partial) in the group treated with cyclosporine.[70] Despite relapses after the cyclosporine was discontinued, at the end of long-term follow-up, there were still significantly more remitters in the treated group. The percentage of patients with reduction of GFR during 4 years was significantly less in the treated group. Nevertheless, because there is a high relapse rate when cyclosporine is discontinued, many clinicians use a 1-year course with slow taper in patients who have had a favorable reduction of proteinuria with cyclosporine.[1,59]

Although data are more limited with tacrolimus and there are no RCTs, the results have been similar.[71,72] Because the major side effects of nephrotoxicity, hypertension, and hyperkalemia are the same for both cyclosporine and tacrolimus, choice may depend on cosmetic and other, less severe adverse side effects (e.g., gum swelling, tremor, hirsutism). Tacrolimus has been effective in some patients who are resistant to or intolerant of cyclosporine.

A multicenter German collaborative study compared the efficacy and safety of corticosteroids plus cyclosporine with corticosteroids plus chlorambucil in corticosteroid-resistant nephrotic adults with FSGS.[73] Total and partial remission rates were similar (~20% full and 40% to 50% partial remissions), and the addition of chlorambucil to the regimen did not improve outcome.

Whether cyclosporine is equivalent or superior to corticosteroids as first-line therapy for FSGS has never been documented. However, some clinicians use cyclosporine as first-line therapy in patients at high risk of corticosteroid complications, such as those with concurrent diabetes or morbid obesity.[5]

Mycophenolate mofetil (MMF; mycophenolic acid) has been used successfully in several uncontrolled series of FSGS patients.[74,75] A multicenter prospective RCT compared cyclosporine and a regimen of oral MMF plus dexamethasone in 138 children and young adults up to age 40 who had corticosteroid-resistant FSGS.[76] The partial or complete remission rates were not significantly different (46% in cyclosporine group; 33% in MMF-dexamethasone group). KDIGO guidelines now recommend MMF and dexamethasone for corticosteroid-resistant patients who do not tolerate CNIs.[66]

The use of sirolimus has been controversial because the drug was reported to induce proteinuria and FSGS lesions in kidney transplant patients. In one series, sirolimus was associated with worsening of renal function, episodes of acute renal failure, and no remissions of the nephrotic syndrome.[77] In another series with 21 corticosteroid-resistant FSGS patients, 19% experienced a complete remission, 38% a partial remission.[78] Given the controversy about toxicity, sirolimus is not recommended for the treatment of FSGS. Plasma exchange, which is successful in treating some patients with recurrent FSGS in the renal allograft (see Chapter 108), has not proved useful in patients with disease in their native kidneys.[20] A study of low-density lipoprotein apheresis and prednisone in corticosteroid- and cyclosporine-resistant children with primary FSGS achieved a remission in 7 of 11 patients.[79]

Rituximab has been used in several studies of small numbers of FSGS patients.[80] It has proved more successful for steroid-dependent than steroid-resistant patients.[81]

Corticotropin (ACTH) has been beneficial in small numbers of FSGS patients resistant to multiple other immunosuppressives, but it also has not been formally studied in large RCTs.[82]

Galactose, a monosaccharide sugar, has been shown to have a high affinity for CLC1 permeability factor.[83] In single cases with FSGS resistant to multiple immunosuppressive regimens, long-term galactose therapy normalized CLC1 and dramatically reduced proteinuria.[84]

Other Therapeutic Interventions

The role, if any, of corticosteroids and other immunosuppressives in the treatment of patients with subnephrotic levels of proteinuria and little damage on renal biopsy is unclear. Most nephrologists would not use corticosteroids to treat FSGS patients with subnephrotic proteinuria. Most would treat all FSGS patients who have no contraindications with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) as well as statins, similar to other progressive glomerular diseases. Clearly, optimal blood pressure control itself is also critical to slow or to prevent the progression of the disease (see also Chapter 80).

Another area of active research is the use of agents to prevent renal fibrosis in patients with FSGS. Pirfenidone, an oral TGF-β inhibitor, was used in 21 patients with FSGS and a declining GFR.[85] Pirfenidone slowed the loss of kidney function over time without altering either blood pressure or proteinuria. A study using an antibody to TGF-β is ongoing in FSGS patients.

For patients with secondary forms of FSGS, attempts to treat the actual cause of the FSGS should be the initial step in management. Patients with FSGS secondary to obesity and heroin nephropathy have had remission of proteinuria after weight reduction or cessation of heroin use, respectively. In patients with HIV-associated nephropathy, therapy with highly active antiretroviral drugs and blockers of the renin-angiotensin system has proved useful (see Chapter 58). The role of immunosuppressives has not yet been documented in RCTs in any form of secondary FSGS. In all forms of secondary FSGS, supportive therapy as outlined in Chapter 80 is essential to prevent progressive renal disease in this population. In patients with primary idiopathic or a secondary form of FSGS who remain nephrotic, control of fluid retention and edema can be managed with salt restriction and diuretics (see Chapter 15).

TRANSPLANTATION

Approximately 40% of patients with primary FSGS who develop ESRD and undergo renal transplantation develop recurrent FSGS in the allograft[86] (see Chapter 108). Children with FSGS and patients who manifest with more severe proteinuria and a more rapid course to renal failure in their native kidneys are at greater risk of recurrence in the allograft. Those who have lost a prior allograft because of recurrent FSGS are at highest risk of recurrence. Recurrence in the allograft may be seen immediately after transplantation, supporting the existence of a circulating factor, or years later. Interestingly, the histologic variant of recurrent FSGS was the same as that documented in the native kidney in 81% of cases, validating the fidelity of the histologic subclassification.[11] Plasma exchange has been used successfully to induce remissions of the proteinuria associated with recurrence, but the results are more favorable in children than in adults. Rituximab has been used in some patients for recurrent FSGS, with varied outcomes.

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CHAPTER 19

Inherited Causes of Nephrotic Syndrome

Gentzon Hall and Michelle P. Winn

Inherited nephrotic syndromes are rare diseases that present with nephrotic syndrome and varying degrees of renal impairment, but at times may also present with subnephrotic proteinuria. Inherited disease may manifest *in utero* or shortly after birth, as in congenital nephrotic syndromes, or later in life with proteinuria and pathologic findings consistent with focal segmental glomerulosclerosis. FSGS as the cause of nephrotic syndrome in adults is increasing according to North American (but not European) biopsy studies, and some believe that up to 18% of FSGS cases are caused by hereditary disorders.[1] Autosomal dominant and recessive renal diseases result from defects in podocytes, the slit diaphragm, and the glomerular basement membrane (GBM). These primary renal disorders by definition do not recur after kidney transplantation. In children, syndromic conditions may be seen in which mutations in transcription factors involved in the development of multiple organ systems also affect renal morphogenesis and result in glomerulopathy. Further insight into these hereditary diseases has been elucidated through animal models, in which mutations in corresponding proteins often result in FSGS and proteinuria. Understanding these mechanisms not only provides better insight into abnormalities involved in idiopathic proteinuric kidney diseases but also allows the possible development of molecular drug targets that may improve the course of the renal disease and delay progression.[2-4]

AUTOSOMAL RECESSIVE DISEASES

Congenital Nephrotic Syndrome of the Finnish Type

In 1956, Hallman described a disorder of massive proteinuria *in utero* in the Finnish population. Congenital nephrotic syndrome of the Finnish type (CNF) or nephrotic syndrome type 1 (NPHS1) is an autosomal recessive disease. It has an incidence of 1 in 8200 births in Finland and has been reported less frequently in other ethnicities. The placenta is larger than the child at birth, and the baby is usually born prematurely. Affected children will have as much as 30 g of proteinuria daily, massive edema, hypoalbuminemia, and hyperlipidemia. On light microscopy, kidneys typically have cystic dilation of the proximal tubules and diffuse mesangial sclerosis (Fig. 19-1). Effacement of podocyte foot processes and loss of the glomerular slit diaphragm are seen with electron microscopy.[2]

The product of the mutated *NPHS1* gene, nephrin, is specifically expressed in podocytes, localized to the slit diaphragm between podocyte foot processes.[3] Nephrin is a transmembrane protein belonging to the immunoglobulin superfamily with an intracellular, transmembrane, and extracellular domain. The extracellular domain forms the zipper-like structure of the slit diaphragm; the short intracellular domain interacts with the podocyte proteins podocin and CD2-associated protein (CD2AP). The most common mutations in nephrin are termed Fin-major and Fin-minor and account for 95% of the disease, but more than 50 other mutations in nephrin have been reported.[4] *NPHS1* knockout mice have massive proteinuria, have no slit diaphragm, and die within 24 hours of birth.[5]

Patients with CNF do not respond to cytotoxic therapy or corticosteroids. Angiotensin-converting enzyme (ACE) inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs) have no effect on reducing proteinuria in those with the Fin-major mutation, but there are some reports of efficacy of these agents in those with other mutations in nephrin. The ultimate goal of treatment of CNF is renal transplantation because without this approach, mortality is almost 100%. Because of overwhelming urinary loss of protein, affected infants without the Fin-major mutation may require medical nephrectomy with ACE inhibitors and NSAIDs, followed by renal replacement therapy before transplantation.

Corticosteroid-Resistant Nephrotic Syndrome

In children with nephrotic syndrome of unknown etiology, 90% respond to corticosteroids. Of the remaining 10%, many have corticosteroid-resistant nephrotic syndrome. Multiple hereditary forms have been identified. Mutations of *NPHS2,* which encodes the essential slit diaphragm protein podocin, cause an autosomal recessive disease seen mostly in children younger than 5 years.[6] Affected children have nephrotic-range proteinuria, extrarenal complications of massive proteinuria (see Chapter 15), and rapid progression to end-stage renal disease (ESRD). On light microscopy, the renal lesions vary along the spectrum of minimal change disease to FSGS.[4] Podocin is a hairpin-shaped transmembrane protein specifically expressed in podocytes[2] (Fig. 19-2). Podocin localizes to the foot processes and seems to be involved in podocyte structure as well as in intracellular signaling, with the recruitment of nephrin and CD2AP to microdomains along the slit diaphragm.[4]

Corticosteroid-resistant nephrotic syndrome attributed to the *NPHS2* mutation affects children between 3 months and 5 years of age. The age when the disease manifests seems to depend on the specific podocin mutation. The presence of at least one podocin mutation that codes for a stop codon or in patients homozygous for the R138Q mutation results in renal disease at about age 2 years. Two missense podocin mutations cause disease just before 5 years. Furthermore, studies demonstrate podocin mutations in some adult-onset FSGS. These patients must have two podocin mutations, one of which must be the podocin R229Q mutation.[7]

Another cause of corticosteroid-resistant nephrotic syndrome is a mutation in the phosphatase receptor type O (PTPRO), also called glomerular epithelial protein 1 (GLEPP1).[8] PTPRO is a 150-kD transmembrane protein expressed on the apical membrane surface of podocytes. PTPRO deficiency has been demonstrated to alter podocyte structure and cause foot process flattening. Homozygous donor splice-site mutations result in skipping of *PTPRO* exon 16 or 19. Patients with *PTPRO* mutations present in the first decade of life with resistant nephrotic syndrome. In immunohistochemical

analyses, the exon 16 mutation did not produce a change in the staining pattern of *PTPRO* in biopsy specimens, whereas the *PTPRO* staining with the exon 19 deletion biopsy specimens was completely absent, consistent with a lack of protein expression secondary to degradation of the messenger RNA product. Ultrastructural analyses of biopsy specimens revealed podocyte foot process effacement and microvillous transformation consistent with findings in the *PTPRO*$^{-/-}$ mouse model. The specific effects of the *PTPRO* mutations in podocytes are unknown.[8,9]

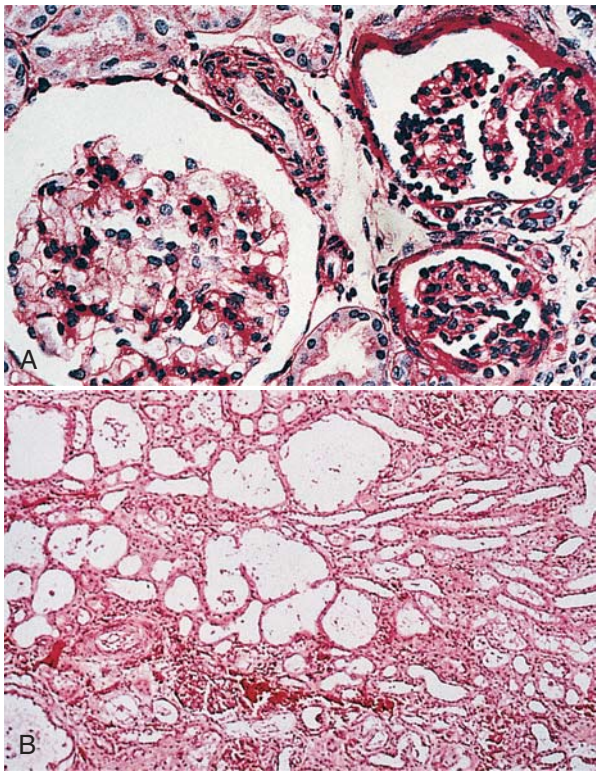

Figure 19-1 Congenital nephrotic syndrome, Finnish type. A, Diffuse mesangial thickening and partially collapsed glomeruli. **B,** Microcystic dilation of the tubules. (**A,** Periodic acid–Schiff reaction; magnification ×260; **B,** hematoxylin-eosin stain; ×150.) *(Modified from reference 30.)*

Isolated Diffuse Mesangial Sclerosis

Diffuse mesangial sclerosis is a pathologic finding in some patients with early-onset nephrotic syndrome. It occurs either "syndromic," when it is associated with a particular clinical syndrome, or "isolated." The isolated disease presents as nephrotic syndrome in the first month of life with rapid progression to ESRD. Light microscopy shows podocyte hypertrophy, mesangial matrix expansion, thickened basement membranes, and decreased size of glomerular capillary lumina. Some cases have shown response to cyclosporine.[10] Diffuse mesangial sclerosis is inherited in an autosomal recessive pattern (Table 19-1). The causative gene *PLCE1* encodes phospholipase C epsilon 1 (PLCε1). PLCε1 is a phospholipase involved in the generation of diacylglycerol and inositol 1,4,5-trisphosphate, which are intracellular second messengers (see Fig. 19-2). A *PLCE1* knockout model in zebrafish revealed edema and pathologic characteristics of nephrotic syndrome during development. The mechanism of disease from the *PLCE1* mutation is not clear, but evidence shows that it interacts with a guanosine triphosphatase (GTPase)–activating protein involved in podocyte development and interaction with nephrin. *PLCE1* is not the only gene responsible for isolated diffuse mesangial sclerosis. More genetic causes are under investigation.[10]

Autosomal Recessive Familial Focal Segmental Glomerulosclerosis

In 2011, mutations of *MYO1E,* which encodes the Myo1E protein, a nonmuscle class I myosin with important functions in the regulation of podocyte cytoskeletal dynamics, were identified as causes of nonsyndromic autosomal recessive FSGS.[11] Mutations of *MYO1E* resulted in early-onset ESRD secondary to FSGS. These mutations have been associated with presentation between 1 and 9 years of age.

Autosomal Recessive Nephrotic Syndromes

Disease	Gene	Protein	Clinical Presentation	Mechanism of Disease
Congenital nephrotic syndrome of Finnish type	*NPHS1*	Nephrin	Proteinuria *in utero* (at times >30 g), large placenta, resistant to conventional therapy; transplant is only treatment.	Mutation in nephrin leads to loss or malfunction of slit diaphragm.
Corticosteroid-resistant nephrotic syndrome	*NPHS2*	Podocin	Clinical manifestations and age of onset of proteinuria vary; resistant to corticosteroids, generally progresses to FSGS	Mutation in podocin leads to loss or malfunction of slit diaphragm.
	PTPRO (GLEPP1)	PTPRO (GLEPP1)	Childhood-onset corticosteroid-resistant nephrotic syndrome; FSGS on biopsy	Unclear, but *PTPRO* mutation results in severe podocyte foot process effacement, swelling, and vacuolization as well as mesangial hypercellularity and focal sclerosis.
Isolated diffuse mesangial sclerosis	*PLCE1*	PLCε1	Nephrotic syndrome in first year of life; rapid progression to ESRD	Unclear, but *PLCE1* mutation results in abnormal podocyte differentiation, possibly through nephrin; other mutations exist not attributable to *PLCE1.*
Corticosteroid-resistant FSGS	*MYO1E*	Myo1E	Corticosteroid-resistant FSGS; early onset between 6 and 18 years of age	*MYO1E* mutation is associated with corticosteroid-resistant FSGS characterized by basement membrane thickening and multilamination as well as podocyte foot process effacement and microvillous transformation; overexpression of *MYO1E* A159P mutant in human podocyte line resulted in mislocalization of Myo1E and CD2AP.

Table 19-1 Autosomal recessive nephrotic syndromes. *ESRD,* End-stage renal disease; *FSGS,* focal segmental glomerulosclerosis; *GLEPP1,* glomerular epithelial protein 1; *Myo1E,* myosin 1E; *PLCE1,* phospholipase C epsilon 1; *PTPRO,* protein tyrosine phosphatase receptor, type O.

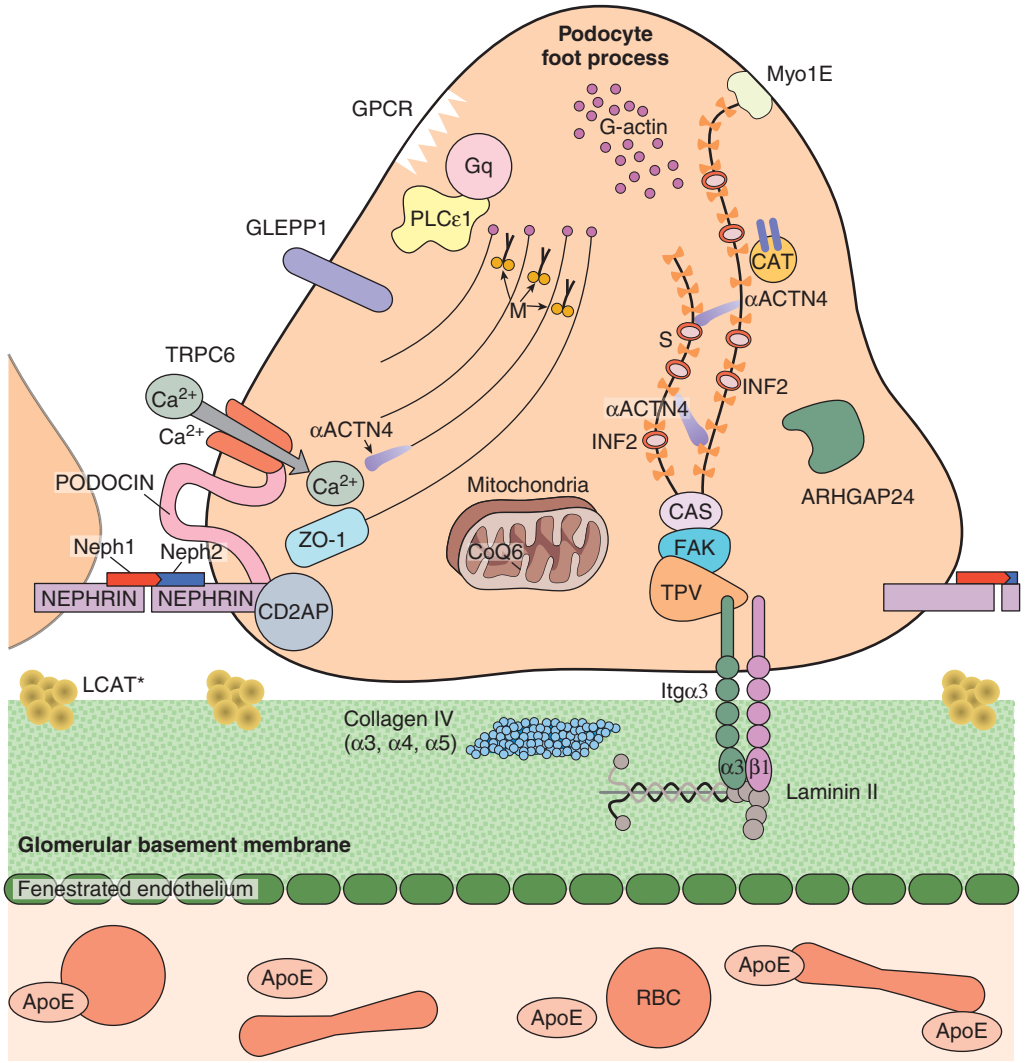

Figure 19-2 Podocyte foot process structure and proteins involved in hereditary nephrotic syndromes. The podocyte contains F-actin, myosin *(M)* and actin-binding proteins synaptopodin *(S)* and α-actinin-4; *αACTN4* is mutated in FSGS type 1. The slit diaphragm contains proteins that include nephrin, podocin, and CD2AP. Nephrin is mutated in congenital nephrotic syndrome of the Finnish type and podocin in corticosteroid-resistant nephrotic syndrome. Zona occludens 1 *(ZO-1)* is a cell-to-cell junction protein. The phospholipase PLCε1 is an enzyme identified as a cause of diffuse mesangial sclerosis. Angiotensin receptor, type 1 is an example of a G-protein coupled receptor *(GPCR)* and can activate TRPC6 via signals transmitted through the G-protein subunit Gq. A *TRPC6* mutation in FSGS type 2 results in increased calcium (Ca^{2+}) transients. Arhgap24 modulates the activity of the cytoskeletal regulator Rac1. Coenzyme Q10 biosynthesis monooxygenase 6 (CoQ6) is an essential component of the mitochondrial respiratory transport chain that is required for the biosynthesis of CoQ10. Talin, paxillin, and vinculin *(TPV)* are connected to laminin-11 via $\alpha_3\beta_1$ integrin dimers and are involved in anchoring the podocyte to the glomerular basement membrane (GBM). Myo1E is a mediator of F-actin filament organization. The protein phosphatase receptor type O (PTPRO, or *GLEPP1*) may regulate podocyte structure and function via its interaction with CD2AP. *INF2* is mutated in FSGS 5 and is a regulator of F-actin assembly. The *LAMB2* mutation is responsible for Pierson syndrome and results in diffuse mesangial sclerosis. Lecithin–cholesterol acyltransferase *(LCAT*)* deficiency leads to lipid deposits in the GBM. Laminated apolipoprotein deposits *(ApoE)* are found in the capillaries in lipoprotein glomerulopathy. *LMX1B* and *WT1* (not shown) are transcription factors mutated in syndromic proteinuric renal diseases. Catenins *(CAT),* p130Cas *(CAS),* and focal adhesion kinase *(FAK)* are structural proteins. *(Modified from reference 31.)*

Clinical signs and symptoms include nephrotic-range proteinuria and microhematuria, as well as hypoalbuminemia and edema. Renal biopsy findings are consistent with FSGS. Treatment with corticosteroids, ACE inhibitors, and cyclosporine A can result in partial remission, although some patients progress to ESRD. *In vitro* studies showed overexpression in a conditionally immortalized podocyte cell line that resulted in mislocalization of Myo1E and its interaction partner CD2AP. Also, targeted *MYO1E* knockout in mice produced basement membrane thickening and podocyte foot process effacement. Myo1E protein is postulated to be important in the regulation of tension development in podocyte foot processes, which may affect their ability to counterbalance variations in the glomerular capillary intraluminal pressure and maintenance of slit diaphragm integrity.[11]

AUTOSOMAL DOMINANT DISEASES

Autosomal Dominant Familial Focal Segmental Glomerulosclerosis

In contrast to inherited nephrotic syndromes that present in childhood, there are familial proteinuric kidney diseases that manifest in adolescence through adulthood. Most of these are inherited in an autosomal dominant manner (Table 19-2). Typical pathology reveals the glomerular changes of FSGS, and there is variability in the rate of progression of renal impairment. Genetic mutations have been identified, and mechanisms of FSGS in sporadic forms can be elucidated from increasing understanding of these familial cases.[12] Mutations of *ACTN4* cause an autosomal dominant form of FSGS. The

Autosomal Dominant Nephrotic Syndromes				
Disease	**Gene**	**Protein**	**Clinical Presentation**	**Mechanism of Disease**
FSGS type 1	*ACTN4*	α-Actinin-4	Slow progression to ESRD; generally presents in adulthood with proteinuria	Mutation in *ACTN4* results in abnormal assembly-disassembly of actin and podocyte structural abnormalities.
FSGS type 2	*TRPC6*	TRPC6	Proteinuria seen in late adolescence to adulthood; 60% progress to ESRD by 10 years	Mutation in *TRPC6* leads to increased calcium transients, which may result in disruption of podocyte structure or function.
FSGS type 5	*INF2*	INF2	Moderate proteinuria seen in late adolescence to adulthood; occasional microscopic hematuria and hypertension	Mutation in *INF2* causes mislocalization of the protein.
FSGS	*ARHGAP24*	Arhgap24	FSGS	*ARHGAP24* mutations cause increased podocyte membrane ruffling and hypermotility through potentiation of Rac1 activity *in vitro.*

Table 19-2 Autosomal dominant nephrotic syndromes. *Arhgap 24,* RhoA-activated Rac1 GTPase-activating protein 24; *ESRD,* end-stage renal disease; *FSGS,* focal segmental glomerulosclerosis; *INF2,* inverted formin 2; *TRPC6,* transient receptor canonical, type 6.

product of this gene is α-actinin 4, which is expressed in podocytes and cross-links with F-actin filaments in the foot processes (see Fig. 19-2). The mutation in *ACTN4* is believed to be a gain-of-function mutation, leading to increased cross-linking of F-actin with α-actinin 4, resulting in dysregulation of actin assembly and disassembly in the podocyte. It was recently found that the relaxation frequency from actin of mutant *ACTN4* was an order of magnitude lower than wild-type α-actinin 4. The resultant structural abnormality is believed to cause proteinuria, renal dysfunction, and subsequent glomerulosclerosis. This has been supported in murine studies; mice with mutated α-actinin 4 with high affinity for F-actin have an FSGS-like phenotype, and mice deficient in α-actinin 4 have abnormal podocytes and develop ESRD.[2,4] Patients with *ACTN4* mutations have variable age at onset and progression of renal disease.

Various mutations of the transient receptor potential cation channel, subfamily C, member 6 *(TRPC6)* have been identified as a cause of autosomal dominant FSGS.[12] TRP channels are involved in various biologic processes, including cell growth, mechanosensation, vasoregulation, and cation entry into cells. The P112Q missense mutation results in a gain of function, with increased calcium influx presumably leading to glomerular dysfunction.[2,4] Disease manifests in the third and fourth decades of life. As many as 60% of affected individuals will progress to ESRD in 10 years. In contrast to other known mutations that result in structural podocyte and slit diaphragm abnormalities, such as podocin, nephrin, and α-actinin 4, this is the first ion channel to be implicated as a cause of hereditary nephrotic syndrome and FSGS. Furthermore, there is increased expression of wild-type TRPC6 in human proteinuric kidney diseases, animal models of kidney injury, and cultured podocytes exposed to complement and antipodocyte antibodies, highlighting the role of TRPC6 in podocyte function and in the pathogenesis of various forms of kidney disease.[13]

Originally identified through its interaction with CD2 in T lymphocytes, the widely expressed protein CD2AP has been implicated in proteinuric renal disease. *CD2AP*-deficient mice die of renal failure at 6 to 7 weeks of age. On histologic examination, foot process effacement and glomerulosclerosis are seen. CD2AP does localize to the slit diaphragm and has been shown to interact with nephrin and podocin (see Fig. 19-2).[4] A corresponding disease in humans caused solely by *CD2AP* mutations has not yet been clearly established.[14]

Mutations in the formin gene *INF2* cause autosomal dominant FSGS.[15] All mutations are located in the diaphanous inhibitory domain of INF2. Individuals in these families present in early adolescence or adulthood with moderate proteinuria that progresses to ESRD. Some individuals also present with microscopic hematuria and hypertension. Pathology shows typical FSGS, although electron microscopy also shows prominent actin bundles within the foot processes. INF2 protein is a member of the formin family. These proteins regulate actin and accelerate actin polymerization. INF2 is widely expressed throughout the body and in podocytes. When transfected into podocytes, mutant *INF2* constructs exhibited different localization patterns than wild-type INF2.

In 2011, a novel missense mutation in the Rac1 regulatory protein Arhgap24 was identified as a cause of autosomal dominant FSGS. RhoA-activated Rac1 GTPase-activating protein (Arhgap24) is recognized as an essential modulator of podocyte actin cytoskeletal dynamics through the modulation of Rac1 GTPase activity.[16] Targeted *ARHGAP24* knockout in mouse podocytes impairs Rac1 deactivation and promotes podocyte motility. The Q158R variant led to impaired inhibition of Rac1 activation when overexpressed in cultured human embryonic kidney cells. The specific effects of the *ARHGAP24* mutation in podocytes have not been elucidated.[16]

SYNDROMIC PROTEINURIC RENAL DISEASE

Denys-Drash and Frasier Syndromes

Denys-Drash syndrome (DDS) and Frasier syndrome are rare diseases manifested with early onset of congenital nephrotic syndrome and male pseudohermaphroditism (Table 19-3). Both are associated with the development of urogenital tumors: nephroblastoma or Wilms tumor in DDS and gonadoblastoma in Frasier syndrome. Patients with DDS have a high incidence of severe hypertension and rapid progression to ESRD. The glomerular lesion of DDS is diffuse mesangial sclerosis, and patients progress to ESRD by age 3 years. In Frasier syndrome, male pseudohermaphrodites typically present as phenotypic females with amenorrhea or nephrotic syndrome, or both. The nephrotic syndrome may be slowly progressive, usually over 10 years, and is typically corticosteroid resistant; the pathologic lesion is FSGS. The patients develop ESRD in the second or third decade of life, with most cases occurring at puberty. Some cases present in much younger children.[17] Rarely, an XX karyotype with a less severe phenotype may not be identified clinically as Frasier syndrome and presents only with renal disease. The gene responsible for both DDS and Frasier syndrome has been localized to chromosome 11p13. The gene product is the Wilms tumor suppressor (WT1), which is a transcription factor involved in gonad and kidney development. WT1 seems to downregulate the expression of a number of genes involved in normal embryonic development of the urogenital system. Therefore, the decreased expression or lack of expression of

Syndromic Proteinuric Renal Diseases					
Disease	**Inheritance**	**Gene**	**Protein**	**Clinical Presentation**	**Mechanism of Disease**
Denys-Drash and Frasier syndromes	AD	*WT1*	WT1	Male pseudohermaphroditism, early nephropathy, and Wilms tumor in Denys-Drash; later onset of nephropathy, FSGS, and gonadoblastoma in Frasier syndrome	Mutation in *WT1* results in abnormal urogenital development.
Nail-patella syndrome	AD	*LMX1B*	LMX1B	Skeletal, nails, eyes, and renal abnormalities; variable renal disease from benign proteinuria to nephrotic syndrome	Mutation in *LMX1B* results in abnormal regulation of podocyte genes.
Pierson syndrome	AD	*LAMB2*	Laminin β2 chain	Microcoria, diffuse mesangial sclerosis, onset shortly after birth	Abnormal GBM is caused by mutations in adult form of laminin.
Galloway-Mowat syndrome	AR	Unknown	Unknown	Microcephaly, abnormal cerebral gyral patterns, seizures, cranial dysmorphia, and glomerulopathy	Mechanism unknown
Congenital nephrotic syndrome	AR	*ITGA3*	Itgα3	Early onset; disease characterized by interstitial lung disease, epidermolysis bullosis, and congenital nephrotic syndrome	*ITGA3* mutations result in disruption of GBM architecture and failure of podocyte foot process attachment.
Corticosteroid-resistant nephrotic syndrome	AR	*COQ6*	CoQ6	Early onset; syndrome characterized by sensorineural deafness, fibrosis, and podocyte foot process effacement; FSGS and diffuse mesangial sclerosis on biopsy	*COQ6* mutations result in impaired Q10 biosynthesis and podocyte apoptosis; effects can be partially ameliorated with coenzyme Q10 supplementation.

Table 19-3 Syndromic proteinuric renal diseases. *AD,* Autosomal dominant; *AR,* autosomal recessive; *CoQ6,* coenzyme Q6; *FSGS,* focal segmental glomerulosclerosis; *GBM,* glomerular basement membrane; *Itgα3,* integrin α_3; *LMXB1,* LIM-homeodomain transcription factor b1; *WT1,* Wilms tumor 1.

WT1 seen in DDS and Frasier syndrome leads to the clinical manifestations,[2,14] as supported by *WT1* knockout mice, who lack kidneys and gonads.[17]

Nail-Patella Syndrome

Nail-patella syndrome (hereditary onycho-osteodysplasia; Fong syndrome) is an autosomal dominant disease involving abnormalities of the skeleton, nails, eyes, and kidneys. Affected patients have nail dysplasia, absence of or poorly developed patellas, dysplasia of the iliac horns and elbows, cataracts, glaucoma, and glomerulopathy.[2] Chapter 48 discusses nail-patella syndrome in detail.

Pierson Syndrome

In 1963, Pierson and colleagues described cases of congenital nephrotic syndrome with distinct eye abnormalities.[18] In this rare syndrome, patients present with hypoplasia of the ciliary body and iris, resulting in fixed narrowing of the pupil (microcoria) as well as massive proteinuria at birth and rapid progression to ESRD. Most die before 2 months of age. Diffuse mesangial sclerosis exemplifies the renal pathology findings in the Pierson syndrome. The resultant mutation is in *LAMB2*, which codes for the laminin β2 chain. *LAMB2* is present in the normal GBM, and the mutation results in abnormal formation of the GBM as well as abnormal differentiation of podocyte foot processes (see Fig. 19-2). *LAMB2* knockout mice demonstrate congenital nephrosis with abnormalities of the retinal and neuromuscular junctions.[2,18]

Galloway-Mowat Syndrome

In 1968, two siblings with nephrotic syndrome, hiatal hernia, and abnormal development of the central nervous system were described by Galloway and Mowat.[19] The Galloway-Mowat syndrome is inherited in an autosomal recessive pattern. The currently recognized clinical features include microcephaly, abnormal cerebral gyral patterns, seizures, psychomotor retardation, cranial dysmorphia, and glomerulopathy. The renal disease generally presents as the nephrotic syndrome within the first few months of life, with rapid progression to ESRD. Most affected children die before age 6 years. Based on the time of biopsy, renal findings on light microscopy include diffuse mesangial sclerosis, mesangial proliferation, FSGS, cystic microdilation of tubules, and normal-appearing glomeruli. Electron microscopy reveals irregular thickening of the GBM and effacement of podocyte foot processes. The genetic abnormality has not been found, but because of multiple reports of the same disease in siblings, the Galloway-Mowat syndrome is presumed to be a familial disorder.[20]

Glomerulopathy Associated with Abnormalities in Lipid Metabolism

Nephrotic-range proteinuria, edema, hypoalbuminemia, lipiduria, and hyperlipidemia are hallmarks of the nephrotic syndrome. However, the hyperlipidemia is thought to be caused by urinary losses of cholesterol and albumin, resulting in increased hepatic synthesis of low-density lipoproteins, very-low-density lipoproteins, and lipoprotein(a).[21] However, some rare proteinuric kidney diseases are caused by abnormal metabolism of lipids, resulting in deposition of lipids in glomeruli and subsequent nephrotic syndrome (Table 19-4).

Lipoprotein glomerulopathy presents in adulthood with proteinuria and often nephrotic syndrome, with rapid progression to renal failure. Light microscopy reveals extensive deposition of laminated lipid thrombi in glomerular capillaries (Fig. 19-3). The lipid deposits contain apolipoproteins A, B, and E (see Fig. 19-2). Because of studies of affected kindreds, particularly in Japan, it is thought to be

Glomerular Diseases Associated with Lipid Abnormalities in Lipid Metabolism					
Disease	**Inheritance**	**Gene**	**Protein**	**Clinical Presentation**	**Mechanism of Disease**
Lipoprotein glomerulopathy	Unknown	*Unknown*	Apolipoprotein E	Type III hyperlipidemia, nephrotic syndrome, renal failure, and deposition of lipid thrombi in glomerular capillaries	Abnormal lipid metabolism and deposition in various tissues
LCAT deficiency	Autosomal recessive	*LCAT*	LCAT	Anemia, corneal opacities, low HDL, elevated LDL, proteinuria, and progressive renal failure	Abnormal lipid metabolism and deposition in various tissues

Table 19-4 Glomerular diseases associated with abnormalities in lipid metabolism. *HDL,* High-density lipoprotein; *LCAT,* lecithin–cholesterol acyltransferase; *LDL,* low-density lipoprotein.

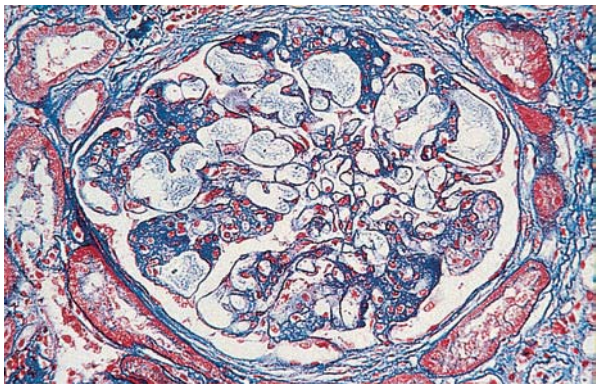

Figure 19-3 Lipoprotein glomerulopathy. Dilated capillary lumina containing a pale-stained, mesh-like or granular substance. (Trichrome stain; ×260.) *(Modified from reference 30.)*

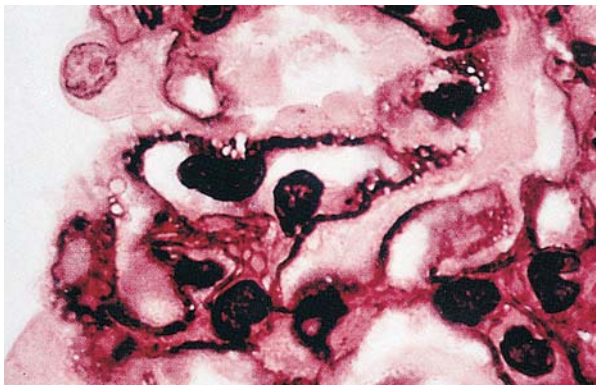

Figure 19-4 Lecithin–cholesterol acyltransferase (LCAT) deficiency. Note the irregular, thickened glomerular capillary walls containing clear vacuoles, which are characteristic of the lesion. (Periodic acid–Schiff reaction; ×1000.) *(Modified from reference 30.)*

a hereditary disease. The *APOE* mutation is believed to be in apolipoprotein E because these patients also have a type III hyperlipidemia, characterized by elevated intermediate-density lipoproteins and apolipoprotein E. Treatment with lipid-lowering drugs such as fibric acid derivatives has shown some benefit.[22] Missense mutations of the antitrypanosomal serum factor apolipoprotein L1 *(APOL1)* have been associated with an increased risk for sporadic FSGS, human immunodeficiency virus–associated nephropathy (HIVAN), as well as hypertension-associated ESRD in blacks. Although *in vitro* analyses demonstrate enhanced trypanosomolytic activity of the *APOL1* mutants, insights into the mechanisms promoting kidney disease remain unclear.[23]

Lecithin–cholesterol acyltransferase (LCAT) deficiency is an autosomal recessive disease characterized by anemia, corneal opacities, decreased high-density lipoprotein level, elevated low-density lipoprotein level, proteinuria, and often nephrotic syndrome with progressive renal failure. LCAT disease generally presents in adulthood and is slow in onset. Light microscopy reveals irregular thickening of the glomerular capillaries with "vacuolization" of the capillary basement membranes caused by lipid droplets (Fig. 19-4). This is the "foamy" appearance characteristic of LCAT deficiency. Mesangial and basement membrane electron-dense lamellar structures are also seen and are unique to this disorder. Patients with LCAT deficiency respond poorly to treatment.[24]

Nephrotic Syndrome Associated with Specific Mutations

In 2012, mutations of *ITGA3,* which encodes the transmembrane integrin α_3 receptor subunit (ITGA3), were reported.[25] ITGA3 is known to play a critical role in the transmission of mechanosensory and biochemical signals between the extracellular and intracellular fluid compartments. *ITGA3* mutations cause a syndrome of congenital nephrotic syndrome, interstitial lung disease, and epidermolysis bullosa. ITGA3 staining was absent in biopsy specimens and was associated with profound irregularities of the basement membrane architecture in the kidney, lungs, and epidermis. Two additional mutations were also identified in two unrelated subjects.[25]

Mutations of the coenzyme Q10 biosynthesis monooxygenase 6 *(COQ6)* cause corticosteroid-resistant nephrotic syndrome and sensorineural deafness. CoQ6 is an evolutionarily conserved and ubiquitously expressed monooxygenase that is necessary for the biosynthesis of CoQ10. CoQ10 is an essential lipophilic antioxidant required for the proper functioning of the mitochondrial electron transport chain. Compound heterozygous truncating or nonsense mutations and homozygous missense mutations of *COQ6* were associated with cyclosporine A–dependent nephrotic syndrome or diffuse mesangial sclerosis.[25a] All mutations segregated in a manner consistent with autosomal recessive inheritance. All the affected children manifested proteinuria by 6 years of age and progressed to ESRD by age 9. Five died in early childhood, and 7 of the 11 patients had biopsy-proven FSGS. In addition, sensorineural deafness was detected in all nine affected individuals screened. In complementary *in vitro* analyses, targeted knockdown of *COQ6* was found to induce apoptosis in a podocyte cell line. This was partially ameliorated with CoQ10 supplementation. Similar results were observed with *COQ6* knockout in zebrafish.[25a]

GENETIC TESTING

Children with a family history of corticosteroid-resistant nephrotic syndrome or after failure of an initial treatment course of corticosteroids should undergo renal biopsy and should be considered for

genetic testing. Mutations in the recessive genes that encode nephrin *(NPHS1)*, podocin *(NPHS2)*, phospholipase Cε1 *(PLCE1)*, WT1 *(WT1)*, and laminin β2 *(LAMB2)* cause proteinuric renal disorders in children. *NPHS1*, *NPHS2*, *LAMB2*, and *WT1* mutations are responsible for 85% of glomerular disease seen in the first 3 months of life and 66% in the first year, and these certainly should be the first tests sent in screening of children for inherited conditions.[7] Diffuse mesangial sclerosis is seen with mutations in *NPHS1*, *PLCE1*, *LAMB2*, and *WT1*. FSGS is seen with mutations in *NPHS2*. The Galloway-Mowat syndrome can have either diffuse mesangial sclerosis or FSGS-like changes, but the genetic defect is not known. Further testing will be determined by the patient's presentation. In most cases of syndromic disease, the clinical characteristics will dictate which genetic tests are necessary and may narrow the analysis to one or two genes. For example, in a patient with pseudohermaphroditism and renal disease, *WT1* mutations are likely, and *LAMB2* testing can be done in those with congenital nephrotic syndrome and microcoria. Inherited nephrotic syndrome in adults generally presents as FSGS and is believed to be responsible for up to 18% of cases identified in those older than 18 years.[1]

In patients with suspected syndromic or nonsyndromic nephrotic syndrome, we recommend pursuit of genetic testing if (1) test results are likely to aid in the diagnosis, (2) test results are likely to alter clinical management or inform discussions of prognosis, or (3) the test result from the presenting affected individual will likely provide data on risk in other family members.[26] In patients with congenital or infantile nephrotic syndrome, or in patients with disease onset after age 1 year who also have a positive family history, and/or a diagnosis of corticosteroid-resistant nephrotic syndrome, screening for autosomal recessive (AR) and autosomal dominant (AD) causes of nephrotic syndrome should be performed (Fig. 19-5).[26]

At present, limited genetic testing for inherited FSGS and nephrotic syndromes is available worldwide, but this is likely to change in the near future. Testing may be expensive but is covered by some insurance companies or subsidized by some hospitals. For idiopathic FSGS, the current KDIGO (Kidney Disease: Improving Global Outcomes) guidelines recommend against routine genetic testing. This is not a graded recommendation but does take into account that according to currently available prevalence data from selected case series, less than 10% of all cases of corticosteroid-resistant nephrotic syndrome are caused by FSGS and less than 2% of all cases of nephrotic syndrome are probably the result of single-gene defects.[27] In this regard, consideration of the associated cost of currently available genetic testing versus benefit should be reviewed with patients and families. The highest probability of detecting a genetic lesion is in infants and children and those with a family history of FSGS or nephrotic syndrome.

CLINICAL MANAGEMENT OF INHERITED NEPHROTIC SYNDROME

Angiotensin receptor blockers (ARBs) and ACE inhibitors are considered appropriate treatment for all individuals (children and adults) with nephrotic syndrome. Lipid-lowering medications are also recommended because adults with nephrotic syndrome have hyperlipidemia and may have increased risk of cardiovascular disease. No randomized clinical trials have been done on immunosuppressant and chemotherapeutic therapy in inherited nephrotic syndromes, but anecdotal data report that these agents may delay the progression of kidney disease in patients with familial forms of disease.[28] Cyclosporine is generally used for initial treatment in FSGS

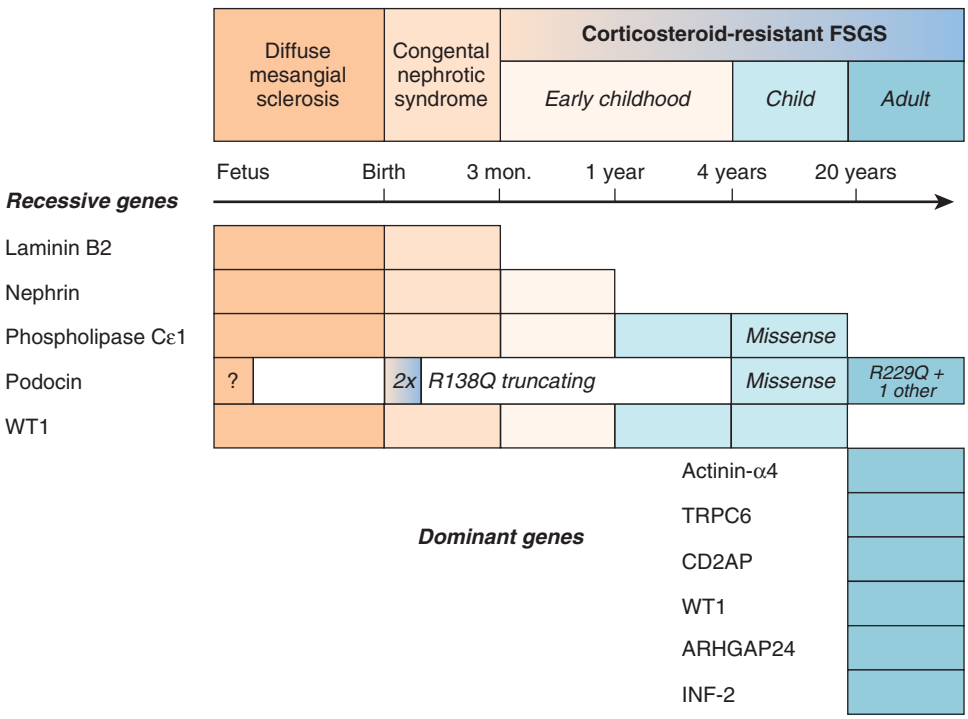

Figure 19-5 Inheritance patterns of nephrotic syndromes. Autosomal recessive diseases generally present early in life as diffuse mesangial sclerosis or congenital nephrotic syndrome. In early childhood, mutations in proteins encoding nephrin *(NPHS1)*, podocin *(NPHS2)*, Wilms tumor suppressor *(WT1)*, and phospholipase Cε1 *(PLCE1)* will also cause disease. Podocin mutations result in disease at different times based on the particular mutation with disease in young adults as well. Autosomal dominant conditions present later in life and have been described in families with FSGS with mutations in *ACTN4* (encoding α-actinin 4), *TRPC6, WT1, INF2,* and *ARHGAP24. CD2AP* mutations are suspected, but have not been described as a sole cause of disease in humans. *(Modified from reference 7.)*

not responsive to corticosteroids (see Chapter 18) and may be appropriate in inherited forms as well. When effective in the treatment of inherited nephrotic syndromes, it may reflect the favorable effects of cyclosporine on the podocyte actin cytoskeleton by a mechanism that may involve blockade of calcineurin phosphatase–mediated dephosphorylation of synaptopodin, which leads to cytoskeletal stabilization.[29]

These disorders result from inherited abnormalities in renal developmental or structural proteins, so there should be no recurrence of the original condition after transplantation because the donor kidney presumably is from a patient without a genetic renal disease (see Chapter 108). However, the reported recurrence rate of nephrotic syndrome in those with inherited disorders is misleading because chronic allograft nephropathy can present with an FSGS-like phenotype. Similarly, reports of recurrence in patients with podocin mutations exist, but given the complex inheritance pattern, with some diseases manifesting in children and others in adults, these are difficult to interpret. More recent data suggest a low recurrence rate of nephrotic syndrome in the transplant in those with *NPHS2* mutations.[7] Reappearance of the nephrotic syndrome in congenital nephrotic syndrome of the Finnish type is not truly a "recurrence" but thought to be caused by antinephrin autoantibodies and not a *de novo* nephrin mutation in the transplanted kidney. Therefore, transplantation is not discouraged in those with congenital nephrotic syndromes, and their postsurgical management should not differ from usual clinical care. In fact, data suggest that patients with inherited nephrotic syndromes and FSGS may have better transplant survival outcomes than those with idiopathic disease.

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CHAPTER 20

Membranous Nephropathy

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DEFINITION

Membranous nephropathy (MN) is an immune complex glomerular disease in which immune deposits of IgG and complement components develop predominantly or exclusively beneath podocytes on the subepithelial surface of the glomerular capillary wall. Podocyte injury resulting from the immune deposits increases glomerular permeability to plasma proteins, which results in proteinuria and potentially, nephrotic syndrome.[1,2] In about 75% to 80% of patients, MN occurs in the absence of any identifiable cause or initiating event and is known as *idiopathic* or *primary* MN. Various conditions have been identified in association with MN, some of which are likely to be causal and some of which probably represent only associations[1] (Table 20-1). Primary MN is an organ-specific autoimmune disease. It is the most common cause of primary nephrotic syndrome in older (>60 years) Caucasian adults, but the age range is broad, and patients may present for the first time in their teenage years.[3]

The term *membranous* refers to thickening of the glomerular capillary wall on light microscopy of a renal biopsy, but the entity now referred to as membranous nephropathy is defined by immunofluorescence and electron microscopy. These techniques reveal diffuse, finely granular immune deposits on immunofluorescence and electron-dense deposits in the subepithelial space that are now regarded as pathognomonic of MN. Consequently, MN is a pathologic diagnosis made in patients with proteinuria whose glomeruli exhibit these immune deposits without associated hypercellularity or inflammatory changes.[2]

ETIOLOGY AND PATHOGENESIS

Experimental Membranous Nephropathy

Much of what we know about the pathogenesis of MN derives from observations in animal models.[4,5] Studies of the Heymann nephritis model of MN in rats in the late 1970s established that the subepithelial immune deposits form *in situ* when circulating antibodies bind to an intrinsic antigen in the glomerular capillary wall. The antigen was subsequently identified as *megalin,* a large (~600 kD) transmembrane receptor of the low-density lipoprotein receptor family expressed on the basal surface of rat podocytes.[6] Binding of circulating antimegalin antibodies induces capping and shedding of the antigen-antibody complexes, where they bind to the underlying glomerular basement membrane (GBM), resist degradation, and persist for weeks or months as immune deposits characteristic of MN (Fig. 20-1, *A*). Proteinuria in this model is caused by complement-fixing antibodies in the immune deposits that overcome local complement regulatory mechanisms and activate complement *in situ.* The primary mechanism involves sublethal podocyte injury induced by the complement membrane attack complex C5b-9, which triggers a cascade of structural and functional changes, including oxidative injury, calcium influx, activation of cytosolic phospholipase A_2, production of arachidonic acid metabolites and cytokines, endoplasmic reticulum stress, DNA damage, and disruption of the actin cytoskeleton[7] (Fig. 20-2). Podocyte foot process effacement is likely the result of the collapse of the actin cytoskeleton and loss of cell-GBM adhesion complexes, and the loss and displacement of slit diaphragms is associated with the onset of severe, nonselective proteinuria. Podocyte injury is also responsible for the production of new extracellular matrix (ECM) proteins that are laid down between and around the immune deposits, giving rise to the characteristic "spikes" and GBM thickening that are hallmarks of MN.

Another mechanism of subepithelial immune deposit formation involves planted antigens[5] (Fig. 20-1, *B*). This is best exemplified by animal models immunized with cationized bovine serum albumin (cBSA). The cBSA binds to negatively charged residues in the GBM, where it serves as a target for circulating anti-BSA antibodies. As in the Heymann nephritis model, podocyte injury and proteinuria result from local complement activation.

Human Membranous Nephropathy

Evidence has recently been obtained that both fixed and planted antigen mechanisms are involved in human MN (see Fig. 20-1). The first demonstration that circulating antibodies reactive with an intrinsic podocyte antigen may be involved in MN was provided by an unusual case of antenatal MN induced by the transplacental passage of alloantibodies to neutral endopeptidase (NEP), a known podocyte protein.[8] The mother of the affected child was found to be deficient in NEP and had been immunized during a previous pregnancy and, like subsequent cases, produced complement-fixing anti-NEP alloantibodies. Although antibodies to anti-NEP do not account for primary MN, alloantibodies probably explain the development of de novo MN after renal transplantation and MN in the setting of chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation (see Table 20-1). The predominant autoimmune system responsible for primary MN is that associated with autoantibodies directed at the M-type phospholipase A_2 receptor (PLA_2R) on podocytes.[9] Circulating anti-PLA_2R antibodies are detectable in the serum of 75% to 80% of patients with primary MN from all ethnic groups and are rarely found in secondary MN.[10,11] The antibodies are predominantly IgG4 and, as in the Heymann nephritis model, the antigen (PLA_2R) and antibodies (anti-PLA_2R) co-localize in the immune deposits in primary (but not in secondary) MN.[9,12,13] PLA_2R is a transmembrane protein of the mannose receptor family[14] (Fig. 20-3). Although it has been shown to undergo constitutive endocytosis and is involved in the production of eicosanoids, reactive oxygen species, DNA damage, and cellular senescence, its role in podocytes is unknown. Reactivity to certain intracellular antigens, including aldose reductase, SOD2, and enolase, has been detected in primary MN and may contribute to the progression of podocyte injury.[15] The best evidence of a planted antigen mechanism in MN is that described in a subset of children

Classification and Causes of Membranous Nephropathy		
Primary		
Anti-PLA_2R associated (70%-80%) Idiopathic (20%-30%)		
Secondary	**Common**	**Uncommon**
Autoimmune diseases	Class V lupus nephritis	Rheumatoid arthritis Autoimmune thyroid disease IgG4-related systemic disease Anti-GBM and ANCA-associated crescentic glomerulonephritis
Infections	Hepatitis B	Hepatitis C virus (HCV) Human immunodeficiency virus (HIV) Syphilis Schistosomiasis
Malignancy	Solid tumors (colon, stomach, lung, prostate)	Non-Hodgkin lymphoma Chronic lymphocytic leukemia (CLL) Melanoma
Drugs or toxins	Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 (COX-2) inhibitors	Mercury-containing compounds Gold salts D-Penicillamine, bucillamine
Miscellaneous		Sarcoidosis Anticationic bovine serum albumin
Alloimmune		
Graft-versus-host disease following hematopoietic stem cell transplantation *De novo* membranous nephropathy in renal allograft Fetomaternal alloimmunization to neutral endopeptidase		

Table 20-1 Classification of conditions and agents associated with membranous nephropathy. The list excludes conditions for which only a single case has been reported or the lesions were atypical of membranous nephropathy. *ANCA,* Antineutrophil cytoplasmic antibody; *GBM,* glomerular basement membrane.

with MN who have been exposed to cBSA, presumably in bottled milk. In such cases, as in the animal models, the cBSA localizes in the GBM, where it forms complexes with circulating anti-BSA.[16] Planted antigens may also be responsible for immune deposition in class V (membranous) lupus nephritis and hepatitis B virus (HBV)–associated MN.

The resolution of MN depends on remission of the immune response, the extent of podocyte damage, and expansion of the GBM. In cases in which immunologic remission occurs before extensive podocyte loss and GBM remodeling, complete recovery is possible. On the other hand, proteinuria may persist for several weeks or months until the normal architecture is restored. Once there is extensive podocyte loss, severe proteinuria persists despite immunologic remission and glomerular sclerosis, tubular atrophy, and interstitial fibrosis may ensue.

EPIDEMIOLOGY AND GENETICS

Membranous nephropathy may occur at any age and in all ethnic groups, but primary MN is more common in men than in women (2:1) and is rare in children. Primary MN has its peak incidence during the fourth and fifth decades of life (Box 20-1). In comparison,

Clinical Features of Membranous Nephropathy
Rare in children: less than 5% of total cases of nephrotic syndrome
Common in adults: 15% to 50% of total cases of nephrotic syndrome, depending on age; increasing frequency after 40
Males > females in all adults groups
Caucasians > Asians > African Americans > Hispanics
Nephrotic syndrome in 60% to 70%
Normal or mildly elevated blood pressure at presentation
"Benign" urinary sediment
Nonselective proteinuria
Tendency to thromboembolic disease*
Other features of secondary causes: infection, drugs, neoplasia, systemic lupus erythematosus

Box 20-1 Clinical features of membranous nephropathy. *Deep venous thrombosis, renal vein thrombosis, and pulmonary embolism.

MN in childhood is more often secondary (e.g., caused by HBV). Primary MN is the most common cause of nephrotic syndrome in nondiabetic Caucasian adults, with an estimated annual incidence of 8 to 10 cases per 1 million population in Western countries. Although association with certain human leukocyte antigen (HLA) class II immune response genes indicated a genetic predisposition,[17-21] primary MN is not a familial disease, except in rare patients with more than one affected family member.[22] The genetic predisposition became more evident after the discovery of PLA_2R as the major antigen, when studies from Korea and Taiwan documented a significant association with non-synonymous single-nucleotide polymorphisms (SNPs)[23,24] in the first C-type lectin-like domain (CTLD) of PLA_2R (Fig. 20-3), a region that is known to undergo conformational changes, as well as another in CTLD7. A subsequent genome-wide association study conducted by a European consortium revealed strong associations with a noncoding SNP in *PLA2R1* (rs4664308) and another in HLA-DQA1 (rs2187668), a member of HLA class II that includes isoforms that predispose carriers to autoimmunity.[25] Although each of these two associated SNPs was significant alone, the odds ratio of MN was almost 80 in individuals who were homozygous for both HLA-DQA1 and *PLA2R1* variants. Other genetic associations have been reported and may contribute to the severity or likelihood of MN progression.[5]

CLINICAL AND SEROLOGIC MANIFESTATIONS

From 70% to 80% of all patients with MN present with the nephrotic syndrome.[26,27] The remaining 20% to 30% present with subnephrotic asymptomatic proteinuria (<3.5 g/24 h). Proteinuria is nonselective. Microscopic hematuria is common (30% to 40%), but red blood cell (RBC) casts are rare and suggest a different glomerular pathologic process. In primary MN, serologic tests for anti-PLA_2R are positive in 75% to 80% of cases,[9,10,28] whereas serum complement levels are normal despite evidence of intraglomerular complement activation, and serologic markers (e.g., antinuclear antibodies, ANCA, rheumatoid factor) are normal or absent. At diagnosis, only 10% to 20% of MN patients have hypertension. Renal function is usually normal at presentation, with only a small fraction (<10%) presenting with renal impairment (Table 20-2). These presenting features can be modulated by age or preexisting hypertension; tubulointerstitial and vascular changes on biopsy may be related to these factors rather than

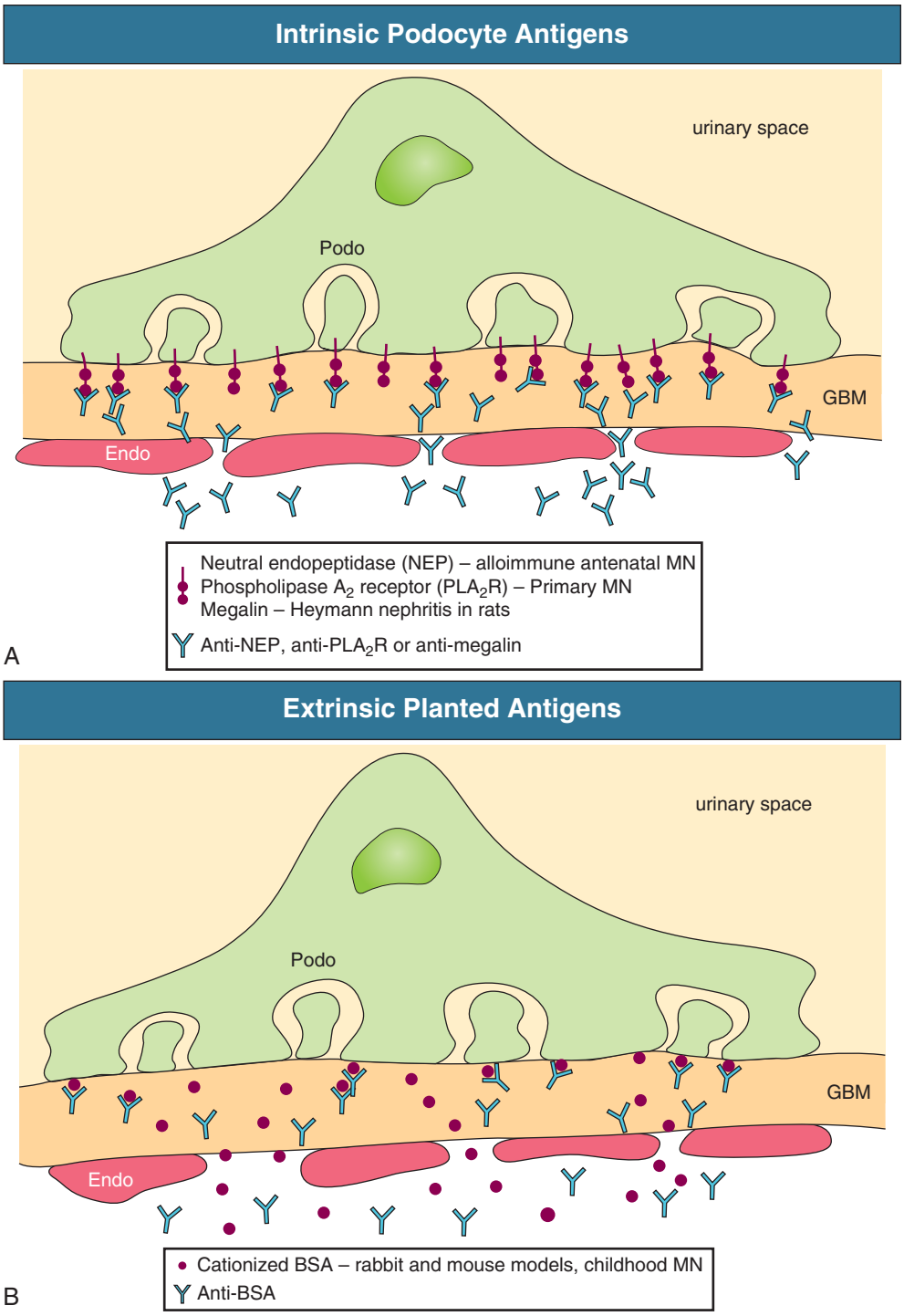

Figure 20-1 Mechanisms of in situ immune complex formation in experimental and human membranous nephropathy (MN). A, Circulating antibodies may cross the glomerular capillary wall and bind to podocyte *(Podo)* antigens exposed on the foot process, as in Heymann nephritis in rats (megalin), alloimmune MN (neutral endopeptidase), and primary MN (PLA_2R). *Endo,* Glomerular endothelial cell; *GBM,* glomerular basement membrane. **B,** Certain extrinsic antigens such as cationized bovine serum albumin *(BSA)* may bind to sites in the GBM and serve as planted antigens and form deposits with circulating antibody.

to the severity of the MN.[29] This is supported by recent evidence that age *per se* does not influence the rate of progression in MN, but does influence the GFR at presentation. Other complications related to the nephrotic syndrome include dyslipidemia, which probably contributes to the increased cardiovascular risk, and a high prevalence (10% to 40%) of thromboembolic events, including renal vein thrombosis.

Recent large MN databases have indicated clinically relevant thromboembolic events occur in the range of 10% of nephrotic MN patients, most frequently in the first 1 to 2 years after presentation.[30,31]

PATHOLOGY

The earliest pathologic feature of MN is the formation of subepithelial immune complexes of IgG and complement along the outer surface of the capillary wall in which glomeruli appear histologically normal and therefore may be mistaken for minimal change nephrotic syndrome, if only light microscopy is performed. MN begins with the formation of immune complexes at the interface of the podocyte and GBM, with subsequent changes in the podocyte, deposition of new extracellular matrix material between and around the immune deposits, thickening of the GBM (membranous change), and in some

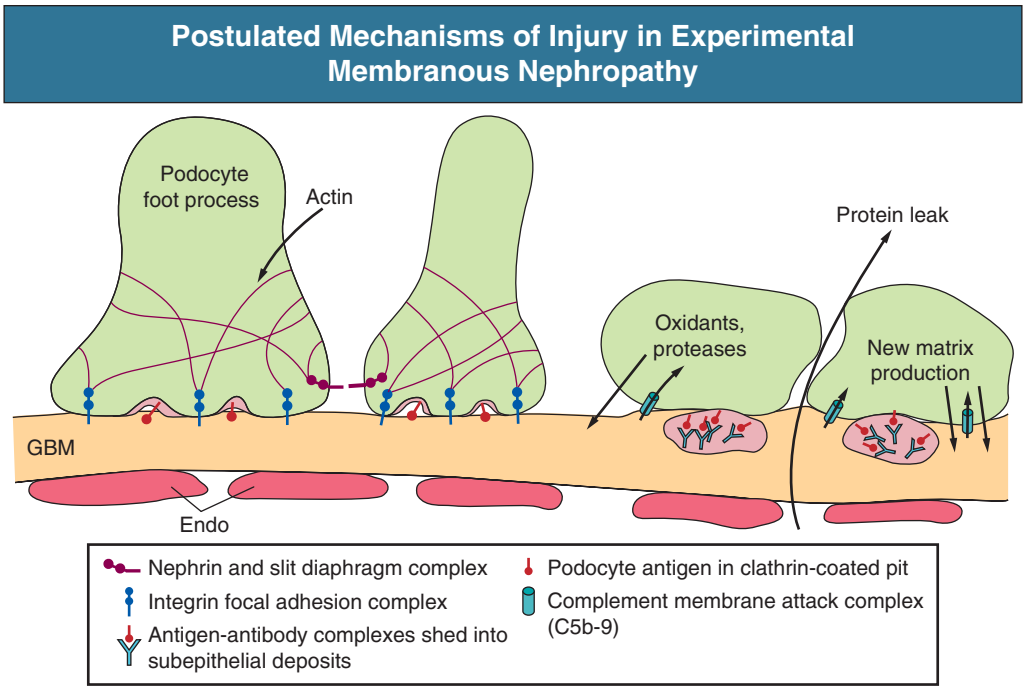

Figure 20-2 Postulated mechanisms of injury in experimental membranous nephropathy. Antibodies against a podocyte antigen in clathrin-coated pits on the foot processes (left podocyte) form complexes that are shed to form deposits in the subepithelial space (right podocytes) and induce complement activation leading to formation of C5b-9. Insertion of C5b-9 is insufficient to cause lysis but stimulates the podocyte to release a host of inflammatory mediators. Disruption of the actin cytoskeleton causes altered cell-matrix adhesion and loss or displacement of slit diaphragms, leading to foot process effacement and loss of the filtration barrier to protein. New matrix production by the damaged podocytes expands the GBM between and around the deposits. *Endo,* Glomerular endothelial cells.

cases, focal glomerulosclerosis, tubular atrophy, and interstitial fibrosis.[2,27]

Light Microscopy

In the earliest stages of MN, the glomeruli and interstitium appear normal on light microscopy, and the diagnosis is made by immunohistology and electron microscopy (Fig. 20-4, *A*). The next stage of MN involves a homogeneous thickening of the capillary wall, seen with light microscopy in sections stained with hematoxylin and eosin or with periodic acid–Schiff (PAS) reagent (Fig. 20-4, *B*). On silver methenamine staining, early projections of the GBM between deposits may be detected in a characteristic spike-like configuration (see Fig. 20-4, *C*). Later, lucencies may develop in the GBM as immune deposits are resorbed, resulting in craters within the thickened GBM.

Leukocyte infiltration is absent in glomeruli in MN, probably because chemotactic products of complement activation follow filtration forces into the urinary space rather than diffusing backward into the capillary lumen, and the intervening GBM prevents immune adherence mechanisms from being operative. As a result, the pathologic lesion of MN is characterized only by changes in podocytes and basement membrane, without associated glomerular hypercellularity.

The podocyte response to this form of injury includes effacement of foot processes visible only by electron microscopy. In general, there are no visible mesangial or endothelial cell abnormalities. The presence of significant mesangial hypercellularity suggests immune deposit formation in the mesangium and is more consistent with a secondary MN, such as class V lupus nephritis (see Chapter 26). In some patients with heavy proteinuria and progressive disease, glomeruli exhibit reduced podocyte numbers and areas of focal sclerosis that are similar to the appearance of secondary focal segmental glomerulosclerosis (FSGS; see Chapter 18). These patients often have a more rapidly progressive course and a poor response to therapy. These sclerotic lesions may be a consequence of glomerular hypertrophy accompanied by an inability of terminally differentiated podocytes to proliferate,[32] leading to areas of denuded GBM, attachment to Bowman capsule, and subsequent capillary collapse. As in all glomerular diseases, tubulointerstitial injury is common and correlates with both renal function and the level of proteinuria. Some studies suggest that the long-term outcome correlates in general with the severity of the tubulointerstitial damage (see Chapter 79).

Immunohistology

The pattern of granular glomerular capillary wall staining for IgG in MN is characteristic and easily recognizable by immunohistology (Fig. 20-5). Positive staining for IgG marks the finely granular subepithelial deposits, which are present on the outer surface of all capillary walls.[2] The predominant IgG subclass in primary MN is IgG4.[33-35] Positive staining for IgG1 or IgG3, IgA, or IgM or significant staining in the glomerular mesangium suggests lupus or other causes of secondary MN as an underlying mechanism.[33-37] Kappa and lambda light-chain staining are typically equal but rare cases of MN due to monoclonal IgG, including anti-PLA_2R have been reported.[38] Complement C3 is also present in most cases of active disease and usually reflects staining for C3c, a breakdown product of C3b that is rapidly cleared. Consequently, positive C3 staining probably reflects active, ongoing immune deposit formation. When sought, staining for C5b-9 is generally present as well, consistent with the proposed pathogenetic role of C5b-9 in this disease.[4] Strong C1q staining is not typically found in primary MN (<20% of cases)[33,39,40] and is more common in lupus-associated MN.[40] Positive staining for C4d in the

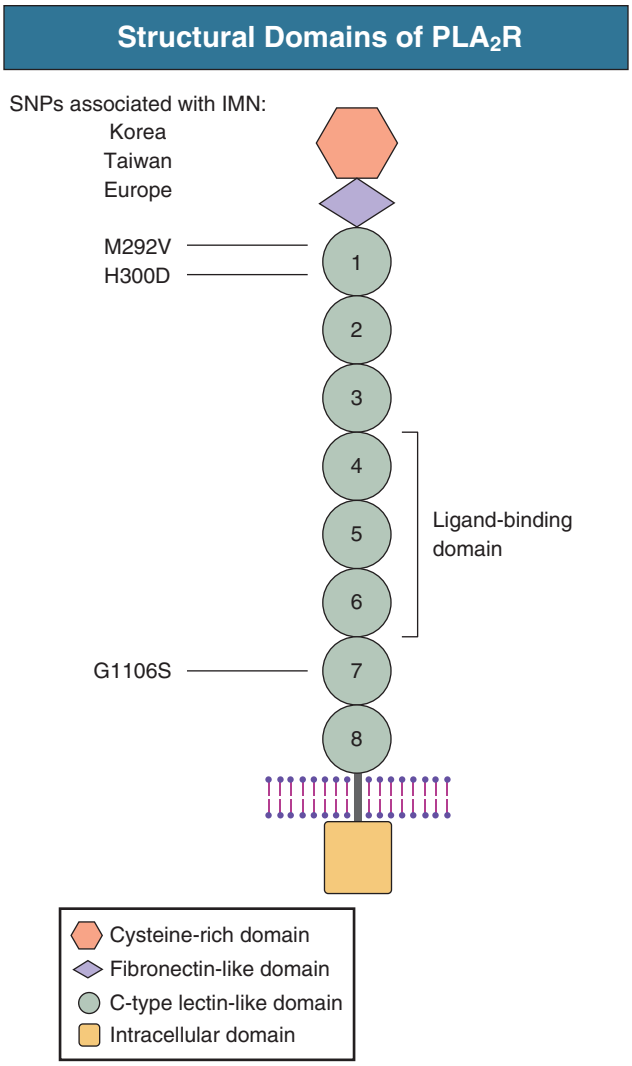

Figure 20-3 Structural domains of phospholipase A_2 receptor (PLA_2R). The M-type phospholipase A_2 receptor is a transmembrane protein and receptor for secretory PLA_2 (CTLD5). The N-terminal region from the cysteine-rich domain through CTLD4 of other members of the mannose receptor family is known to exist in extended or folded configurations. PLA_2R is involved in the production of eicosanoids, reactive oxygen species, DNA damage and cellular senescence. Its role in podocytes is unknown. *SNPs,* Single-nucleotide polymorphisms.

absence of C1q is another feature of primary MN[41,42] and may be consistent with activation of the mannose-binding lectin pathway of complement.[43] Although not used in routine clinical practice, another feature that helps distinguish primary and secondary MN is the presence of PLA_2R staining in the immune deposits in a pattern that co-localizes with IgG in anti-PLA_2R-associated MN but not in secondary MN.[9,12,44] Thus, several histopathologic features help distinguish primary and secondary forms of MN (Table 20-3).

Electron Microscopy

The presence of subepithelial electron-dense deposits by electron microscopy (EM) parallels IgG staining. In primary MN, immune deposit formation occurs in a subepithelial distribution; subendothelial deposits are not seen and mesangial deposits are rare (Table 20-3). These deposits in early stages of the disease process are homogeneous and may even be confluent in some areas, with overlying podocyte foot process effacement and little change in the underlying

Diagnosis and Management of Patients with Membranous Nephropathy

Patient Groups	Test
All patients	Blood pressure Renal function (serum creatinine and creatinine clearance) Urine protein excretion (24-hour urine or urine protein-creatinine ratio) Serum albumin Serum cholesterol, including LDL-HDL ratio Urinalysis Renal biopsy Anti-PLA_2R
Associated disease	Hepatitis B (HBs antigen) Hepatitis C (HCV antibody) Antinuclear antibody (ANA), anti–double-stranded DNA (hallmark of systemic lupus erythematosus) Complement C3, C4 (usually normal in idiopathic MN)
Select Patients	
With suspected thromboembolic events, flank pain, hematuria, acute renal failure	Renal venous Doppler ultrasound Contrast CT, MRI
With sudden decrease in renal function, development of active urine sediment	Anti-GBM antibody Antineutrophil cytoplasmic antibody (ANCA) Assess for interstitial nephritis
Suggestive symptoms or age >50 years	Cancer screening (see text)

Table 20-2 Diagnosis and management of patients with membranous nephropathy (MN). *LDL/HDL,* Low-density/high-density lipoprotein; *Anti-PLA_2R,* anti–phospholipase A_2 receptor antibody; *GBM,* glomerular basement membrane; *CT,* computed tomography; *MRI,* magnetic resonance imaging.

Distinguishing Histopathologic Features of Primary Versus Secondary Membranous Nephropathy

Primary	Secondary
Immunofluorescence Microscopy	
IgG4 > IgG1, IgG3	IgG1, IgG3 > IgG4
IgA, IgM absent	IgA, IgM may be present.
Mesangial Ig staining absent	Mesangial Ig staining may be present.
C1q negative or weak	C1q positive
PLA_2R positive and co-localizes with IgG	PLA_2R negative
Electron Microscopy	
Subepithelial deposits only ± mesangial deposits rarely	Subepithelial deposits ± mesangial and subendothelial deposits

Table 20-3 Histopathologic features that help distinguish primary from secondary membranous nephropathy. *Ig,* Immunoglobulin; *PLA_2R,* phospholipase A_2 receptor.

GBM (stage I). As the disease persists, basement membrane material is laid down between the deposits and corresponds to the spikes seen on light microscopy with use of a silver methenamine stain and are easily visible by EM (stage II; Fig. 20-6, *A*). Later, the spikes extend and the deposits may become surrounded by new basement

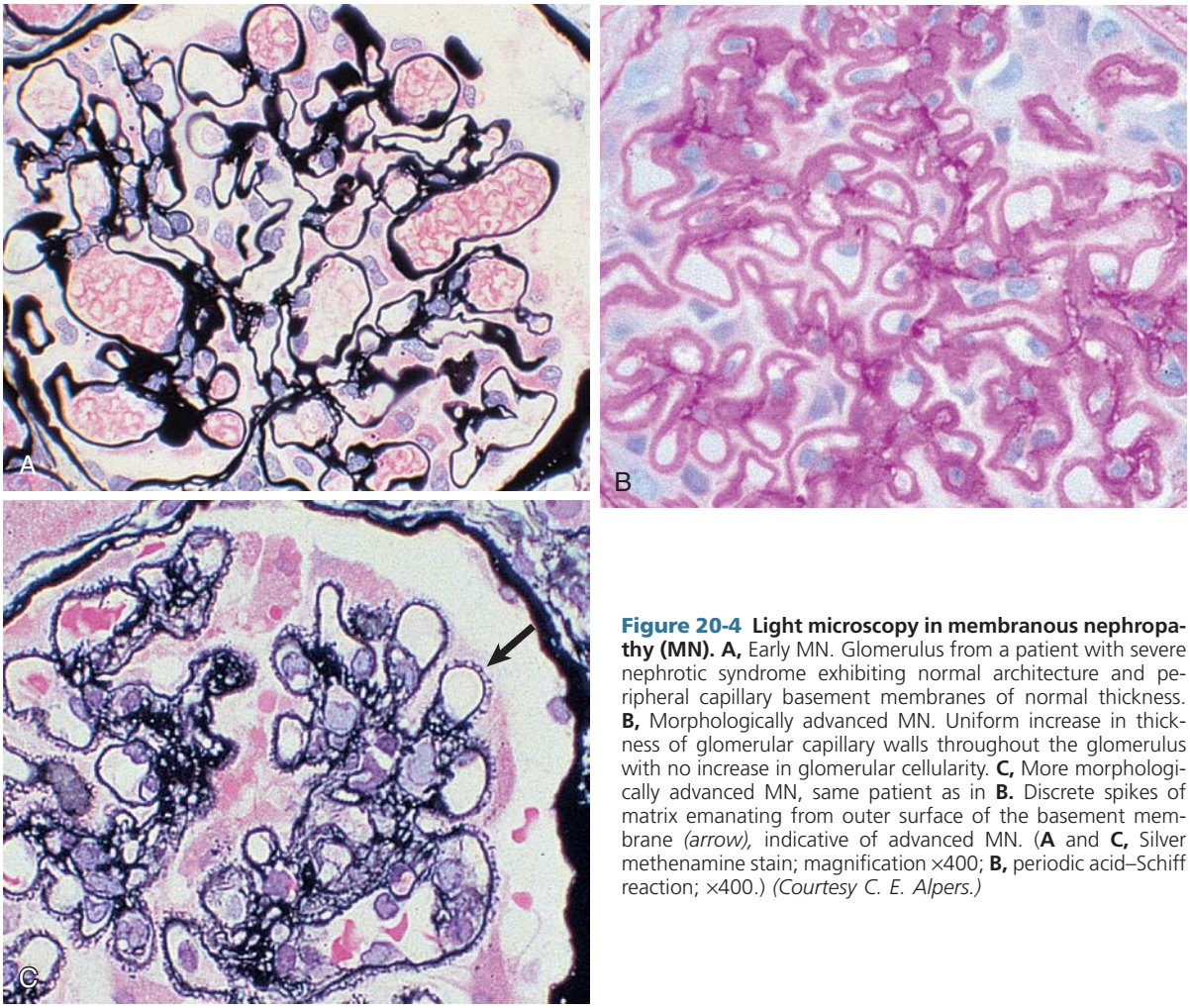

Figure 20-4 Light microscopy in membranous nephropathy (MN). A, Early MN. Glomerulus from a patient with severe nephrotic syndrome exhibiting normal architecture and peripheral capillary basement membranes of normal thickness. **B,** Morphologically advanced MN. Uniform increase in thickness of glomerular capillary walls throughout the glomerulus with no increase in glomerular cellularity. **C,** More morphologically advanced MN, same patient as in **B.** Discrete spikes of matrix emanating from outer surface of the basement membrane *(arrow),* indicative of advanced MN. (**A** and **C,** Silver methenamine stain; magnification ×400; **B,** periodic acid–Schiff reaction; ×400.) *(Courtesy C. E. Alpers.)*

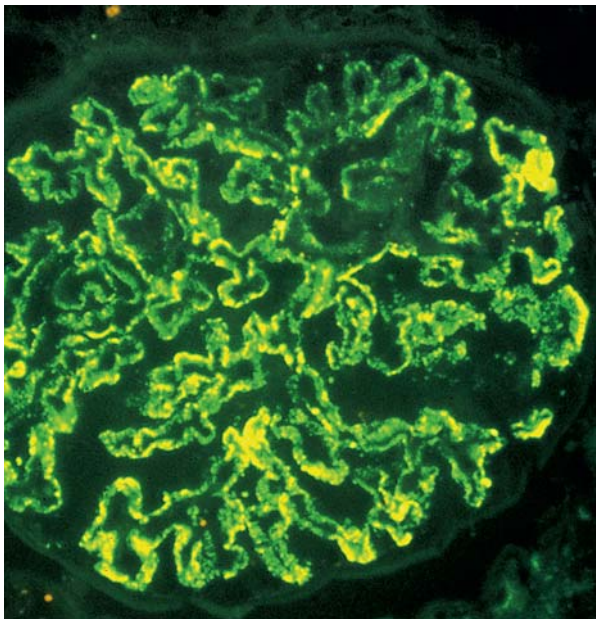

Figure 20-5 Immunofluorescence in membranous nephropathy. Glomerulus with diffuse, finely granular deposition of IgG along outer surface of all capillary walls. The antibody is believed to represent autoantibody directed at some constituent of the podocyte membrane. In primary MN, the antibodies eluted from the glomeruli are reactive with PLA_2R. (Original magnification ×400.) *(Courtesy C. E. Alpers.)*

membrane–like material (stage III; Fig. 20-6, *B*). In stage IV disease, the basement membrane is overtly thickened, the deposits incorporated in it become more lucent, and the spikes are less apparent (stage IV; Fig. 20-6, *C*). Although clearly reflecting the duration of disease, these GBM changes do not correlate well with clinical manifestations or outcome. The overlying podocyte foot processes are effaced with condensation of the actin cytoskeleton; the filtration slits between the foot processes may be occluded; and in those still open, the slit diaphragms may be displaced or disrupted. Microvillous changes of the podocyte membrane are common, as are protein reabsorption droplets within podocytes and proximal tubular cells. The presence of tubuloreticular inclusions in the endothelial cells is strongly suggestive of lupus-associated MN, although these may rarely be found in primary MN as well.[45]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

When the initial presentation includes the nephrotic syndrome, the differential diagnosis includes minimal change disease (MCD), FSGS, membranoproliferative glomerulonephritis pattern of injury (either MPGN type I or dense deposit disease [DDD]), amyloidosis, light-chain deposition disease, lupus nephritis, and diabetic nephropathy. In the 20% to 25% of patients whose initial presentation is asymptomatic non-nephrotic proteinuria, the differential is even more extensive.[46] Although clinical clues in proteinuric patients may increase the likelihood of one specific histologic pattern over another,

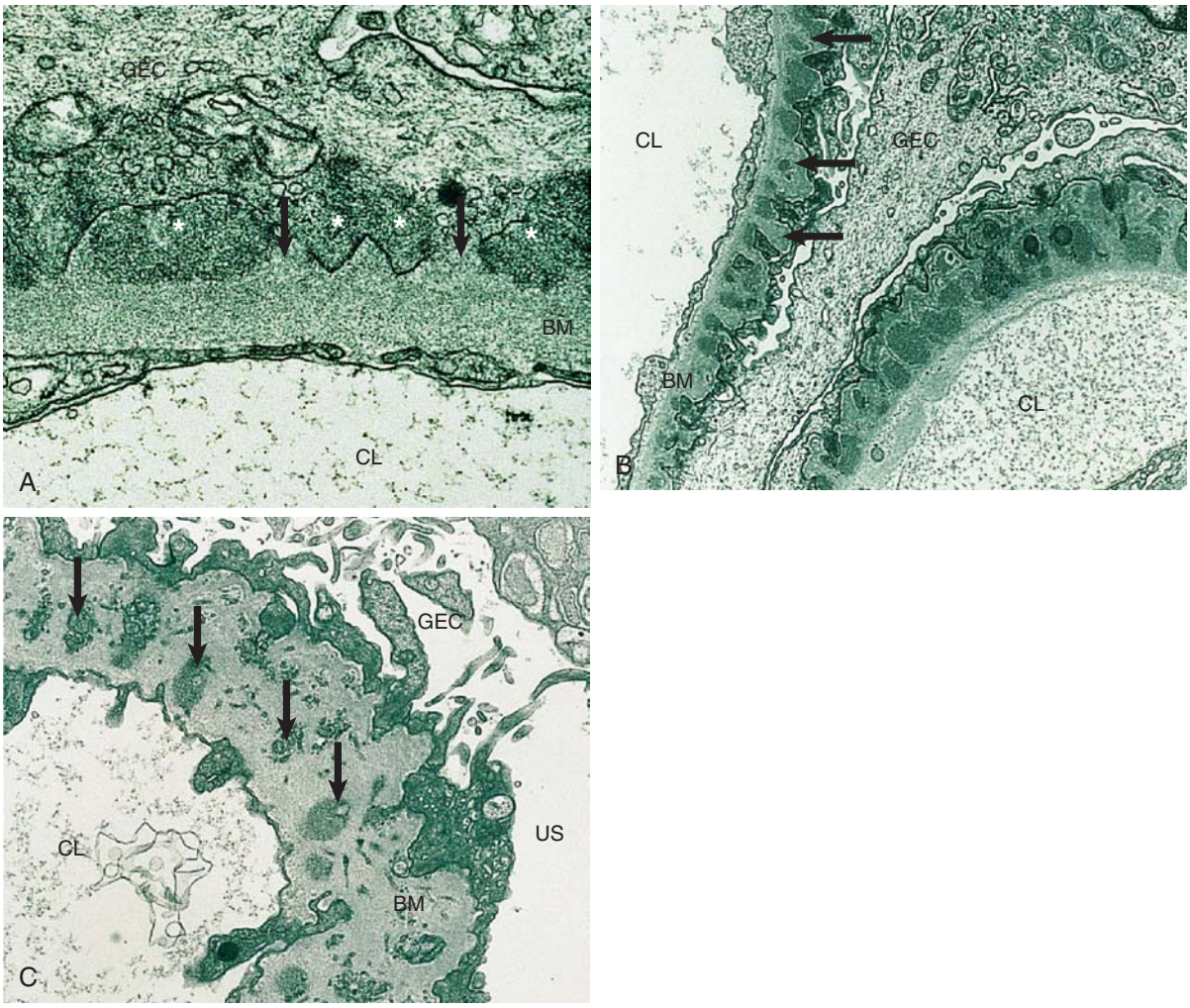

Figure 20-6 Electron microscopy in membranous nephropathy (MN). A, Early (stage II) MN. Glomerular capillary wall with discrete, electron-dense deposits on the subepithelial surface of the basement membrane *(BM)* corresponding to granular deposits of IgG detected by immunofluorescence microscopy (corresponding to light micrograph in *B*). There are diffuse, granular immune complex deposits *(white asterisks)* along outer surface of the capillary wall, with effacement of overlying podocyte foot processes. Small extensions of BM between deposits *(arrows)* are also evident and represent the projections that are seen as spikes by light microscopy with silver methenamine staining. *CL,* Capillary lumen; *GEC,* glomerular epithelial cell. **B,** More advanced (stage III) MN. Two glomerular capillary loops show involvement of the BM by the immune complex deposition *(arrows).* There is prominent membrane synthesis surrounding and incorporating these deposits into the BM (corresponding to spikes seen on silver-stained histologic preparations). Overlying cells continue to demonstrate widespread effacement of foot processes. **C,** Morphologically advanced (stage IV) MN. Capillary BM is diffusely thickened; scattered electron-dense immune deposits *(arrows)* are present throughout its thickness, in addition to scattered subepithelial deposits. Overlying GECs continue to demonstrate effacement of foot processes. *US,* Urinary space. (Original magnifications ×18,000.) *(Courtesy C. E. Alpers.)*

confirmation that MN is the underlying cause of nephrotic syndrome generally requires a kidney biopsy. However, the diagnosis can be made with a high degree of confidence with a positive serologic test for anti-PLA_2R under circumstances in which a biopsy cannot be performed. On the other hand a negative test for anti-PLA_2R does not exclude the diagnosis of idiopathic MN.

Secondary MN represents 20% to 30% of all cases (see Table 20-1); the most common causes are systemic lupus, hepatitis B, malignant neoplasms, and drugs. In addition to a careful history and physical examination, appropriate laboratory evaluation for potential secondary causes should include a complement profile, antinuclear antibodies, hepatitis serology, chest radiography, stool testing for occult blood, mammography in women, and prostate-specific antigen testing with digital rectal examination in men. In women age 20 to 50, a high index of suspicion is warranted for underlying lupus.[47] This diagnosis can be particularly difficult to make because the majority of these patients have no systemic symptoms, and serologic markers of systemic lupus erythematosus are often absent. Membranous lupus accounts for 8% to 27% of cases of lupus nephritis[47] (see Chapter 26).

In adults, regardless of age, malignant neoplasia is an important secondary cause of MN (see Table 20-1). The colon, kidney, and lung are the most common primary sites, and in some patients, the tumor may not have been discovered at presentation with renal disease. Although it is hypothesized that antigens derived from the tumor account for deposit formation and injury in glomeruli, very few tumor-related antigens have actually been demonstrated.

Hepatitis B virus–associated MN is also a common secondary cause in countries where HBV is endemic. It can affect both adults and children who are chronic carriers of HBV (positive HBsAg, HBcAg, and usually HBeAg).[48] This can occur with or without a history of overt liver disease. In children, HBV-associated MN most often presents as the nephrotic syndrome and usually follows a benign course.[49] In adults, progressive renal impairment is a more common outcome. Hypocomplementemia is present in approximately 50% of MN patients with HBV.

Membranous nephropathy secondary to drugs usually resolves after discontinuation of the offending agent.[50,51] The time to resolution, however, varies significantly, from as early as 1 week (e.g., for NSAIDs) to several years for gold or D-penicillamine. Many other renal disorders have been seen in association with or superimposed on MN, including IgA nephropathy, FSGS, crescentic glomerulonephritis (GN) (anti-GBM disease, ANCA vasculitis), acute interstitial nephritis, and diabetic nephropathy.

Preliminary data suggest that the absence of circulating autoantibody to PLA_2R and the pattern of antigen expression of PLA2 at the glomerular level on biopsy favor a secondary etiology of the MN.[12]

CLINICAL COURSE, OUTCOMES, AND COMPLICATIONS

The clinical course of MN varies widely. Spontaneous remissions in proteinuria have been reported in up to 30% of patients. As the severity of proteinuria at presentation increases, the frequency of spontaneous remission appears to decrease. Female gender and lower-grade (non-nephrotic) proteinuria at presentation are the only two features associated with a higher likelihood of spontaneous remission.[19] This is likely to produce a bias in renal survival because the majority of studies reporting 10-year outcomes in untreated patients have included those with subnephrotic proteinuria (<3.5 g/24 h). For example, one study reported a 72% renal survival at 8 years for 100 untreated patients, but 37% of the patients were non-nephrotic at presentation, and more than 50% had less than 5 g/day.[20] In addition, deaths were excluded from the kidney survival analysis. Even so, there was a 25% end-stage renal disease (ESRD) rate by 8 years and almost 50% by 15 years. Thus, patients presenting with less than 3.5 g/day of proteinuria, no RBC casts, no hypertension, normal renal function, and no systemic features suggestive of a secondary cause have a relatively benign prognosis. If no renal biopsy is performed, these patients must be monitored, because up to 50% are likely to develop nephrotic-range proteinuria at some time in the disease course, most within the first 2 years after presentation.

In summary, although the majority of MN patients do reasonably well long term, MN is still the second or third leading cause of ESRD in patients with primary GN. The factor still missing from most MN survival data is the much higher-than-expected mortality from cardiovascular disease or thromboembolic events seen in patients who remain nephrotic. When another renal condition is superimposed on MN, there is often an associated acceleration in the rate of deterioration in renal function. The most common conditions to consider in this setting are drug-induced interstitial nephritis, superimposed crescentic GN including anti-GBM disease, and renal vein thrombosis.

Patients with primary MN who develop ESRD are generally suitable candidates for kidney transplantation, although the disease may recur in up to 50% (see Chapter 108).[52] Recurrence may be asymptomatic and found only on protocol biopsy, but those with recurrence of nephrotic syndrome have a high rate of graft loss. A positive serologic test for anti-PLA_2R at transplantation may forecast early recurrence.[53,54]

Predictors of Poor Outcome

Given the wide variation in the natural history of MN, markers that predict individual outcome would be valuable. Testing for circulating anti-PLA_2R autoantibody has the potential to be critical in this domain as a monitoring tool of MN immunologic activity changing in advance of the classic laboratory parameters.[28,55] Table 20-4 lists the more traditional factors associated with progression and the strength of those associations. Both age and gender influence outcome, with male sex and increasing age associated with a higher risk for renal failure. However, both have limitations.[56] Age seems to be related to the underlying pathologic process at presentation rather than the severity of disease, because age does not influence rate of deterioration in function, and the gender of the patient seems more closely related to the severity of proteinuria at presentation rather than representing an independent risk factor for progression. The severity of chronic changes seen on the biopsy specimen (i.e., degree of glomerulosclerosis, tubulointerstitial fibrosis, and vascular disease) has been associated with a poor prognosis but more closely reflects initial GFR than the subsequent rate of renal functional deterioration.[29] Other pathologic features, including the percentage of glomeruli with glomerulosclerosis and the configuration of the immune deposits (synchronic/single stage or heterogeneous/multistage) on EM, have also been suggested as predictors of both outcome and response to treatment but have not been validated in prospective studies. The degree of renal impairment at presentation has also been found to correlate with long-term renal survival, but a better and more sensitive predictor of long-term prognosis is the ongoing rate of renal function loss, as measured by the decline in creatinine clearance over time.

One of the best models to calculate risk of MN takes into consideration the initial creatinine clearance, the slope of the creatinine clearance during a fixed period, and the lowest level of proteinuria during that observation period[57] (see Table 20-3). This risk score assessment has a reported sensitivity of 60% to 89%, specificity of 86% to 92%, and overall accuracy of 79% to 87%. The model predicts that patients with a normal creatinine clearance at presentation that

Factors Associated with Worse Renal Survival in Membranous Nephropathy

Factors	Predictor	PPV (%)
Clinical Features		
Age	Older > younger	43
Gender	Male > female	30
HLA type	HLA/B18/DR 3/Bffl present	71
Hypertension	Present	39
Serum Levels		
Albumin	<1.5 g/dL	56
Creatinine	Above normal	61
Urine Protein		
Nephrotic syndrome	Present	32
Proteinuria	>8 g for >6 months	66
IgG excretion	>250 mg/day	80
β_2-Microglobulin excretion	>54 μg/mmol creatinine	79
C5b-9 excretion	>7 μg/mg creatinine	67
Biopsy Changes		
Glomerular focal sclerosis	Present	34
Tubulointerstitial disease	Present	48

Table 20-4 Univariate factors associated with worse renal survival in membranous nephropathy. Univariate factors associated with increased likelihood of progression and their positive predictive value *(PPV). (Positive predictive values modified from references 57 and 59.)*

Renal Disease Risk Categories		
Low Risk	**Medium Risk**	**High Risk**
Normal serum creatinine and creatinine clearance plus proteinuria <4 g/day over 6 months of observation	Normal or near-normal creatinine clearance and persistent proteinuria >4 g/day to <8 g/day over 6 months despite maximum conservative treatment	Deteriorating renal function and/or persistent proteinuria >8 g/day for 3 (up to 6) months of observation

Table 20-5 Risk categories of renal disease progression in membranous nephropathy.

remains stable during 6 months, and with persistent proteinuria of less than 4 g/24 h, have less than a 5% chance of progression, and only conservative treatment is recommended. In contrast, those patients with proteinuria that remains above 4 g but less than 8 g/24 h during the same time frame have a 55% probability for development of chronic renal impairment; and those with persistent proteinuria above 8 g/24 h have a 66% to 80% probability of progression to chronic kidney disease within 10 years (Table 20-5). Recent data also suggest that a greater than 50% reduction in the baseline proteinuria estimate at 1 year is an independent predictor of spontaneous remission.[58] Other biomarkers, including urinary α_1-microglobulin, β_2-microglobulin, IgM, and IgG have also been strongly associated with MN progression.[59] These markers measured together at a single time point have a higher positive predictive value than proteinuria alone, but none has yet been validated in an independent data set. However, there is increasing evidence of a relationship to the autoantibody titer. Most recently, for example, high levels of anti-PLA_2R antibodies were found to be associated with active disease and a higher risk of declining renal function than lower levels during follow-up.[28]

Relapse After Complete Remission or Partial Remission

Relapse from a complete remission occurs in approximately 25% to 40% of MN cases with an unpredictable time line. Relapses have been reported up to 20 years after the primary remission. However, the great majority of patients will relapse only with subnephrotic-range proteinuria and will maintain stable long-term kidney function with conservative management alone.[60] In contrast, the relapse rate is as high as 50% in those achieving only a partial remission. Achievement of either a complete or a partial remission, however, significantly slows progression and increases renal survival. A recent review of 348 nephrotic MN patients documented a 10-year renal survival in patients with a complete remission of 100%; with partial remission, 90%; and with no remission, only 45%.[61]

TREATMENT

Nonimmunosuppressive Therapy

Conservative management of MN is directed at control of edema, hypertension, hyperlipidemia, and proteinuria and is similar to that used for nephrotic syndrome of any etiology (see Chapter 15). Blood pressure control is important for both renal and cardiovascular protection. For patients with proteinuria of more than 1 g/day, the target for blood pressure is 125/75 mm Hg unless contraindicated for clinical reasons.[62] Numerous studies have shown that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are cardioprotective and can reduce proteinuria and slow progression of renal disease in both diabetic and nondiabetic patients with chronic nephropathy (see Chapter 80). A recent meta-analysis of the largest renal protection trials using ACE inhibitors showed that the degree of protection is closely correlated to the degree of proteinuria reduction. None of these studies has focused on the specific effect of renin-angiotensin system (RAS) blockade in MN. In secondary analyses, the number of patients with MN has been small, and although the use of ACE inhibitors has been associated with significant improvement in some series, their antiproteinuric effect was modest (<30% reduction in proteinuria) in others.[63] When effective, the benefit of RAS blockade occurs early, usually within the first 3 months of initiation of treatment. Even patients at low risk for progression (proteinuria <4 g/24 h) should be treated with ACE inhibitors or ARBs because this may reduce proteinuria and offer additional renal protection, with minimal risk of significant adverse effect. Patients must also follow a low-salt diet (1.5 to 2 g sodium/day) to achieve the maximum benefit from RAS blockade.

Proteinuria is also an independent risk factor for cardiovascular morbidity and mortality. When the proteinuria is in the nephrotic range, there is a clear increase in cardiovascular risk, with a threefold to fivefold increase in both coronary events and death rates in this population.[64] Patients with significant proteinuria almost always have elevated serum cholesterol and triglyceride levels. Although not proven, we recommend the use of statins to reduce low-density lipoprotein cholesterol to 100 mg/dl (2 mmol/l) or lower[65,66] (see Chapters 80 and 82).

It is recommended that both RAS blockade and lipid control be initiated early in the MN patients, although reaching a goal of complete remission or even partial remission in patients at higher risk of progression (with persistent proteinuria >5 g/24 h) with conservative treatment alone is unlikely. Dietary protein intake may be restricted to 0.8 g/kg/day of high-quality protein,[25] with additional dietary protein (gram per gram) to correct for urinary losses. Dietary protein restriction has been associated with reduced proteinuria (15% to 25%) and a slowing in renal disease progression, but has never been shown to induce a complete remission or to add to effects obtained with RAS blockade. Protein restriction must be carefully monitored in nephrotic patients to avoid malnutrition.

Patients with severe nephrotic syndrome are at increased risk for thromboembolic complications (see Chapter 15). Retrospective reviews have shown that prophylactic anticoagulation is beneficial in reducing fatal thromboembolic episodes in nephrotic patients with MN, without a concomitant increase in the risk of bleeding.[67] No randomized controlled trial (RCT) has ever been done, however, and thus there is no current consensus about prophylactic anticoagulation and no laboratory test that can predict with any accuracy such an event. A thromboembolic event is more likely in certain patients, including those with severe and persistent nephrotic syndrome (proteinuria >10 g/day and/or serum albumin <25 g/l). Two additional recent clinical observations indicate the majority of thromboembolic events occur within the first 2 years of presentation and that there is an increasing likelihood of an event associated with progressively lower levels of serum albumin levels less than 30 g/l.[31] The majority of practicing nephrologists, however, will still wait until a primary thromboembolic event has occurred before using anticoagulants, at least until the level is persistently below 2 g/l, at which point the benefits of prophylactic anticoagulant therapy appear to outweigh the risk.

Other agents that have been tried with modest effects in small numbers of patients with MN include probucol,[68] a lipid peroxidation scavenger, and high-dose intravenous immune globulin, an agent with multiple effects on antibody-mediated tissue injury.[69]

Immunosuppressive Therapy

Several regimens using a variety of immunosuppressive agents have been shown to be successful in reducing proteinuria in MN patients. Many questions remain unresolved, however, including duration of conservative therapy while awaiting a spontaneous remission, determination of when to initiate immunosuppressive therapy, most effective and safest of the available agents, and duration of treatment before futility is assessed.[70] Many of these issues, based on clinically available evidence, are discussed in the recent KDIGO clinical practice guidelines for glomerulonephritis.[71]

The current evidence would support that specific immunosuppressive drug therapy should not be considered unless the patient has had persistent nephrotic-range proteinuria (>4 g/day) and unless the proteinuria has not declined more than 50% from baseline, over a minimum observation period of 6 months, despite maximum antihypertensive and antiproteinuric therapy. Other suggested criteria for early intervention are the presence of severe disabling or life-threatening symptoms related to the nephrotic syndrome or a rise in serum creatinine greater than 30% within 12 months documented as related to disease progression and not a complication such as a renal vein thrombosis, transformation to crescentic MN variant, or interstitial nephritis from diuretics. Recent biomarkers data also suggest that persistent, very high levels of the autoantibody to PLA_2R might be an indication for early intervention.[28]

Corticosteroids

In the three RCTs of corticosteroids in primary MN treatment, the overall consensus has been no significant long-term beneficial effect on proteinuria, rate of disease progression, or renal survival.[72,73] The use of oral corticosteroids as a single agent for the treatment of MN is therefore not recommended. The one exception may be the East Asian (Japanese) population, in whom long-term observational studies have indicated improvement in both proteinuria and renal function preservation with use of corticosteroids as monotherapy.[74]

Cytotoxic Agents Combined with Corticosteroids

In patients at moderate risk of progression, a significant benefit has been described with the combination of a daily oral dose of a cytotoxic agent (cyclophosphamide or chlorambucil) alternating monthly with corticosteroids: methylprednisolone pulses, 1 g intravenously daily for 3 days at the start of months 1, 3, and 5, followed by oral prednisone, 0.5 mg/kg/day for 27 days for 6 months.[75-77] Complete or partial remission of the nephrotic syndrome was seen in almost 80% of treated patients, a threefold to fourfold increase compared with the control group. Both progression rate and renal survival were significantly improved. Both treatment regimens were remarkably safe, although relapses were seen within 2 years in 30% of the treatment group. Similar results were obtained in an RCT ($n = 93$) using this same regimen to treat MN patients of Asian (East Indian) ethnicity.[40] Because the results of a cyclophosphamide-based regimen were similar to one based on chlorambucil,[78] cyclophosphamide is most often used because of a better safety profile.

The most recent RCT in MN studied a select population of 108 patients with documented deteriorating renal function (>20% decline in GFR within 3 to 24 months of study entry).[79] The combination of corticosteroids and a cytotoxic drug (chlorambucil) showed better protection against progressive kidney disease than placebo or cyclosporine. A difficult study to complete, trial entry took 10 years, and of the 108 patients entered, only 42% had 1 year of data, and less than 20% had 3 years of data. There were 117 severe adverse events reported, usually hematologic issues in the chlorambucil group and renal function deterioration in the cyclosporine group and infections in both groups. Statistically, there was a small benefit in terms of preventing further progression in the chlorambucil/corticosteroid group (60% progressed) versus no difference between the cyclosporine compared to the placebo group (80% progressed), a 20% differential. However, the very high dropout rate and inability to manage these therapies safely in MN patients with significantly declining renal function should give pause to applying any of these options under these conditions.[79]

One smaller RCT ($n = 26$) using intravenous cyclophosphamide in patients at high risk of progression (mean creatinine 2.3 to 2.7 mg/day; proteinuria 11 g/day) noted no statistical differences in proteinuria, remission rate, or rate of decline of renal function between the corticosteroid-alone and the combined-treatment group.[80] However, this RCT used monthly intravenous doses of cyclophosphamide rather than the oral regimen used in the Italian and Indian studies and in the recent UK trial.

In older, smaller studies, these cytotoxic agents, even with appropriate adjustments in dose, have produced variable effects on outcome and significant adverse events in a high percentage of patients.[81-83] The most recent longer-term studies in high-risk patients prospectively studied 65 patients with MN and serum creatinine concentration above 1.5 mg/dl treated with oral cyclophosphamide for 12 months and corticosteroids (same as previous regimen).[84-86] Renal survival was 86% after 5 years and 74% after 7 years. Partial remission occurred in 86% of the patients. The relapse rate was similar to earlier cytotoxic-corticosteroid regimens, 30% at 5 years. Treatment-related complications were significant and occurred in two thirds of patients, mainly bone marrow suppression and infections. The majority of adverse events could be managed by dose reduction, although some required permanent discontinuation of treatment.

A recent meta-analysis showed that the use of alkylating agents was associated with higher remission rates (partial or complete remission), but no statistical benefit of cytotoxic drug therapy was demonstrated compared with placebo in rates of ESRD or death.[87] The difficulty with this type of analysis is that the end point of renal survival is far beyond the termination point of most clinical trials. The latest UK study, for example, had few patients still in follow-up after 3 years in any of the three treatment groups, so it was not possible to demonstrate any effect on long-term preservation of renal function.

In summary, cyclophosphamide used in combination with corticosteroids appears to be effective in the treatment of patients with nephrotic-range proteinuria due to primary MN, especially if renal function is well preserved at initiation of therapy. This combination may work even in those with impaired renal function, but the supporting data are much less compelling, adverse effects are higher, and the likelihood of benefit is reduced, especially in patients with advanced renal failure (GFR <30 ml/min).[86] The favorable effects are maintained beyond the 1-year treatment period, but relapse rates approach 35% by 2 years. The adverse effects of long-term cyclophosphamide therapy are the major drawbacks to the universal application of this treatment. These include increased susceptibility to infections, anemia, thrombocytopenia, nausea, vomiting, sterility, and over time, malignant disease. Evidence from the vasculitis literature suggests that the incidence of cancer is increased at a much lower level of exposure than previously considered; the standardized incidence ratio was increased in a number of malignant neoplasms with total cyclophosphamide exposure as low as 36 g (~100 mg/day for 1 year).[88]

Calcineurin Inhibitors

Early uncontrolled studies using the calcineurin inhibitor (CNI) cyclosporine suggested an initial benefit but a high relapse rate.

Cyclosporine may reduce proteinuria not only through its immunosuppressive effects but also by direct effects on the podocyte. In a single-blinded RCT, 51 patients with corticosteroid-resistant MN were treated for 6 months with cyclosporine (2 to 5 mg/kg) plus low-dose prednisone and compared with placebo plus prednisone.[89] Complete remission and partial remission were seen in 75% of cyclosporine-treated patients versus 22% of the placebo controls. Cyclosporine was well tolerated, with no adverse events requiring discontinuation of treatment. However, 38% relapsed within 6 months of discontinuation of treatment.

Only one RCT has used cyclosporine in patients with high-grade proteinuria and progressive renal failure.[90] Both proteinuria and rate of renal function loss were reduced with cyclosporine compared with placebo and when the treatment group was compared to their status 6 months before starting cyclosporine. This improvement in proteinuria was sustained for up to 2 years after cyclosporine was discontinued. The entry criteria included documented GFR decline and high-grade proteinuria, but in contrast to the UK study, the cyclosporine was introduced at a lower dose and slowly increased to minimize toxicity (mean treatment dose 3.5 mg/kg/day). Treatment with longer-term cyclosporine (i.e., 12 months) has resulted in a higher rate of complete remission and partial remission (84%). In addition, persistence of remission was maintained with doses of cyclosporine as low as 1 to 2 mg/kg, although relapses were still common if the cyclosporine level fell below 100 ng/ml. Time to remission with use of cyclosporine varies from a few weeks to several months. This suggests that if no significant reduction in proteinuria (<30%) is noted within 3 to 4 months, a change in therapy should be considered.

Significant adverse effects seen with cyclosporine include hypertension, gingival hyperplasia, gastrointestinal complaints, muscle cramps, and most important, nephrotoxicity, which depends on both dose and duration of treatment. Patients at particular risk are those with initial impaired renal function, especially if accompanied by extensive intrarenal vascular disease or chronic tubulointerstitial damage on biopsy.

In a recently completed 12-month RCT (n = 48), tacrolimus monotherapy was compared with a control group (conservative therapy only).[91] Proteinuria remission was 76% with tacrolimus versus 35% in the control group, and progression rate was also substantially slowed by the CNI. The relapse rate after stopping of the drug, however, approached 50% by the end of 2 years of follow-up.

In summary, both cyclosporine and tacrolimus have been shown to be effective in reducing proteinuria in RCTs of MN. Although relapses are common after short exposure (6 to 12 months), a longer exposure time and lower maintenance doses of CNI can be used to maintain the partial remission state. No studies using CNIs have been of sufficient duration to confirm that maintenance of remission in proteinuria prolongs renal survival. Side effects are substantial, with the major concern being nephrotoxicity. This is particularly common if the medication is not introduced at a low dose and slowly increased until an effective drug level is reached. Clinical experience indicates increased potential for nephrotoxicity with the CNIs if the level of renal function is low (GFR <40% of normal), if there is a high degree of interstitial or vascular pathology accompanying the membranous lesion, or if the patient's renal function is rapidly deteriorating.[71,79]

Mycophenolate Mofetil

Studies using mycophenolate mofetil (MMF) in MN patients report conflicting results. However, even in the most optimistic study, although initial response was high (used in combination with prednisone), the relapse rate within months approached 50%. The most pessimistic study (the only RCT), compared with conservative management only, showed no difference in remission rates in MN patients.[92,93] Follow-up was limited and numbers in the latter study were small, but the reason for the marked differences between these two trials is not clear. In a small, retrospective study in corticosteroid-resistant Asian MN patients, a higher response with MMF was observed, with partial remission rate approaching 50%, possibly related to the ethnic characteristics of the population studied. The role of MMF in the treatment of MN is currently uncertain.

Rituximab

In several pilot studies, rituximab, despite substantial variations in the dose and timing of the drug, consistently reduced proteinuria by 60% to 70%.[94-97] The response rate to rituximab in patients who previously failed immunosuppressive therapy was similar to patients receiving the drug as first-line therapy. A delayed response in proteinuria reduction was seen, similar to cytotoxic therapy, with remissions continuing to occur up to 12 months after the last rituximab infusion. The anti-PLA_2R antibody was measured in both the Mayo Clinic cohorts, and a decline in titer preceded proteinuria reductions by as long as 3 months and was associated with patients subsequently achieving a partial or complete remission compared to those with no change in titer.[55] The relapse rate with rituximab, however, may be significantly less than with CNI or cytotoxic-based regimens. The best predictor of which patients will respond to rituximab is unknown, although the absence of interstitial disease on the biopsy specimen may improve response rate; an RCT is needed. The results of a recently initiated RCT comparing rituximab to cyclosporine are required before widespread use of this agent is advocated, given the high cost and unknown long-term toxicity of rituximab in patients with MN.

Eculizumab

Eculizumab is a humanized anti-C5 monoclonal antibody designed to prevent the cleavage of C5 into its proinflammatory byproducts. An RCT in 200 patients with MN that compared eculizumab with placebo during a total of 16 weeks showed no significant effect on proteinuria or renal function, but effective complement inhibition was not achieved.

Adrenocorticotropic Hormone

Two small studies have reported the use of an intramuscular long-acting synthetic form of adrenocorticotropic hormone (ACTH) in MN.[98,99] The exact mechanism of action of this agent in MN is unknown but likely unrelated to corticosteroid effects because corticosteroids alone are not beneficial in MN. A dose escalation study showed prolonged remission in the majority of MN patients treated with the synthetic form of ACTH, 1 to 2 mg weekly intramuscularly for a year. In a small RCT (n = 32) with a similar dose regimen, ACTH was compared to a standard cytotoxic plus corticosteroids regimen. The remission rate was the same in the two groups, 80% to 90%, but the relapse rate in the ACTH group was lower, 14% versus 30%, after a follow-up of 1 year. Side effects of ACTH were few and included fluid retention, sleep disturbances, and bronze skin discoloration. Potassium supplementation was required in the majority of patients in one trial.[99]

Treatment Summary

Control of proteinuria, specifically achieving either complete or partial remission of the nephrotic syndrome, is associated with prolonged renal survival and a slower rate of renal disease progression in patients with MN. Supportive or conservative care

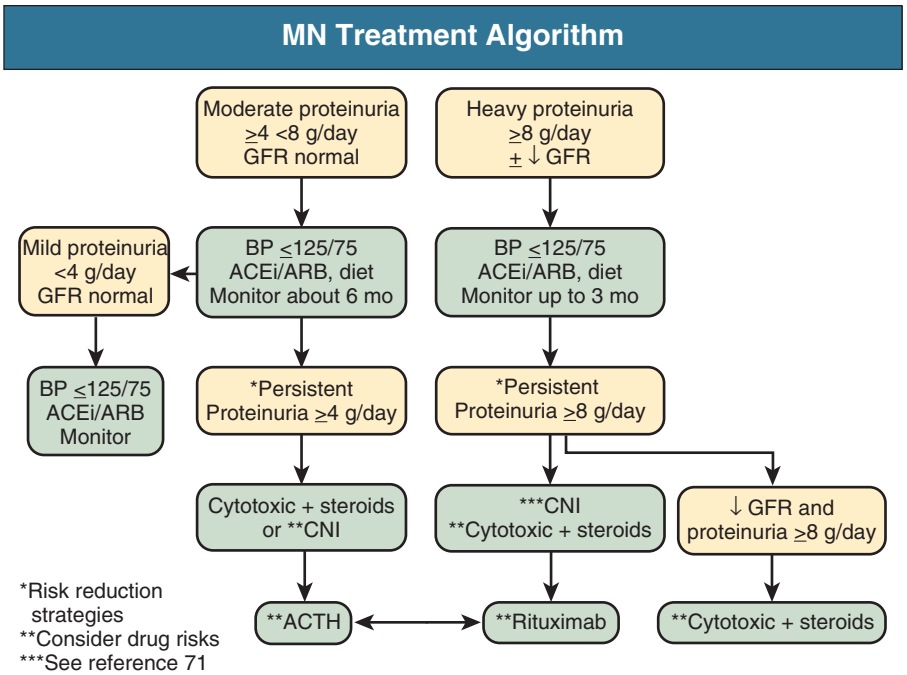

Figure 20-7 Algorithm for treatment of the patient with membranous nephropathy (MN). Details of possible therapies are discussed in the text. *ACEi,* Angiotensin-converting enzyme inhibitor; *ACTH,* adrenocorticotropic hormone; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *CNI,* calcineurin inhibitor; *GFR,* glomerular filtration rate.

should be provided to all patients first, including diuretics, antihypertensive agents such as ACE inhibitors and ARBs (potentially renal protective), and lipid-lowering agents, with lifestyle modifications such as salt restriction, weight normalization, and smoking cessation (see Chapter 80). In MN patients who require disease-specific therapy, the choice of agents remains controversial. Figure 20-7 outlines a suggested management algorithm based on the level and persistence of proteinuria.

Both cytotoxic-corticosteroid combinations and CNIs have proved effective in reducing proteinuria in moderate or high-risk MN patients. The physician, in concert with the patient, must take into account all risk/benefit factors to arrive at the best decision about which of these therapies should be used first. These approaches are not mutually exclusive and can be used in sequence if the first one chosen does not succeed in inducing a remission, or if adverse effects are untenable. Ideally, the approach should leave 2 to 3 months between treatment regimens to help immune system recovery. Alternatively, a second course of the same immunosuppressive regimen could be used, but at the potential cost of cumulative toxicity, or another treatment regimen may be indicated if the patient's risk profile has changed. Although the risks of malignancy from alkylating agents are reduced by limiting treatment to 6 months (especially with the alternating regimen), tobacco smokers are at increased risk of bladder and lung cancer and might be candidates for an alternative treatment regimen. In addition, men wanting to procreate are advised to bank sperm before treatment with alkylating agents.

Preliminary evidence on the use of rituximab or long-acting ACTH suggests that both may be effective and are safer than current regimens, but both need to be assessed further before being widely recommended. Patients with severe renal impairment (GFR <30 ml/min), especially if the MN course has been slowly progressive and histopathology indicates significant interstitial fibrosis and glomerular obsolescence, are less likely to benefit from immunosuppressive therapy, and the risks of treatment may favor conservative therapy as the best option for these patients.

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CHAPTER 21

Membranoproliferative Glomerulonephritis and Cryoglobulinemic Glomerulonephritis

Francesco P. Schena and Charles E. Alpers

DEFINITION

Membranoproliferative glomerulonephritis (MPGN), or mesangiocapillary glomerulonephritis, is characterized by persistent antigenemia and circulating immune complexes, diffuse proliferative lesions involving both the mesangium and the peripheral capillary walls, and widening of the capillary loops, often with a double-contoured appearance expressing a capillary wall remodeling. MPGN may be idiopathic, but primary MPGN is increasingly recognized as a diagnosis of exclusion, with many previously "idiopathic" cases now found to be secondary to chronic infections, cryoglobulinemia, or systemic autoimmune disorders that result in aberrant immune complex formation.

On the basis of electron microscopy (EM) findings, MPGN has been traditionally classified into three categories. Type I was characterized by immune deposits in the subendothelial space and in the mesangium. Type II, now known as *dense deposit disease* (DDD), was characterized by dense deposits within the mesangium and in the basement membranes. Type III was considered a variant of type I (see Pathology). However, a more modern classification has emerged of MPGN based on underlying pathogenetic mechanisms. In this approach, which we follow in this chapter, MPGN is used to describe an immune complex disorder that includes most of those cases formerly considered MPGN type I and some cases of MPGN type III of Burkholder type. Cases of the former MPGN type II (DDD) and type III of Strife and Anders type are considered part of the spectrum of diseases now called *C3 glomerulopathies,* discussed separately in Chapter 22. Some cases formerly considered MPGN type I, in which deposits of complement (C3) are detected but not immunoglobulin, are also best considered as belonging to the class of C3 glomerulopathies, although evidence of alternative complement pathway dysregulation may not always be available for these cases.[1]

ETIOLOGY AND PATHOGENESIS

Membranoproliferative glomerulonephritis denotes a pattern of injury that is similar, whether the disease is primary or not. Therefore, the histologic diagnosis of MPGN should initiate a search for secondary causes[2] (Table 21-1). In older adults (>30 years), MPGN is frequently associated with cryoglobulinemia and hepatitis C virus (HCV) infection.

Membranoproliferative GN is most likely to occur in the setting of chronic immune complex diseases, for example, when the host cannot eliminate a foreign antigen effectively despite a humoral response. This may account for the MPGN observed with chronic blood-borne viral (hepatitis C and hepatitis B), bacterial (endocarditis, infected ventriculoatrial shunt), and malarial infections (see Chapter 57). A histologic pattern resembling MPGN can also be observed in chronic immune complex diseases such as lupus. Chronic immune complex disease and MPGN may also occur if the host has a defect in clearing immune complexes, as in complement deficiency, or when the reticuloendothelial system is impaired, as occurs with liver or splenic disease. Hereditary deficiencies of the classical pathway of complement (C1q, C2, C4) and of C3 may predispose to lupus and bacterial infections, then to development of MPGN. The disease is also associated with some malignant neoplasms, especially chronic lymphocytic leukemia (CLL) and lymphoma.

Membranoproliferative GN results from the glomerular deposition of immune complexes or from *in situ* immune complex formation (see Chapter 16). These complexes preferentially localize in the mesangium and subendothelial space of the capillary walls. Once localized, they typically activate complement through the classical pathway, leading to the generation of chemotactic factors (C5a), opsonins (C3b), and the membrane attack complex (C5b-9), with corresponding lowering of circulating C3 and C4 serum levels. In some patients, complement activation may be enhanced by C4 nephritic factors; in other cases, activation of complement may occur by the mannose-binding lectin (MBL) pathway[3] (Fig. 21-1). Complement activation results in the release of chemotactic factors that promote leukocyte accumulation and direct recruitment of leukocytes by engagement of Fc receptors present on these cells (Fig. 21-2). These features likely are important in the influx of monocytes, a noteworthy feature of MPGN. Leukocytes release oxidants and proteases, mediating capillary wall damage and proteinuria and a decrease in glomerular filtration rate. Cytokines and growth factors released by both exogenous and endogenous glomerular cells lead to mesangial proliferation and matrix expansion.

Cryoglobulins (i.e., immunoglobulins) precipitate in the cold and are categorized as types I to III (Table 21-2). The mixed cryoglobulinemias (types II and III) are most often associated with MPGN and have been strongly associated with chronic HCV infection in up to 80% to 90% of patients with cryoglobulinemic vasculitis.[4] The non-HCV cases have been associated with other infections (chronic hepatitis B, bacterial endocarditis), autoimmune diseases (systemic lupus), and other immunologic disorders (notably postinfectious GN). CLL may also be associated with cryoglobulinemia and MPGN, but cases of CLL and lymphoma also have been associated with MPGN in the absence of cryoglobulinemia.[5]

Many patients with HCV infection and cryoglobulinemia have an IgM-κ monoclonal antibody with rheumatoid factor (RF) activity. Complexes of this IgM RF can be found with anti-HCV and IgG, along with HCV peptides, and HCV RNA can be found in cryoprecipitates from patient serum. It has been postulated that the IgM is produced by dysregulated B cells infected with HCV. Cryoglobulinemia does not develop until many years (often >10) after HCV infection; but by the time chronic active hepatitis or cirrhosis

Etiology of Membranoproliferative Glomerulonephritis and Dense Deposit Disease	
Type	**Secondary Causes**
MPGN Type I	
With mixed (type II or III) cryoglobulinemia	Hepatitis C virus (70%-90% of patients) Other infections: bacterial endocarditis, chronic hepatitis B viral infection Collagen vascular disease: systemic lupus erythematosus, Sjögren syndrome Malignancy: chronic lymphocytic leukemia, non-Hodgkin lymphoma
Without cryoglobulinemia	Bacterial infections: endocarditis, abscess, infected ventriculoatrial shunt Viral infections: hepatitis B, C, and G; human immunodeficiency virus; hantavirus Malarial *(Plasmodium malariae)* Collagen vascular disease (systemic lupus erythematosus, hypocomplementemic urticarial vasculitis) Hereditary complement deficiency (C1q, C2, C4, or C3) Acquired complement deficiency (presence of C4 nephritic factor) Chronic liver disease: especially associated with hepatitis B or C infection, chronic schistosomal infection, with splenorenal shunt for liver fibrosis, and with α_1-antitrypsin deficiency Sickle cell disease Malignancy: chronic lymphocytic leukemia, lymphoma, thymoma, renal cell carcinoma
Dense Deposit Disease (MPGN Type II)	
Associated with C3 nephritic factor (C3 Nef)	With or without partial lipodystrophy and retinal abnormalities
Associated with factor H defect	Inherited mutations of factor H (deficiency) Autoantibodies to factor H
MPGN Type III	
	Secondary causes similar to MPGN type I (hepatitis C or B, and others)

Table 21-1 Etiology of membranoproliferative glomerulonephritis.

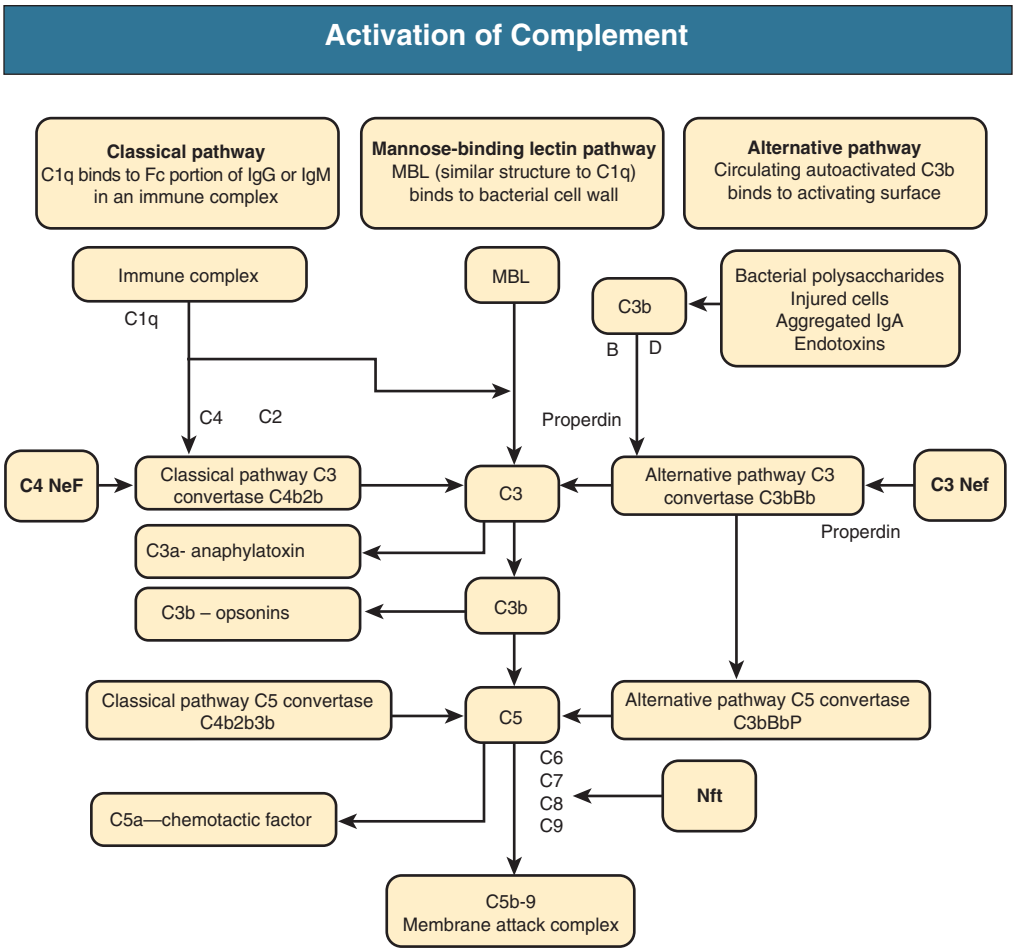

Figure 21-1 Mechanisms in the activation of complement pathways. These activators include nephritic factors *(C4 NeF, C3 Nef); Nft,* nephritic factor of the terminal pathway.

develops, as many as 30% to 40% of patients will have circulating cryoglobulins or other evidence of cryoglobulinemia.[6] Most of these patients will not develop renal disease, but in some, possibly those in whom the cryoglobulins have an affinity for fibronectin, the cryoglobulins containing HCV antigens will deposit in glomeruli.[7]

Specific HCV-related proteins have been detected in glomeruli (Fig. 21-3), tubulointerstitium, and vessels in patients with cryoglobulinemic HCV-positive MPGN,[8] although difficulties with the antisera available to detect HCV render such findings controversial. Glomerular HCV deposits have displayed two different patterns: (1) a linear homogeneous deposition along glomerular capillary walls, including endothelial and subendothelial spaces, and (2) a granular appearance on immunofluorescence microscopy with distinct deposits in mesangial and paramesangial areas. IgG, IgM, and C3 deposits have a distribution comparable to those of HCV RNA and core protein deposits, suggesting that in cryoglobulinemic HCV-positive MPGN, deposits consist of HCV-containing immune complexes that may directly contribute to renal damage.[9] Further pathogenetic insight will likely be provided by new murine models, including the transgenic thymic stromal lymphopoietin (TSLP) mouse, which develops mixed cryoglobulinemia and MPGN.[10] Monocytes/macrophages appear to mediate progression of renal damage in this model.[11]

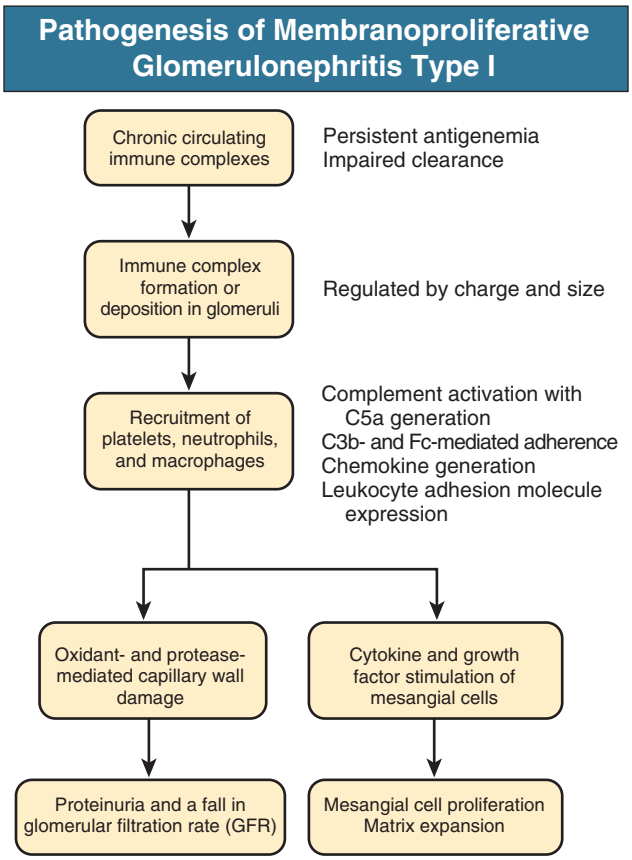

Figure 21-2 **Pathogenesis of MPGN type I.**

EPIDEMIOLOGY

In North America and Europe, MPGN constitutes less than 5% of all primary glomerulopathies. MPGN accounts for 5% to 10% of primary renal causes of nephrotic syndrome in children and adults.[12] Affecting males and females equally, MPGN in the United States is relatively more common in Caucasians than African Americans.

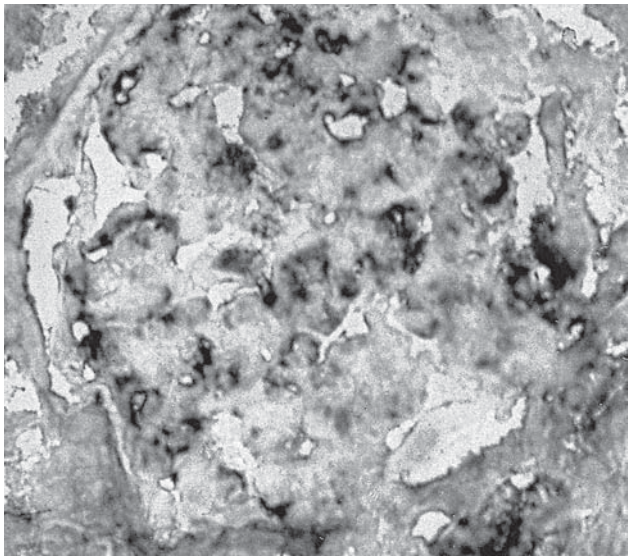

Figure 21-3 **Hepatitis C virus (HCV)–related antigen (c22-3).** In capillary wall of glomerulus from patient with cryoglobulinemic membranoproliferative glomerulonephritis (MPGN). (Light microscopy; magnification ×3100.)

Classification of Cryoglobulins

Type	Composition	Associated Disease
I	Monoclonal IgG, IgA, or IgM	Multiple myeloma (IgG, IgM) Chronic lymphocytic leukemia Waldenström macroglobulinemia (IgM) Idiopathic monoclonal gammopathy Lymphoproliferative disorders
II	Polyclonal IgG and monoclonal IgM (with rheumatoid factor activity)	Hepatitis C virus Neoplasms: chronic lymphocytic leukemia, diffuse lymphoma, B lymphocytic neoplasia Mixed cryoglobulinemia
III	Polyclonal IgG and polyclonal IgM	Infections: viral (hepatitis B and C, Epstein-Barr virus, cytomegalovirus), bacterial (endocarditis, leprosy, poststreptococcal glomerulonephritis), parasitic (schistosomiasis, toxoplasmosis, malaria) Autoimmune disorders: systemic lupus erythematosus, rheumatoid arthritis Lymphoproliferative disorders Chronic liver disease Mixed cryoglobulinemia

Table 21-2 **Classification of cryoglobulins.**

MPGN remains the most common cause of GN in many developing countries, especially in Africa and South America (such as Peru).

The renal biopsy registries show a declining incidence and prevalence of MPGN in the last 40 years in industrialized countries, whereas it remains common in developing countries, where the occurrence of infections is high. The disease may be familial in rare cases, and different histologic lesions may occur in family members.

CLINICAL MANIFESTATIONS

Membranoproliferative GN may present as microhematuria and non-nephrotic proteinuria (35%), as nephrotic syndrome with minimally depressed renal function (35%), as a chronically progressive GN (20%), or as a nephritic syndrome with rapidly deteriorating renal function with proteinuria and red blood cell casts (10%). Hypertension is present in 50% to 80% of patients, occasionally so severe that the presentation may be confused with that of malignant hypertension.

Pediatric Population

When presenting in childhood, primarily between ages 8 and 14 years, MPGN is usually idiopathic. Previously reported series have frequently included both immune complex–mediated MPGN and DDD together in characterizing the features of MPGN in children. Asymptomatic Japanese children diagnosed through a urinalysis screening program at school had lower blood pressure, proteinuria, and serum creatinine concentration than individuals diagnosed after presenting with symptoms.[13] Thus, early identification of the disease by urinary screening may allow early treatment.

Adult Population

When presenting in adults, MPGN is most often associated with cryoglobulinemia and HCV infection. Such patients usually present with the triad of weakness, arthralgias, and purpura. The arthralgias are only rarely accompanied by arthritis, are usually symmetric, and classically involve the knees, hips, and shoulders. The purpura is usually painless, palpable, and nonpruritic, occurring in "crops" that last 4 to 10 days, and preferentially localizes to the extremities (Fig. 21-4). Other manifestations may include ulcerative, vasculitic lesions that classically involve the lower extremities (Fig. 21-4) and buttocks (Fig. 21-5), Raynaud phenomenon, digital necrosis (Fig. 21-6), peripheral neuropathy, hepatomegaly, and rarely signs of cirrhosis (clubbing, spider angiomas, ascites). Although most patients with cryoglobulinemia have a chronic waxing and waning course, occasional patients may have a more fulminant presentation, with congestive heart failure (from an HCV-induced cardiomyopathy), infiltrates in the lung from deposition of cryoglobulins (Fig. 21-7), pulmonary hypertension, severe systemic hypertension, or mesenteric ischemia.

In view of the conditions associated with MPGN, signs of bacterial infection, viral infection, systemic lupus, malignant disease, and chronic liver disease should be sought (see Table 21-1).

Laboratory Findings

Membranoproliferative GN is often associated with depressed complement levels (C3 and total hemolytic complement [CH50]). In immune complex–mediated MPGN and in cryoglobulinemic MPGN, the classical pathway is often activated (with low circulating levels of C3, C4, and CH50). C3 nephritic factor (C3Nef) activity, strongly but not exclusively associated with DDD, is sometimes detected in plasma by the hemolytic test or the C3Nef IgG solid-phase assay.[14] The presence of C3Nef should prompt genetic analyses of complement factors, whereas RFs or cryoglobulins should prompt testing for anti-HCV antibody and HCV RNA. However, MPGN can be associated with HCV infection in the absence of cryoglobulinemia or RFs.[15] Failure to detect the cryoglobulins may result from improper specimen handling or transient cryoglobulinemia; however, in some patients, especially renal transplant recipients, test

Figure 21-4 Purpura in patient with HCV-associated cryoglobulinemia. Raised purpuric lesions are present on the legs of this individual. The differential diagnosis of purpura and renal disease includes cryoglobulinemia, Henoch-Schönlein purpura, vasculitis, and endocarditis.

Figure 21-5 Purpura in patient with HCV-associated cryoglobulinemia. Purpuric lesions are present on the patient's buttocks and thigh. Interestingly, note the purpuric lesions along the superior and inferior elastic border of the undergarment line.

results for cryoglobulinemia may be persistently negative. Serum and urine electrophoresis, immunofixation tests, and free light-chain assays may be required to exclude the presence of a monoclonal gammopathy in older persons. In patients with positive tests, a bone marrow aspiration is necessary for a more precise diagnosis. Tests for autoimmune disease must be included. Clinical or laboratory evidence of liver disease should prompt a search for causes of chronic liver disease, including hepatitis C, hepatitis B, and if appropriate, rare entities such as schistosomiasis and α_1-antitrypsin deficiency. Laboratory tests to detect infection include blood cultures, polymerase chain reaction, and serologic tests for bacterial, viral, and fungal infections.

Figure 21-6 Necrosis in patient with cryoglobulinemia. Distal portion of the little finger is necrotic in a young woman with essential mixed cryoglobulinemia.

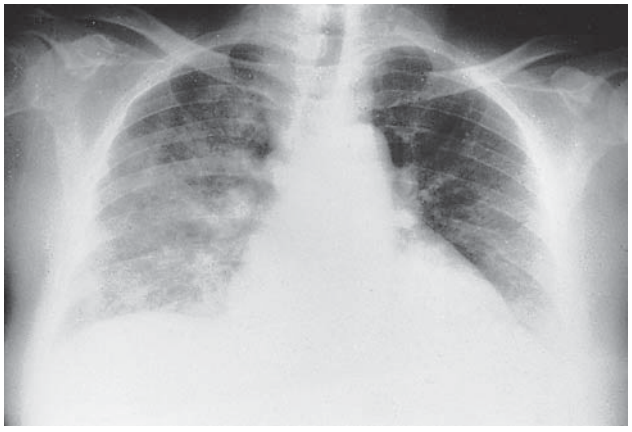

Figure 21-7 Lung infiltration in patient with hepatitis C. Chest radiograph shows nodular infiltrates in the lung secondary to cryoglobulinemic vasculitis in a patient with HCV infection.

PATHOLOGY

On light microscopy, MPGN is classically described as *hypercellular* because of both the influx of circulating leukocytes, in particular monocytes and macrophages, and the intrinsic glomerular cell proliferation, typically mesangial cells, leading to a characteristic accentuation of the normal glomerular lobular architecture[2,16] (Fig. 21-8, *A*). Accumulation of extracellular material, predominantly matrix, contributes further to the frequent mesangial expansion. The glomerular appearance can range from extremely hypercellular to predominantly sclerotic. In its most advanced form, sclerosis can manifest as nodules indistinguishable from diabetic nodular mesangial sclerosis. Silver stain often shows a double contouring of the glomerular basement membrane (GBM) ("tram tracks") as a result of the interposition of mesangial cells, leukocytes, or endothelial cells in the capillary wall with the synthesis of new basement membrane material (Fig. 21-9).

Immunofluorescence in MPGN frequently shows the deposition of IgG, IgM, and C3 in a granular capillary wall distribution (Fig. 21-8, *B*), although the immunoglobulin deposits may be scant. Staining for C3 in a peripheral (lobular) pattern involving capillary walls and mesangial areas is the most constant and strongest pattern, but when present in isolation, should prompt consideration of C3 glomerulopathy (see Chapter 22). Staining for classical pathway complement components (C1q, C4) may also be seen in MPGN. EM reveals discrete immune deposits in the subendothelial portions of the capillary walls and mesangial regions in MPGN, often in association with leukocyte infiltration (Fig. 21-8, *C*). The deposits are often discrete but may be confluent in their involvement of the capillary wall. Deposits can be small and sparse or so large and numerous that they are visible by light microscopy. A separation of the endothelium from the GBM can occasionally be observed, usually with some synthesis of new basement membrane material under endothelial cells that have detached from the original basement membrane. Between these layers (old and new) of basement membranes, interposed cells of mesangial, endothelial, or leukocyte origin may be found, as well as immune deposits and matrix.

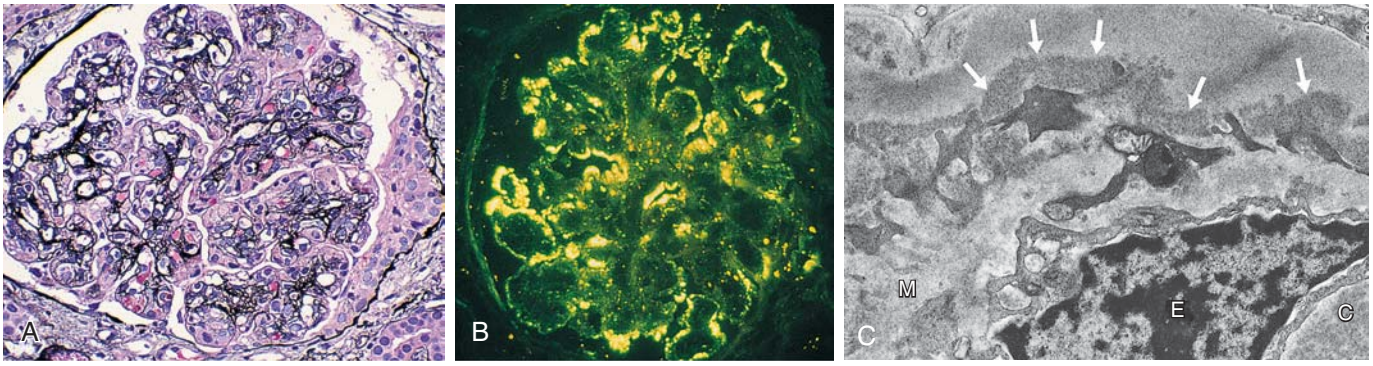

Figure 21-8 Pathology of membranoproliferative glomerulonephritis (MPGN) type I. A, Light microscopy shows a hypercellular glomerulus with accentuated lobular architecture and a small cellular crescent (methenamine silver stain). **B,** Immunofluorescence usually shows discrete, granular staining of the peripheral capillary wall for IgG (seen here) and C3 and occasionally for IgM and earlier complement components (C1q and C4). **C,** Electron microscopy shows numerous subendothelial deposits *(arrows)* between the duplicated basement membrane that extend into the mesangium *(M); C,* capillary lumen; *E,* endothelial cell nucleus.

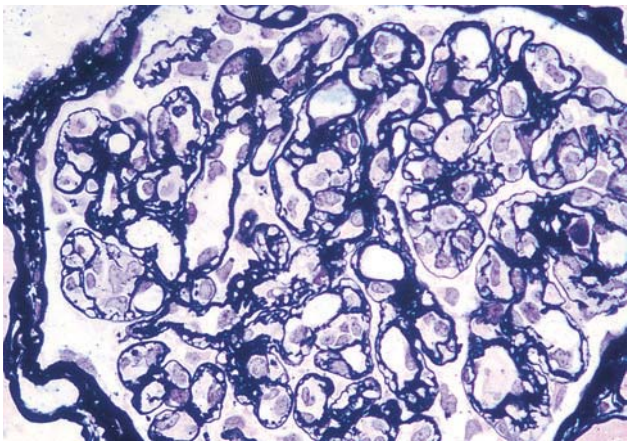

Figure 21-9 "Tram tracks" in MPGN type I. Silver staining shows a double contouring of the glomerular basement membrane (GBM) can be observed in MPGN type I, resembling tram tracks.

Type I and type III MPGN are long-established terms to subclassify MPGN on the basis of pathologic appearance, but these cases form a morphologic continuum and thus are not always separable by light microscopy. Type I and type III MPGN were historically distinguished on the basis of some differences in the location of immune deposits in glomerular capillary walls, as revealed by EM. However, once cases of C3 glomerulopathy have been removed from the category of MPGN, it is doubtful whether this ultrastructural distinction has any value in defining etiology, and it does not modify clinical management. Perhaps 15% of MPGN cases demonstrate both subendothelial and subepithelial deposits associated with minute disruptions of the lamina densa and newly elaborated lamina densa–like material (formerly called MPGN type III). Furthermore, there can be a continuum of subepithelial deposits in MPGN type I and type III from none or scanty to numerous, making it difficult to separate all cases into type I (scanty or no subepithelial deposits) or type III (numerous deposits) categories using this classification system.[17] Therefore, in transitioning to a more pathogenetically based classification system for MPGN, the use of the terms MPGN type I, II, or III is no longer advocated.

Cryoglobulinemic MPGN may appear histologically identical to MPGN type I. However, the cryoprecipitates can occasionally be observed by light microscopy as intracapillary hyaline-like globules (Fig 21-10, *A*), and there is often a more pronounced infiltration of macrophages within capillary lumina. EM may also show highly organized microtubular or finely fibrillar structures consisting of the precipitated cryoglobulins (Fig. 21-10, *B*).

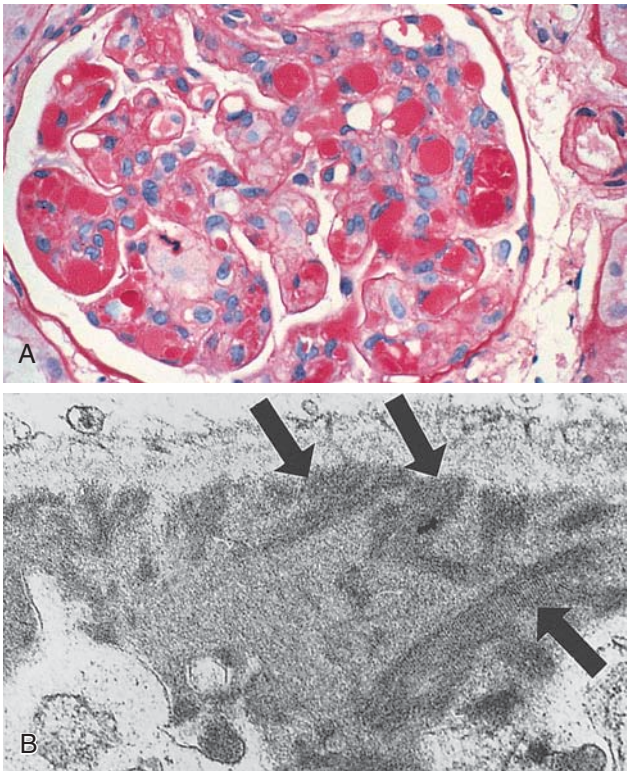

Figure 21-10 Pathology of cryoglobulinemic MPGN. A, Although cryoglobulinemic MPGN may histologically appear similar to MPGN type I (see Fig. 21-8), discrete precipitates of cryoglobulins may occasionally be found occluding individual capillary loops. **B,** In addition, electron microscopy shows organized fibrillar or tubular structures consistent with cryoglobulins *(arrows)*. (***B** from reference 31, Copyright © 1993 Massachusetts Medical Society.) (All rights reserved.)*

Diseases that Histologically Resemble Membranoproliferative Glomerulonephritis

- Paraproteinemias: especially fibrillary glomerulonephritis, light-chain nephropathy
- Thrombotic microangiopathies: hemolytic uremic syndrome, scleroderma, radiation nephropathy, malignant hypertension
- Glomerulosclerosis in liver diseases
- Postinfectious glomerulonephritis
- "Transplant" glomerulopathy
- Rare diseases: collagen III glomerulopathy, C1q nephropathy, lipoprotein nephropathy

Box 21-1 Diseases that histologically resemble MPGN.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Membranoproliferative GN is diagnosed by renal biopsy in patients presenting with nephrotic or non-nephrotic proteinuria, accompanied by microhematuria, or by nephritic syndrome. On light microscopy, other entities may appear histologically similar, including diffuse lupus nephritis, poststreptococcal GN, the thrombotic microangiopathies, paraproteinemias, and fibrillary GN (Box 21-1). Immunofluorescence and EM are essential for separating these diseases. Systemic lupus usually can be eliminated by serologic testing.

Low complement levels can also be observed in atheroembolic renal disease (low C3 with eosinophilia), in thrombotic microangiopathy, in chronic liver disease (because of decreased synthesis), and in several glomerular diseases, including systemic lupus (low C3 and C4) and poststreptococcal GN (low C3). The detection of C3Nef activity in plasma suggests DDD, but C3Nef can also be identified in a proportion of patients with MPGN and even in healthy individuals. Once MPGN is diagnosed, careful evaluation for secondary causes should be conducted (see Table 21-1 and Chapter 57).

NATURAL HISTORY

Idiopathic MPGN in childhood has a relatively poor prognosis, with 40% to 50% of untreated patients progressing to renal failure over

10 years. Idiopathic MPGN in adults also carries an unfavorable prognosis. Five years after biopsy, 50% of patients either die or need renal replacement therapy (dialysis or transplantation). This proportion increases to 64% after 10 years. Risk of progression increases with elevated creatinine, nephrotic proteinuria, and severe hypertension, or if a biopsy specimen shows more than 50% crescents or marked interstitial fibrosis.[18] Patients with nephritic syndrome and high C1q staining in glomerular deposits have a poor prognosis.[19]

TRANSPLANTATION

The severity of crescent formation in native kidney biopsy specimens has predictive value for recurrence of disease in subsequent renal allografts.[20,21] For further discussion of recurrent MPGN in kidney transplantation, see Chapter 108.

TREATMENT

The initial approach to the patient with MPGN seeks to identify the etiology, if possible, and initiate supportive antiproteinuric and antihypertensive measures. Treatment plans for the various types of MPGN are discussed in the following sections (Table 21-3).

Idiopathic Membranoproliferative Glomerulonephritis in Children and Adults

For patients with normal renal function and asymptomatic nonnephrotic–range proteinuria, supportive antiproteinuric and antihypertensive measures only are required (see Chapter 80). Close follow-up every 3 to 4 months is recommended.[22] In adults or children with presumed idiopathic MPGN accompanied by nephrotic syndrome and a progressive decline of kidney function, oral cyclophosphamide or mycophenolate mofetil (MMF) plus low-dose alternate-day or daily corticosteroids has been suggested, with initial therapy limited to less than 6 months.[23] These drugs in combination with high-dose pulse corticosteroids have also been administered in patients with a rapidly progressive course and crescents on renal biopsy. In an alternative approach, in patients with nephrotic syndrome and normal or impaired renal function, a 3- to 6-month course of corticosteroids (prednisone 1 mg/kg/day) may be prescribed. If there is considerable reduction of proteinuria, corticosteroids may be continued at the minimal effective dose.

Rituximab (1 g intravenously on days 1 and 15) has been administered in four adult patients with idiopathic MPGN unresponsive to previous immunosuppressive drugs, with two complete and two partial remissions.[24] Eculizumab, which inhibits C5 activation, recently was used for MPGN type I refractory to previous immunosuppressive therapy and normalized the kidney function and resolved proteinuria.[25]

Hepatitis B Virus–Associated Membranoproliferative Glomerulonephritis

In hepatitis B virus (HBV)–associated MPGN, treatment with antiviral agents aimed at eradication of HBV is the recommended initial treatment. Immunosuppressive agents are discouraged because they promote further HBV replication and occasional deterioration of hepatic function (see Chapter 57).

Hepatitis C Virus–Associated Membranoproliferative Glomerulonephritis and Cryoglobulinemia

Treatment options in mixed cryoglobulinemia with renal involvement include corticosteroids, cytotoxic drugs such as cyclophosphamide, rituximab, and antiviral therapy (see Chapter 57). Subcutaneous administration of pegylated interferon alfa-2a or alfa-2b often improves extrarenal manifestations associated with reduced levels of viremia, but relapse is common after cessation of therapy. The current treatment of choice in patients with HCV-associated MPGN or cryoglobulinemic MPGN with moderate proteinuria and nonrapid but progressive renal failure is pegylated interferon alfa-2a (180 μg every week) or alfa-2b (1.5 μg kg^{-1} every week) and ribavirin (800 to 1200 mg/day in two divided doses), adapting the dose to the stage

Suggested Management of Membranoproliferative Glomerulonephritis

Type	Treatment
All types	Supportive therapy following recommendations discussed in Chapter 80
Idiopathic MPGN in children	Non-nephrotic proteinuria, normal renal function: follow with 3-month visits Normal renal function and moderate proteinuria (>3 g/day): prednisone 40 mg/m^2 on alternate days for 3 months Nephrotic or impaired renal function: prednisone 40 mg/m^2 on alternate days (maximum 80 mg) for 2 years, tapering to 20 mg on alternate days for 3-10 years
Idiopathic MPGN in adults	Non-nephrotic, normal renal function: follow with 3-month visits Nephrotic or impaired renal function: 6-month course of corticosteroid with/without cyclophosphamide, cyclosporine, tacrolimus, or mycophenolate (MMF) Rapidly progressive renal failure with diffuse crescents: treat as for renal-limited pauci-immune crescentic GN (see Chapter 25) In the presence of heavy proteinuria: ACE inhibitors
MPGN associated with HCV or cryoglobulinemia	Non-nephrotic, normal renal function: treat with interferon alfa (see Chapter 57) based on severity of liver disease (diagnosed by biopsy) Nephrotic syndrome, reduced renal function, or signs of cryoglobulinemia: pegylated interferon alfa-2b (1 μg/kg weekly) and ribavirin (15 mg/kg/day) for 12 months, followed by short-term course of low-dose corticosteroids; if relapse occurs, consider high-dose interferon alfa (10 million U daily for 2 weeks, then every other day for 6 more weeks). Rapidly progressive renal failure or severe symptoms of vasculitis (heart failure, pulmonary disease): methylprednisolone (1 g/day) for 3 days, followed by oral prednisone (60 mg/day) with slow taper over 2-3 months Cyclophosphamide (2 mg/kg/day with adjustment for renal function) and cryofiltration may be added as adjunctive therapy; when prednisone reduced to 20 mg/day and cyclophosphamide discontinued, add interferon alfa. MPGN in renal or liver transplant recipient: consider course of oral ribavirin (0.6-1 g/day).

Table 21-3 Suggested management of membranoproliferative glomerulonephritis (MPGN).

of chronic kidney disease.[26] Patients with genotypes 1 and 4 should receive 48 weeks of interferon therapy if an early viral response is obtained at 12 weeks (>2 log fall in viral titer). The added use of protease inhibitors so far has been largely restricted to patients without renal impairment. Genotypes 2 and 3 should be treated for 24 weeks. High-dose pegylated interferon alfa may cause severe influenza-like symptoms, depression or psychosis, development of hypothyroidism, and rarely development of proteinuria (with minimal change type of lesion). The most frequent serious adverse effect of ribavirin is hematopoietic toxicity as well as hemolytic anemia and teratogenic effect.

Rituximab, a CD20 antibody selectively targeting B cells, seems to be as efficient as cyclophosphamide in blocking cryoglobulin production, is better tolerated, and does not enhance HCV replication. Rituximab should be administered at a dose of 375 mg/m^2/week for 4 weeks.[27,28] Alternatively, oral cyclophosphamide may be used (2 mg/kg/day for 2 to 4 months).

In patients with nephrotic-range proteinuria or progressive renal failure, the anti-HCV therapy is the same. Moreover, treatment may include plasma exchange (3 liters of plasma three times weekly for 2 or 3 weeks) and methylprednisolone pulses (0.5 to 1 g/day for 3 consecutive days) followed by oral prednisone (60 mg/day) with slow tapering over 2 to 3 months.[27] Imatinib (400 mg/day), corticosteroids and plasma exchange have been administered with success in a case of noninfectious type II cryoglobulinemia with MPGN[29] after the benefit observed in an experimental model of TSLP transgenic mice with established MPGN.[30]

Other Types of Membranoproliferative Glomerulonephritis

Patients with MPGN associated with other infections may respond to effective treatment of the underlying pathogenic agent. Those with MPGN caused by an autoimmune disease should receive therapy for the principal disease. MPGN associated with α_1-antitrypsin deficiency has been reported to be cured by liver transplantation, which cures the genetic defect. Patients with MPGN associated with malignant disease, such as B cell lymphoma, may respond to effective treatment of the underlying cancer.

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CHAPTER 22

Glomerulonephritis Associated with Complement Disorders

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DEFINITIONS

Glomerular diseases associated with abnormalities of the complement system include thrombotic microangiopathy and glomerulonephritides. Activation of complement in most cases of glomerulonephritis (GN) is secondary to other processes in the glomerulus, such as deposition of immune complexes. In a small number of cases, however, abnormalities of the complement system itself, both genetic and acquired, are the cause of GN, and these patients are the focus of this chapter. Abnormalities of the classical pathway of complement have been associated with GN. Most important, deficiencies in early components of the classical pathway of complement have been associated with autoimmunity and GN.[1] This is most clearly seen in the rare individual with C1q deficiency, who typically has a lupus-like illness. This is thought to result from failure of clearance of immunogenic apoptotic bodies and other cellular debris in the absence of normal classical pathway complement activation.

The largest group of patients with complement abnormalities and GN has an abnormality of control of the alternative pathway of complement activation, with glomerular deposition of C3 in the absence of immunoglobulin, now termed *C3 glomerulopathy* (Box 22-1).

C3 GLOMERULOPATHY

A recently introduced term, C3 glomerulopathy encompasses glomerular disease characterized by the accumulation of complement component C3 in glomeruli caused by abnormal control of complement activation, deposition, or degradation, particularly abnormal control of the alternative pathway of complement activation.[2] Characteristically, glomeruli show strong immunohistologic staining for C3 without significant staining for immunoglobulins or for components of the classical pathway of complement activation, C1q and C4. Thus defined, C3 glomerulopathy is distinct from atypical hemolytic uremic syndrome (HUS), which may also be associated with alternative pathway activation; in HUS, complement activation is on the renal endothelium and on electron microscopy (EM) is not associated with well-defined deposits (see Chapter 29). C3 glomerulopathy may show a variety of appearances on light microscopy, including mesangial proliferation, a membranoproliferative pattern, endocapillary proliferation, and crescent formation. It is now recognized that many cases previously classified morphologically as "membranoproliferative glomerulonephritis" (MPGN) are cases of C3 glomerulopathy. This includes cases that had been classified as MPGN types I, II, or III. Indeed, it appears that most cases previously called MPGN type III are examples of C3 glomerulopathy (see Chapter 21).

On EM, C3 glomerulopathy may have a variable appearance as well. However, a common presentation is of *dense deposit disease* (DDD). This condition is characterized by replacement of the basement membrane by dense bands on EM (Fig. 22-1). In some cases, the light microscopy appearance in DDD resembles membranoproliferative glomerulonephritis, which was previously designated "MPGN type II." However, most cases of DDD do not have MPGN morphology on light microscopy.

Cases of C3 glomerulopathy that do not have typical highly dense deposits of DDD show a range of appearances on EM, with deposits that may be mesangial, subendothelial, or subepithelial, and that may be more or less well defined. These cases of non-DDD C3 glomerulopathy have been given the collective name of *C3 glomerulonephritis* (C3GN).[3,4]

ETIOLOGY AND PATHOGENESIS

The pathogenesis of C3 glomerulopathy involves a dysregulation of the alternative pathway of complement (see Fig. 29-10). In health, the alternative pathway is constantly being activated, but at an extremely low rate. With constant generation of small amounts of activated C3, this low-grade activation allows the pathway to be rapidly switched on when needed. In the presence of pathogens, rapid amplification of C3b is achieved through a positive feedback loop termed the *C3b amplification loop* that can generate millions of C3b molecules within minutes. Because this amplification can progress so rapidly, efficient systems are required to prevent inappropriate activation of the pathway. The most important protein in the circulation that controls the alternative pathway is complement factor H (CFH). CFH exerts this control in three ways: (1) blocking the formation of alternative pathway C3 convertases by binding to C3b and thus inhibiting interaction between C3b and factor B, (2) promoting the spontaneous dissociation of these convertases, and (3) working with another plasma protein, factor I, to cleave C3b to iC3b. Mice that have been genetically engineered to lack factor H have undetectable circulating C3 because their C3 is constantly consumed by the uncontrolled alternative pathway.[5]

Factor H is an abundant single-chain glycoprotein predominantly made in the liver. It is composed of protein subunits, termed *short consensus repeat* (SCR) domains. The activity of CFH can be modulated by a group of closely related proteins called *factor H–related proteins* (CFHRs), five of which exist in humans. CFHRs are coded for by genes adjacent to the gene for CFH and have a similar structure to CFH. The high degree of homology of these genes has led to a number of recombination and deletion events that have resulted in both common polymorphisms and rare pathogenic mutations at this locus. The most common polymorphism is a deletion of *CFHR1* and

Definitions of Glomerulonephritic Complement Disorders

C3 Glomerulopathy

Disease process caused by abnormal control of complement activation, deposition, or degradation and characterized by predominant glomerular C3 fragment deposition with electron-dense deposits on electron microscopy.

Dense Deposit Disease (DDD)

A form of C3 glomerulopathy with a characteristic electron microscopy appearance of intensely osmiophilic transformation of the glomerular basement membrane.

C3 Glomerulonephritis (C3GN)

C3 glomerulopathy without the characteristic appearances of dense deposit disease.

Glomerulonephritis with Dominant C3

Morphologic term for cases of glomerulonephritis with dominant staining for C3c. *Dominant* is defined as C3c intensity ≥2 orders of magnitude more than any other immune reactant on a scale of 0 to 3 (including 0, trace, 1+, 2+, 3+). Many, but not all, of these will represent cases of C3 glomerulopathy.

Box 22-1 Definitions of complement disorders associated with glomerulonephritis.

CFHR3 that is present in homozygosity in 5% to 20% of healthy individuals, depending on ethnic origin. It is now clear that the CFHRs are able to compete with the binding of CFH to C3b in some circumstances.[6] CFHRs, unlike CFH, are unable to inhibit complement activation and thus are now thought to antagonize the action of CFH.

In many cases of C3 glomerulopathy, the pathogenesis is a failure of CFH to control the activation of the alternative pathway in the circulation, which is associated with low levels of circulating C3 because of uncontrolled consumption. Up to 80% of patients with DDD and up to half of patients with C3GN have low levels of serum C3.[3] Many of these patients have a C3 nephritic factor (C3NeF). C3NeFs are autoantibodies that are able to stabilize the alternative pathway C3 convertase by preventing CFH from carrying out its normal functions. It therefore seems likely that C3NeF plays an important etiologic role in these patients. However, the role of C3NeF is complicated because C3NeFs may also be found in patients with other forms of GNs and even in healthy patients. In other cases, genetic mutations lead to failure of alternative pathway control, including patients with complete CFH deficiency caused by gene deletion, mutations in CFH that interfere with its binding to C3b, and mutations in C3 that change its structure to prevent its inhibition by CFH. In some patients, failure of alternative pathway control is associated with autoantibodies directed against factor H that target its regulatory domain.

In cases of C3 glomerulopathy not associated with excessive activation of C3 in the circulation, the nephrologist can assume that there is a failure to control the alternative pathway locally within the glomerulus. This might be caused by a failure to control activation or by inappropriate handling of the fragments of C3 generated by alternative pathway activation. In most cases the pathogenesis is still not clear, but there is an example of a familial form of C3 glomerulopathy, called *CFHR5 nephropathy,* without systemic C3 activation. This is a common cause of kidney disease in the population of Cyprus, in which the mutation is a duplication of the first two exons of the *CFHR5* gene.[6] This leads to an abnormal protein that forms multimers able to deregulate the activity of CFH on surfaces.[7] Therefore, the abnormal protein interferes with the action of CFH locally within the glomerulus and enhances alternative pathway activation.

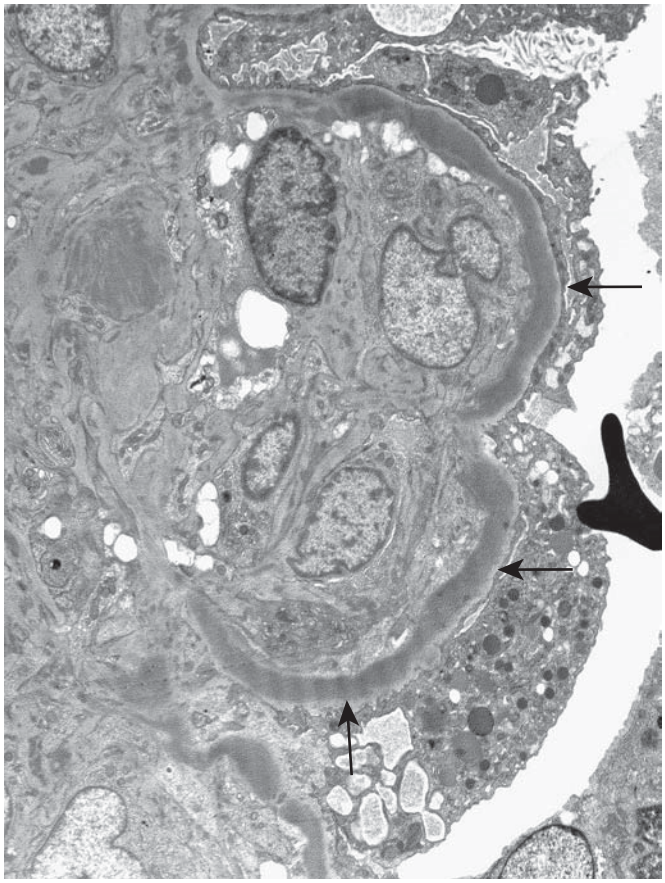

Figure 22-1 Dense deposit disease (DDD). Electron micrograph of a glomerulus with typical appearance of DDD showing very osmiophilic transformation of the basement membrane *(arrows)*.

In addition to those just described, other mutations and polymorphisms in complement genes have been associated with C3 glomerulopathy, but their role is uncertain at present. It is also notable that an association appears to exist between monoclonal gammopathy and C3 glomerulopathy.[8] In some patients, the monoclonal immunoglobulin may act as a C3NeF.

EPIDEMIOLOGY

With a reported prevalence of 2 to 3 per 1 million population, DDD is primarily a disease of children and young adults. However, in a 2009 series from New York, 39% of the adult patients were over 60 years of age.[9] DDD affects males and females equally in many cohorts, although some studies have shown a female predominance. In one large series from France, the ratio of C3GN to DDD was about 2:1, and patients with C3GN were significantly older, with a mean age at diagnosis of 30 years.[3] In the United Kingdom and Ireland, we found a C3GN-DDD ratio of about 3:1 and estimated the incidence of C3 glomerulopathy at 1 to 2 per million population per year.[10] The apparent incidence of C3GN likely will increase as the entity becomes better recognized by nephrologists and pathologists. There is no reliable information on geographic variation in incidence; the one notable exception is C3GN caused by a mutation in *CFHR5* in which almost all the cases have been found in Cyprus, where the mutation apparently occurred a few hundred years ago.[7]

CLINICAL MANIFESTATIONS

Dense Deposit Disease

At presentation, almost all patients with DDD have proteinuria, usually with hematuria. Nephrotic-range proteinuria is present in two thirds of patients,[9,11] and frank nephrotic syndrome in 12% to 65% in different series. In a series of 98 patients from North America, about one fifth did not suspect a problem, and kidney disease was detected as part of a routine annual examination.[12] A number of patients have initial signs and symptoms of acute nephritic syndrome and may have episodes of acute kidney injury that show complete clinical resolution.[13] Decreased kidney function is common at presentation and is more common in adults with DDD. Hypertension is often found either at clinical onset or during the disease course. In about half of patients, clinical onset of DDD is preceded by acute infection, often an upper respiratory tract infection, with elevated ASO titers in 20% to 40%.

Patients with DDD may develop ocular *drusen,* lipoproteinaceous deposits of complement-containing debris within the Bruch membrane beneath the retinal pigment epithelium (Fig. 22-2). This pathology is similar to age-related macular degeneration (AMD) but, in contrast to AMD, drusen in DDD may be found as early as the second decade of life. There is no correlation between disease severity in the kidney and in the eye. A small minority of patients with DDD have acquired partial lipodystrophy (APL), a condition with symmetric loss of adipose tissue from the face, arms, and upper portions of the trunk (Fig. 22-2).

The overall long-term outcome in DDD is poor. In the series cited earlier, 50% of the 98 patients progressed to end-stage renal disease (ESRD) within 10 years of diagnosis, with young women having the greatest risk for kidney failure.[12]

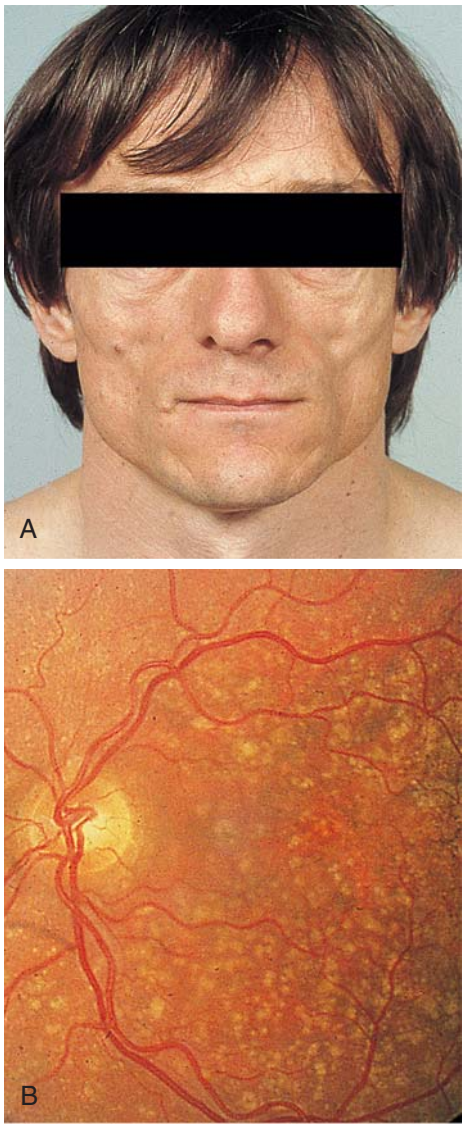

Figure 22-2 Facial and retinal features of dense deposit disease (MPGN type II). A, Partial lipodystrophy; note the absence of subcutaneous fat from the face. **B,** Drusen bodies in the retina. *(Courtesy Dr. C. D. Short, Manchester, UK.)*

C3 Glomerulonephritis

Because C3GN has only recently been recognized, clinical manifestations are less well defined. In the French series, 27% of patients with C3GN had nephrotic syndrome at presentation.[3] Approximately two thirds of patients had microhematuria at presentation, and one third had elevated blood pressure. In this series, rate of progression to ESRD in C3GN patients was similar to that in patients with DDD.

In CFHR5 nephropathy in Cyprus, the major clinical feature in young patients is hematuria. Microhematuria was present in 90% of patients, and 20% reported episodes of macrohematuria, often associated with upper respiratory tract infection.[14] Proteinuria became more common with increasing age and was seen in 80% of men and 20% of women older than 50. Impaired kidney function was more common with increasing age, particularly in men, and of 18 patients who reached ESRD, 78% were men. The reason for the striking gender difference in outcome is unclear.

LABORATORY FINDINGS

Low levels of serum C3 are found in approximately 80% of patients with DDD and up to 50% of patients with C3GN. In the case of C3GN caused by CFHR5 nephropathy, serum C3 levels are typically normal. Serum levels of the early components of the classical pathway (C1q and C4) are usually normal. Most patients with DDD are positive for serum C3NeF and in more than 50% of patients, C3NeF persists throughout the clinical course.[15] However, C3NeF is not a specific serologic marker because it also occurs with MPGN type I, lupus nephritis, and poststreptococcal glomerulonephritis, although less frequently. C3NeF is seen in fewer than half of patients with C3GN. It is important to note that methods for measuring C3NeF are not standardized.

Box 22-2 shows a list of investigations that may be helpful in C3 glomerulopathy. It is recommended that investigations in this second category be discussed with experts and performed in laboratories with experience in complement assays. Complement laboratories across the world are listed on the International Complement Society (www.complement.org) and European Complement Network (www.ecomplement.org) websites. Depending on the clinical scenario, it may be possible to prioritize some of these assays. For example, in patients with C3 glomerulopathy and low serum C3 levels in the absence of C3NeF, it would be important to screen for anti-CFH autoantibodies. In familial cases of C3 glomerulopathy, a search for genetic mutations may be important for elucidating pathogenesis and for genetic counseling.

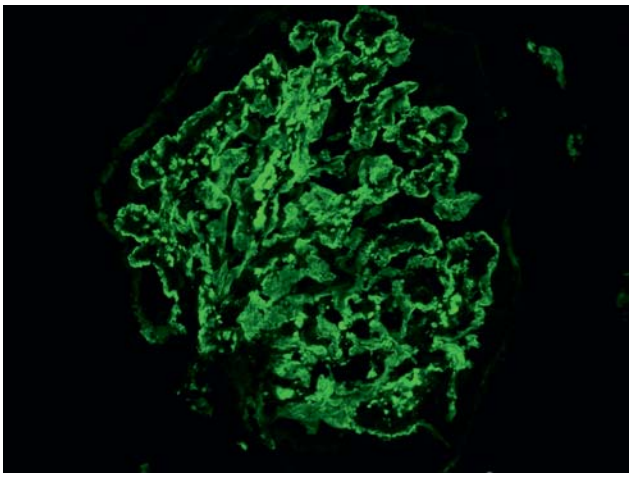

Figure 22-3 C3c in dense deposit disease. Immunofluorescence shows widespread staining of capillary walls and focal granular mesangial staining.

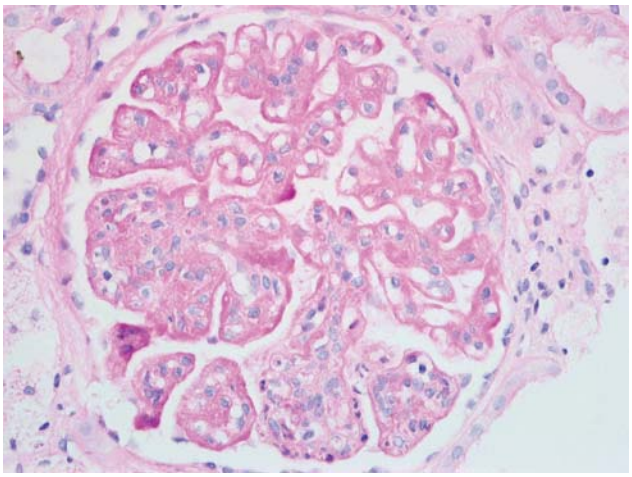

Figure 22-4 C3 glomerulonephritis. Light microscopy shows a glomerulus with a membranoproliferative pattern of injury with increased mesangium, capillary wall thickening, and segmental endocapillary hypercellularity. (Periodic acid–Schiff reaction.)

Serologic and Genetic Evaluation of C3 Glomerulopathy

Tests recommended in *all* patients with C3 glomerulopathy:

- Measurement of serum levels of C3 and C4
- Measurement of C3 nephritic factor
- Measurement of factor H
- Serum paraprotein detection

Patients with C3 glomerulonephritis (C3GN) should be screened for the genetic mutation of CFHR5 nephropathy

Tests that should be considered on a case-by-case basis:

- Measurement of serum factor B and C5
- Measurement of markers of C3 and C5 activation (e.g., C3d, soluble C5b9)
- Detection of autoantibodies to factor H and factor B
- Mutation screening of complement regulatory genes (e.g., CFH, CFI, CD46), activation protein genes (C3, CFB) and assessment of copy number variation across the CFH-CFHR locus

Box 22-2 Serologic and genetic evaluation of C3 glomerulopathy.

PATHOLOGY

The defining feature of C3 glomerulopathy is the presence of C3 (usually detected with an antibody to C3c) in glomeruli on immunohistology (Fig. 22-3). In most cases, C3 staining is seen on capillary walls and in the mesangium, but in some cases, the staining may be mainly mesangial. In some patients, particularly those with DDD, C3 may also be found on Bowman capsule or on tubular basement membranes.

The light microscopy appearances are variable. In both DDD and C3GN, the presence of membranoproliferative changes is typical, with increased glomerular lobulation, increase in mesangial matrix and cells, and capillary wall thickening with double-contour formation (Fig. 22-4). Some cases show a predominantly mesangioproliferative pattern or an endocapillary hypercellularity, partly caused by influx of macrophages or neutrophils. This hypercellularity may affect almost all the glomeruli, giving an appearance of diffuse endocapillary proliferative GN similar to that typically seen with postinfectious glomerulonephritis (PIGN). Crescent formation may be present and may be sufficiently prominent to merit the designation of *crescentic* GNs (>50% crescents). In a series of 69 patients with DDD, the incidence of different histologic patterns was membranoproliferative (25%), mesangioproliferative (45%), crescentic (18%), and acute proliferative and exudative (12%).[16] In the French series of C3GN patients, 71% showed an MPGN pattern on light microscopy.[3]

The EM appearance of C3 glomerulopathy also varies greatly, although in many cases the diagnosis can be suspected from the EM changes. By definition, DDD shows the presence of typical osmiophilic, dense transformation of the glomerular basement membrane (GBM; see Fig. 22-1), with similar features often seen in Bowman capsule and tubular basement membranes. However, these changes may be segmental within glomeruli, in some cases making it difficult to define DDD with certainty. In DDD, typically there are large electron densities in the mesangium.

In other cases of C3GN, there is electron-dense material that expands the GBM similar to the changes in DDD, but without such marked electron density; the distinction between these cases and DDD may not be clear-cut and depends on a subjective interpretation by the pathologist. Other cases have more distinct subendothelial and mesangial electron-dense deposits, reminiscent of those seen in immune complex GN. Some cases show a very complex pattern of intramembranous deposits that was previously designated as a form of MPGN type III (Fig. 22-5).

In both DDD and C3GN, subepithelial hump-shaped deposits are frequently seen. These are identical to those characteristically seen in PIGN. Their significance is not clear, although these humped deposits are more common in infectious exacerbations of disease.

Few data are available on the relationships among histology, clinical presentation, clinical course, and underlying genetic abnormalities. In several series of DDD patients, the presence of crescents was associated with a more rapid decline in renal function.

DIFFERENTIAL DIAGNOSIS

The diagnosis of C3 glomerulopathy is relatively straightforward if there is isolated C3 deposition with typical deposits on EM. However, it is now clear that some patients have an otherwise typical appearance of DDD or C3GN, but also have small amounts of immunoglobulin in glomeruli, which presents a diagnostic challenge. A recent consensus conference on C3 glomerulopathy suggests that the

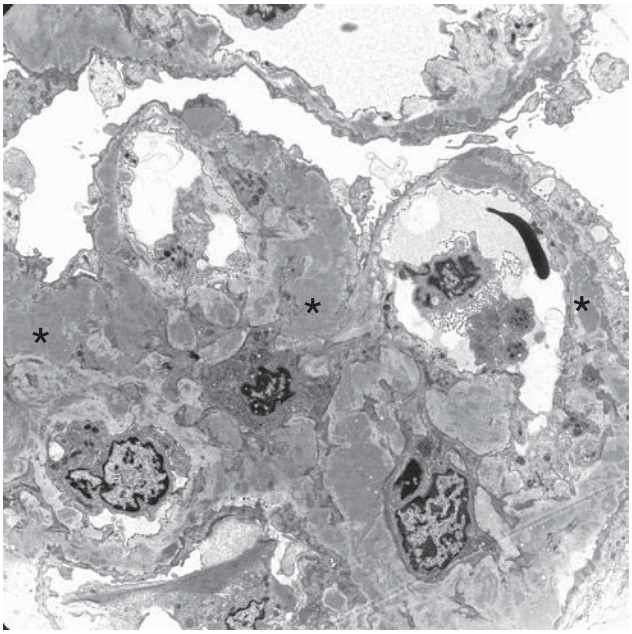

Figure 22-5 C3 glomerulonephritis. Electron micrograph of a glomerulus shows a complex pattern of thickening of the glomerular basement membrane with intramembranous electron-dense material. *Similar deposits are also seen in the mesangium.

term *glomerulonephritis with dominant C3* should be used for cases in which the staining intensity of C3 is 2 or more orders of magnitude greater than any other immune reactant on a scale of 0 to 3. Most of these cases will be C3 glomerulopathy.

Another problem is the distinction of C3 glomerulopathy from PIGN. PIGN may show greatly reduced serum C3, and glomeruli may stain for C3 without immunoglobulin. In some cases, the distinction from C3GN may only be possible by following the patient to see if resolution of the disease occurs. It has been suggested that PIGN could be considered a self-limiting form of C3 glomerulopathy. Some patients who have been labeled as "atypical" postinfectious glomerulonephritis have C3 glomerulopathy.[17] In addition, HCV-associated MPGN may be associated with C3 and minimal or absent IgG (although IgM is usually present). Thus, testing for HCV should be part of the differential.

TREATMENT

The optimal treatment for C3 glomerulopathy remains undefined. Most information relates to DDD because C3GN was not previously recognized as a specific diagnostic category. In many studies, however, DDD was grouped together with forms of MPGN, which makes it difficult to develop specific recommendations for DDD. Attempted treatments include renin-angiotensin system blockade, corticosteroids and other immunosuppressants, anticoagulants, and plasma exchange.[18] Recent KDIGO (Kidney Disease: Improving Global Outcomes) clinical guidelines (www.kdigo.org) suggest, on the basis of low-quality evidence, that "adults and children with presumed idiopathic MPGN accompanied by the nephritic syndrome and progressive decline in kidney function" receive oral cyclophosphamide or mycophenolate mofetil (MMF) plus low-dose daily or alternate-day corticosteroids, with initial therapy of less than 6 months. However, whether these recommendations also apply to C3 glomerulopathy with an MPGN-like pattern remains doubtful, and effective therapy for this group of diseases is still largely undefined.

In many cases of C3 glomerulopathy, the deposition of C3 in glomeruli leads to subsequent activation of C5, and there is considerable interest in the possibility of using the anti-C5 antibody eculizumab for treatment. There are a number of case reports and a small, open-label nonblinded clinical trial of eculizumab for C3 glomerulopathy.[19] Some patients have shown clinical improvement, and some showed decreased glomerular inflammation on repeat biopsy. In the rebiopsied patients, IgG-κ was found, consistent with binding of the monoclonal eculizumab to C5 in the biopsy, giving a histologic pattern similar to monoclonal immunoglobulin deposition disease[20] (see Chapter 27). However, the exact role of eculizumab remains to be defined. Rational treatment of C3 glomerulopathy would involve inhibition of C3 activation, and several drugs are in preclinical development that may achieve this and allow more targeted therapy in the future.

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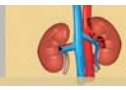
CHAPTER 23



IgA Nephropathy and Henoch-Schönlein Nephritis

John Feehally and Jürgen Floege

DEFINITIONS

IgA nephropathy (IgAN) is a mesangial proliferative glomerulonephritis characterized by diffuse mesangial deposition of IgA. Also called Berger disease, IgAN was first recognized in 1968 by Jean Berger when immunofluorescence techniques were introduced for the study of renal biopsy specimens. IgAN is unique among glomerular diseases in being defined by the presence of an *immune reactant* rather than by any other morphologic feature on renal biopsy, and the light microscopy changes are variable. IgAN is the most prevalent pattern of glomerular disease seen in most Western and Asian countries where renal biopsy is widely practiced. The term *benign recurrent hematuria* was previously used for IgAN, but it is now known that IgAN is an important cause of end-stage renal disease (ESRD). It is likely that IgAN is not a single entity but rather a common response to various injurious mechanisms.

Henoch-Schönlein purpura (HSP) is a small-vessel vasculitis affecting the skin, joints, gut, and kidneys that predominantly affects children. It is defined by tissue deposition of IgA. HSP was described separately by Schönlein in 1837 and Henoch in 1874. Typically, there is clinical involvement in the skin, gut, and kidneys. The nephritis associated with HSP is also characterized by mesangial IgA deposition; indeed, the renal histologic features of Henoch-Schönlein (HS) nephritis are indistinguishable from those of IgAN. HS nephritis is differentiated from IgAN by the extrarenal manifestations.

ETIOLOGY AND PATHOGENESIS

Although infective episodes precede HSP in up to 50% of cases and usually precipitate macrohematuria episodes in young IgAN patients, no evidence indicates a role for any specific antigen. The clinical association of visible hematuria with upper respiratory tract infection in IgAN indicates that the mucosa may be a site of entry for foreign antigens. An infectious source has long been suspected, and there have been occasional reports of IgAN in association with microbial infection, both bacterial (e.g., *Campylobacter, Yersinia, Mycoplasma, Haemophilus*) and viral (e.g., cytomegalovirus, adenovirus, coxsackievirus, Epstein-Barr virus). A severe form of IgAN, which may be crescentic, has been reported in association with severe staphylococcal infection. No organism, however, has been consistently implicated by the finding of microbial antigen in glomerular deposits in typical cases of IgAN. In addition there is evidence for a mucosal hyperresponsiveness to a variety of food antigens in IgAN patients.[1] The mesangial IgA may thus represent a common immune response to a variety of foreign antigens. Another common feature of this immune response is that the deposited IgA is undergalactosylated, and that the occurrence of this type of IgA in the circulation may elicit an autoimmune IgA- and IgG-response (see later discussion).

The regular recurrence of IgAN and HS nephritis after renal transplantation strongly implies an abnormality in the host IgA immune system (see Chapter 108).

IgA Immune System

IgA is the most abundant immunoglobulin in the body and is chiefly concerned with mucosal defense. It has two subclasses, IgA1 and IgA2. Mucosal antigen challenge provokes *polymeric* IgA (pIgA) production by plasma cells of the mucosa-associated lymphoid tissue; the pIgA is then transported across epithelium into mucosal fluids, where it is released after coupling to secretory component as *secretory* IgA (sIgA). The function of circulating IgA is less clear; it is bone marrow derived and mostly *monomeric* IgA1 (mIgA1). Circulating IgA1 is cleared by the liver through hepatocyte asialoglycoprotein receptors and Kupffer cell Fcα receptors.

The mesangial IgA in IgAN is predominantly pIgA1. The clinical association with mucosal infection or superantigens from *Staphylococcus aureus* originally suggested that the mesangial pIgA1 comes from the mucosal immune system. In IgAN, however, pIgA1 production is downregulated in the mucosa and upregulated in the bone marrow. Moreover, the pIgA response to systemic immunization with common antigens is increased, whereas the response to mucosal immunization is impaired. Impaired mucosal IgA responses allowing enhanced antigen challenge to the marrow could be the primary abnormality in IgAN, although this remains unproven. Similarly attractive, yet still unproven, is the hypothesis that some mucosal IgA-producing plasma cells translocate to the bone marrow in IgAN; this could also explain the particular glycosylation of serum IgA in IgAN. Tonsillar pIgA1 production is also increased, although IgAN can occur after tonsillectomy, and the tonsil is a very minor source of IgA production compared with the mucosa or marrow. There are reports of sIgA in the mesangium, but this finding is not easily explained by current pathogenic concepts of IgAN. Hepatic clearance of IgA is reduced, possibly because of the altered molecular characteristics of IgA in IgAN (see later discussion).

Serum IgA levels are increased in one third of patients with IgAN and HSP. There are elevations in both mIgA and pIgA. However, high serum IgA itself is not sufficient to cause IgAN. High circulating levels of monoclonal IgA in myeloma or polyclonal IgA, in acquired immunodeficiency syndrome (AIDS), only infrequently provoke mesangial IgA deposition.

Circulating macromolecular IgA is characteristic of IgAN. It is often described as IgA immune complexes, although the antigen is only rarely identified. There are circulating IgA rheumatoid factors (IgA against constant domain of IgG) in 30% of patients with

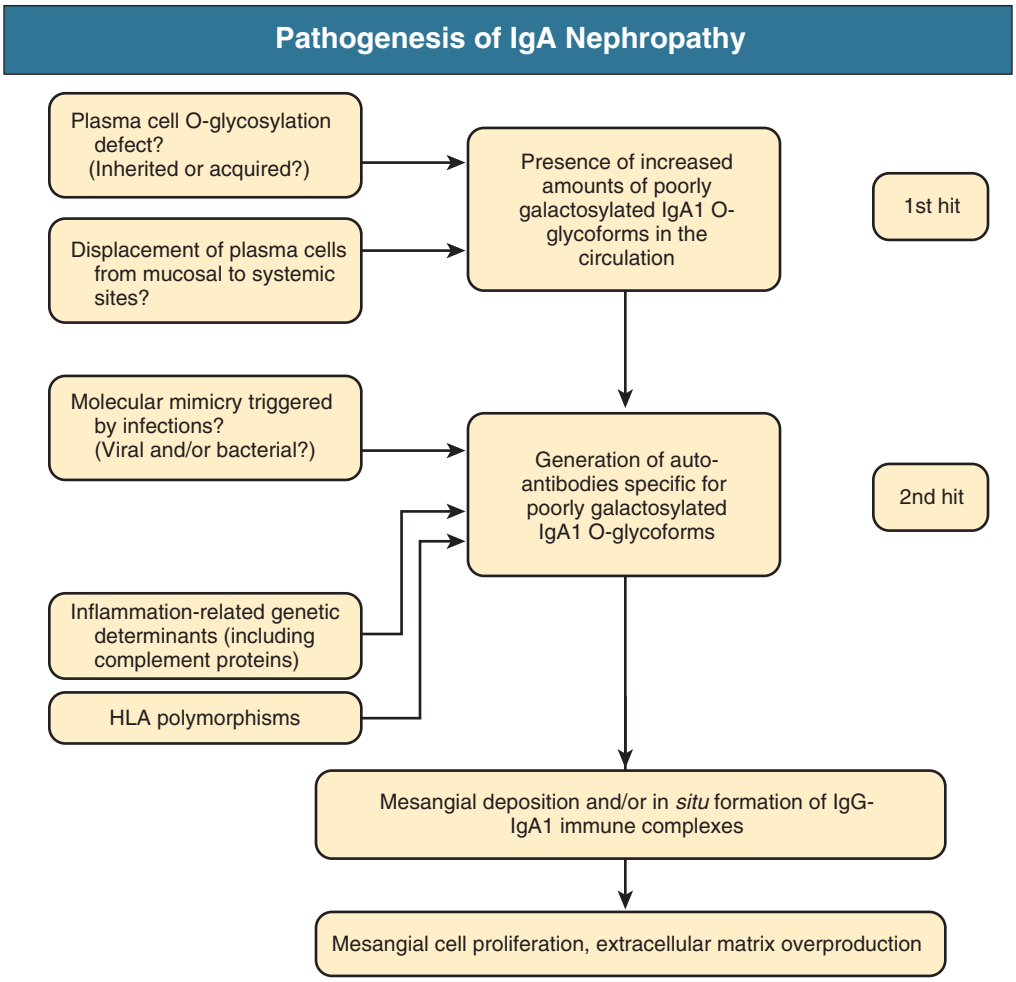


Figure 23-1 Pathogenesis of IgA nephropathy. Proposed mechanisms leading to mesangial deposition of abnormally glycosylated IgA1 and mesangial injury. Not shown in this scheme is the role of generic progression factors (e.g., primary hypertension, smoking, obesity).

IgAN and 55% of those with HSP. Studies *in vitro* indicate that IgA production by mononuclear cells is exaggerated in IgAN, and that these cells show abnormal patterns of cytokine production. However, the direct relevance of these observations to events *in vivo* is uncertain.

IgA Glycosylation

IgA1 carries distinctive *O*-linked sugars at its hinge region; IgA2 has no hinge and carries no such sugars. There is good evidence that circulating IgA1 in IgAN and HS nephritis has abnormal *O*-linked hinge-region sugars with reduced galactosylation because of altered IgA production in lymphocytes of patients with IgAN.[1] Some data indicate defective function of the relevant glycosyltransferases that *O*-glycosylate IgA1, possibly with a genetic basis. Other findings suggest that the primary abnormality may be that IgA of mucosal type, which has glycosylation patterns different from serum IgA1, reaches the circulation, for example, by translocation of mucosal lymphocytes to the bone marrow. The latter is consistent with experiments, where immortalized lymphocytes from IgAN patients continue to produce dimeric and polymeric IgA with altered galactosylation *in vitro*.[2]

Mesangial IgA1 in IgAN has the same abnormalities of *O*-glycosylation.[3,4] The altered glycosylation may lead to IgG anti-IgA autoantibodies and promote mesangial IgA1 deposition by predisposing to the formation of circulating IgA1 immune complexes or by directly modifying IgA1 interactions with matrix proteins and mesangial cell or monocyte Fc receptors.[5] It may also impair IgA1 clearance by inhibiting IgA1 interactions with hepatic and circulating myeloid cell IgA receptors. Figure 23-1 summarizes some key elements involved in the pathogenesis of IgAN.

Glomerular Injury After IgA Deposition

Polymeric IgA deposition in the mesangium is typically followed by mesangial proliferative glomerulonephritis (GN). In animal models, co-deposition of IgG and complement is necessary for inflammation, but this is not mandatory in human disease. Complement deposits are usually C3 and properdin without C1q and C4. There may be complement activation via the mannose-binding lectin pathway. The extent to which IgA engages inflammatory cells in the circulation and especially in the kidney will determine the intensity of inflammation. Fc receptors for IgA (Fcα receptors) on myeloid and mesangial cells may play a key role.[6]

The mechanisms of mesangial proliferative GN have been studied in detail in animal models, particularly anti–Thy 1 nephritis in the rat. These studies have shown the key role of cytokines and growth factors in mesangial cell proliferation, particularly the B and D isoforms of platelet-derived growth factor[7] (PDGF) and in the subsequent matrix production and sclerosis, particularly transforming growth factor-β (TGF-β). Studies of renal biopsy specimens in human IgAN also support a role for PDGF and TGF-β. These

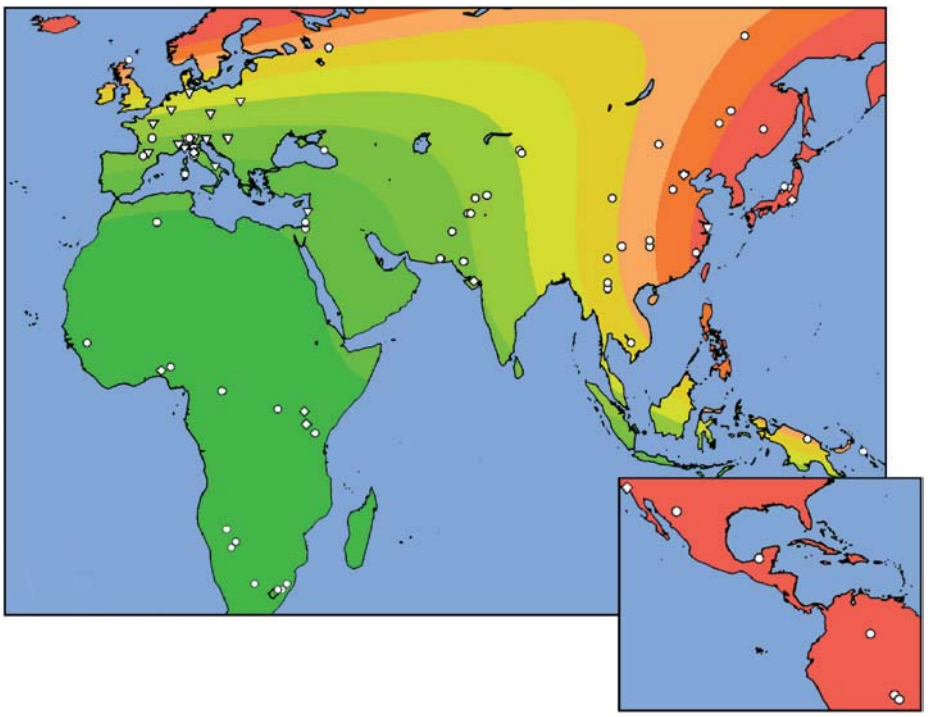


Figure 23-2 Geographical variation in genetic risk for IgA nephropathy. Genome-wide association studies indicate a geographical gradient of risk from green (low risk) to red (high risk). *(From reference 11.)*

mechanisms are not unique to IgAN but are likely involved in all forms of mesangial proliferative GN, including those without IgA deposition.

Animal Models of IgA Nephropathy

Animal IgA does not have the same characteristics as human IgA1, and some animals also have IgA clearance mechanisms distinct from those in humans. Therefore, animal models, even if they provoke mesangial IgA deposits, are not particularly informative about the mechanisms that underlie human mesangial pIgA1 deposition, although they have provided many insights into events after IgA deposits have developed. There is no animal model in existence for HSP.

Relationship Between IgA Nephropathy and Henoch-Schönlein Purpura

Despite some differences in age at onset and natural history of IgAN and HS nephritis,[8] there is much evidence to support a close pathogenetic link between the two conditions, and the outcome of the two diseases may be similar.[9] Monozygotic twins who developed IgAN and HSP, respectively, at the same time have been described. The evolution of IgAN into HSP in the same patient is described in both adults and children, and HSP patients with ESRD receiving a renal transplant may experience recurrent disease in the form of IgAN. Many of the abnormalities of IgA production and handling reported in IgAN are also detected in HSP.

EPIDEMIOLOGY

IgA nephropathy is the most prevalent pattern of glomerular disease in most countries where renal biopsy is widely used as an investigative tool. Its estimated frequency is at least 2.5 cases per year per 100,000 adults.[10] However, the striking geographic variation has been associated with the presence of particular gene alleles that protect from IgAN[11] (Fig. 23-2). This racial predisposition is maintained in other locations; in the United States, for example, IgAN is less common in Blacks than in Caucasians of European origin. Perceived prevalence of IgAN may also be influenced by attitudes to the investigation of microhematuria. A country with an active program of routine urine testing will inevitably identify more individuals with urine abnormalities, but IgAN will be identified only if renal biopsy is performed. Even then, the prevalence of IgAN will be underestimated; a study of kidney donors suggests that the prevalence of IgAN with mesangial proliferative changes and glomerular C3 deposits in the general population in Japan may be 1.6%.[12] This suggests that the vast majority of IgAN patients never come to medical attention and spontaneously remit.

In children, HSP is usually diagnosed on clinical grounds without biopsy confirmation of tissue IgA deposition. Transient urine abnormalities are common in the acute phase. However, only those with persistent urine abnormalities or with more overt renal disease will come to renal biopsy. Therefore, the incidence of HS nephritis is almost certainly underestimated, with many unidentified mild and transient cases. There is no information on geographic variations in HSP.

Genetic Basis of IgA Nephropathy

Urine abnormalities increase in frequency among the relatives of IgAN patients, although only in a few pedigrees is IgAN found in multiple generations. One large pedigree has been described in Kentucky, and other large families have been found in Italy and Canada. However, more than 90% of all cases of IgAN appear to be sporadic.

Large worldwide genome-wide association studies have identified genetic modulators that seem to affect the prevalence of sporadic IgAN and modulate its course.[11-13] Variations in major histocompatibility gene loci (HLA-DR, -DQ, -DP and HLA-B) have consistently been identified. Other gene loci are less consistent and include

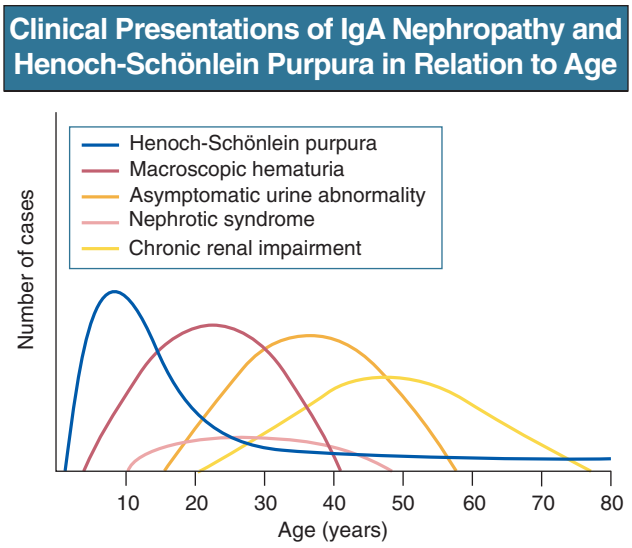


Figure 23-3 Age in clinical presentation of IgA nephropathy and Henoch-Schönlein purpura. HSP is most common in childhood but may occur at any age. Macrohematuria is very uncommon after age 40. The importance of asymptomatic urine abnormality as the presentation of IgAN will depend on attitudes to routine urine testing and renal biopsy. It is uncertain whether patients presenting late with chronic renal impairment have a disease distinct from that of those presenting younger with macrohematuria. *(Data from patients presenting in Leicester, UK, 1980-1995.)*

inflammatory mediators (tumor necrosis factor and α-defensin) and gene loci affecting complement factor H.[14]

CLINICAL MANIFESTATIONS

IgA Nephropathy

The wide range of clinical presentations of IgAN varies in frequency with age (Fig. 23-3). No clinical pattern is pathognomonic of IgAN. In populations of Caucasian descent, IgAN is more common in males than females by a ratio of 3:1, whereas the ratio approaches 1:1 in most Asian populations.

Macroscopic Hematuria

In 40% to 50% of patients with IgAN, the clinical presentation is episodic macroscopic hematuria, most frequently in the second decade of life. The urine is usually brown rather than red, and clots are unusual. There may be loin pain caused by renal capsular swelling. Hematuria usually follows intercurrent mucosal infection, typically in the upper respiratory tract (the term *synpharyngitic hematuria* has been used) or occasionally in the gastrointestinal tract. Hematuria is usually visible within 24 hours of the onset of the symptoms of infection, differentiating it from the 2- to 3-week delay between infection and subsequent hematuria in postinfectious (e.g., poststreptococcal) GN. The macroscopic hematuria resolves spontaneously over a few days. Microscopic hematuria persists between attacks. Most patients have only a few episodes of frank hematuria, which become less frequent and resolve over a few years or sooner. Such episodes may be associated with acute kidney injury (AKI).

Asymptomatic Hematuria and Proteinuria

Asymptomatic urine testing identifies 30% to 40% of patients with IgAN in most reported series. Microhematuria with or without proteinuria (usually <2 g/24 h) is noted. The number of patients identified in this way will depend on local attitudes to urine screening as well as on the use of renal biopsy in patients with isolated microscopic hematuria. Most patients with IgAN are asymptomatic and would be identified only when the urine is tested.

Proteinuria and Nephrotic Syndrome

It is rare for proteinuria to occur without microscopic hematuria. Whereas nephrotic-range proteinuria may occur, in particular in the presence of uncontrolled hypertension, full-blown nephrotic syndrome is uncommon, occurring in only 5% of all patients with IgAN. Nephrotic syndrome may occur early in the course of the disease, with minimal glomerular change or with active mesangial proliferative GN. Alternatively, it may occur as a late manifestation of advanced chronic glomerular scarring.

Acute Kidney Injury

Although uncommon in IgAN (<5% of all cases), one study reports that AKI may be the presentation in up to 27% of patients older than 65 years.[15] AKI develops by three distinct mechanisms. There may be acute severe immune and inflammatory injury with necrotizing GN and crescent formation (crescentic IgAN); this may be the first presentation of IgAN, or it may be superimposed on established, less aggressive disease. Rapid deterioration in IgAN in pregnancy may be caused by crescentic transformation. Alternatively, AKI can occur with mild glomerular injury when heavy glomerular hematuria leads to tubule occlusion by red blood cells (RBCs). Third, especially in elderly patients, chronic IgAN will predispose to AKI from a variety of incidental renal insults (see Chapter 69).

Chronic Kidney Disease

Some patients already have renal impairment and hypertension when they are first diagnosed with IgAN. These patients tend to be older, and they probably have longstanding disease that previously remained undiagnosed because the patient neither had frank hematuria nor underwent routine urinalysis. Hypertension is common, as in other chronic glomerular disease; accelerated hypertension occurs in 5% of patients.

Clinical Associations with IgA Nephropathy

Mesangial IgA deposition is a frequent finding in autopsy studies in chronic liver disease. Although particularly associated with alcoholic cirrhosis, IgA deposition can occur in other chronic liver disease, including that caused by hepatitis B and schistosomiasis. It is thought to result from impaired clearance of IgA by the Kupffer cells, which express Fcα receptors, and hepatocytes, which express the asialoglycoprotein receptor. Clinical evidence of renal disease is more common than previously appreciated, and patients occasionally develop ESRD.

A number of case reports have associated IgAN with human immunodeficiency virus and AIDS. It is not clear whether the polyclonal increase in serum IgA, which is a feature of AIDS, is the predisposing factor.

There are case reports associating IgAN with many other conditions, particularly with a number of immune and inflammatory diseases (Table 23-1). Their relationship to abnormalities of the IgA immune system is not always clear, and some may represent the coincidental development of unrelated but relatively common conditions.

Henoch-Schönlein Purpura

Although most prevalent in the first decade of life, HSP may occur at any age. A palpable purpuric rash, which may be recurrent, occurs

Diseases Reported in Association with IgA Nephropathy			
Disease	**Common**	**Reported**	**Rare**
Rheumatic and autoimmune disease	Ankylosing spondylitis Rheumatoid arthritis Reiter syndrome Uveitis	Behçet syndrome* Takayasu arteritis† Myasthenia gravis	Sicca syndrome
Gastrointestinal disease	Celiac disease	Ulcerative colitis	Crohn's disease Whipple's disease
Hepatic disease	Alcoholic liver disease Nonalcoholic cirrhosis Schistosomal liver disease		
Lung disease	Sarcoid		Pulmonary hemosiderosis
Skin disease	Dermatitis herpetiformis		
Malignancy		IgA monoclonal gammopathy	Bronchial carcinoma Renal carcinoma Laryngeal carcinoma Mycosis fungoides Sézary syndrome
Infection	HIV, hepatitis B (in endemic areas)	Brucellosis	Leprosy
Miscellaneous		Wiskott-Aldrich syndrome‡	

Table 23-1 Diseases reported in association with IgA nephropathy: common, reported, and rare. Rare associations have been made in one or two reported cases only. In a disease as common as IgA nephropathy, it is therefore uncertain whether these are truly related. *HIV,* Human immunodeficiency virus. *Behçet syndrome: systemic vasculitis typified by orogenital ulceration and chronic uveitis. †Takayasu arteritis: systemic vasculitis involving the aorta and its major branches, most often found in young women. ‡Wiskott-Aldrich syndrome: X-linked disorder in which increased serum IgA is associated with the triad of recurrent pyogenic infection, eczema, and thrombocytopenia.

Figure 23-4 Henoch-Schönlein purpura. The rash is a palpable purpuric vasculitis on the lower limbs spreading on extensor surfaces to the buttocks and occasionally to the upper limbs. Histology shows leukocytoclastic vasculitis with IgA deposits in blood vessel walls.

on extensor surfaces (Fig. 23-4). There may be polyarthralgia (usually without joint swelling) and abdominal pain caused by gut vasculitis. This may be severe, with bloody diarrhea if intussusception develops. In practice, the diagnosis is made by clinical criteria in the great majority of children, in whom HSP is a self-limiting illness. In adults, clinical features include purpura, arthritis, and gastrointestinal symptoms in 95%, 60%, and 50% of patients, respectively.[16] Renal involvement in adults with HSP does not differ from isolated IgAN. Tissue confirmation of IgA deposition by renal or skin biopsy is necessary to establish the diagnosis.

Much renal involvement in HSP is transient. Urine abnormalities are noted during the acute presentation but may disappear. Of those referred to a nephrologist, asymptomatic urine abnormality is still the most frequent clinical manifestation. Nephrotic syndrome occurs in 20% to 30% of patients. AKI may develop as a result of crescentic GN.

PATHOLOGY

The renal histopathologic findings in IgAN and HSP nephritis may be indistinguishable (Fig. 23-5).

Immune Deposits

Diffuse mesangial IgA is the defining hallmark of IgAN (Fig. 23-5, *A*). C3 is co-deposited in up to 90% of cases. IgG in 40% and IgM in 40% of cases may also be found in the same distribution. IgA may also deposit along capillary loops, a pattern more common in HS nephritis; in IgAN, this pattern is associated with a worse prognosis. C5b-9 is found with properdin but not C4, indicating alternative complement pathway activation. Disappearance of IgA deposits after prolonged clinical remission has been documented in both children and adults. About one third of the patients also have deposits of sIgA in the mesangium and are characterized by more severe disease.[17]

Light Microscopy

Light microscopy changes are remarkably variable and do not correlate topographically with the IgA deposits. There can be almost normal glomerular architecture, mesangial hypercellularity that may be diffuse (Fig. 23-5, *B*), or segmental, or in rare cases, focal segmental necrotizing GN with extracapillary proliferation. Typical cases are characterized by an increase in mesangial cells and mesangial matrix with normal-appearing capillary loops, although endocapillary hypercellularity can occur (Fig. 23-5, *C*). Focal segmental or global glomerular sclerosis indicates that the disease has been ongoing for some time (Fig. 23-5, *D*). In addition to glomerular changes, the

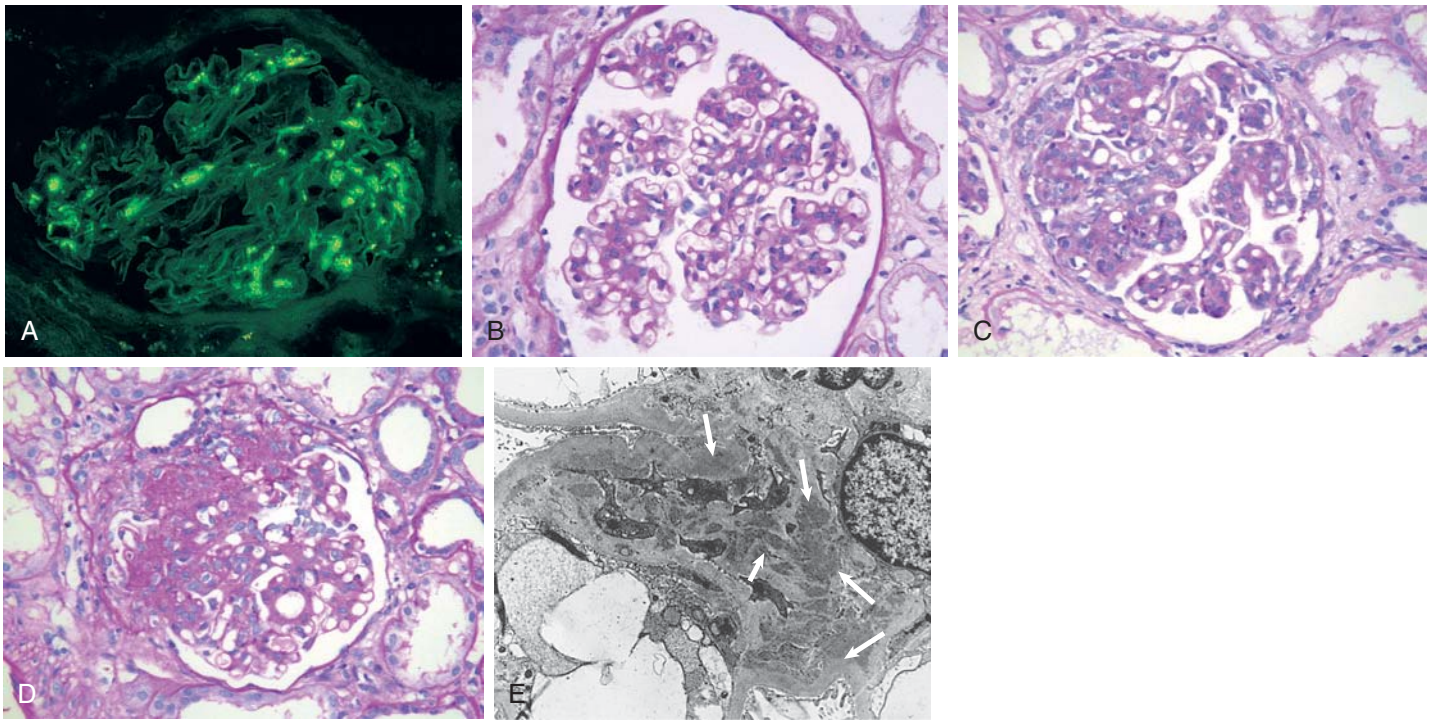


Figure 23-5 Renal pathology in IgA nephropathy. A, Diffuse mesangial IgAN seen on indirect immunofluorescence with fluorescein isothiocyanate–anti-IgA (magnification ×3300.) **B,** Diffuse mesangial hypercellularity (M1, Oxford classification). **C,** Endocapillary hypercellularity (E1). **D,** Segmental sclerosis (S1). (**B, C,** and **D,** Light microscopy with periodic acid–Schiff reaction; ×3300.) **E,** Mesangial electron-dense deposits *(arrows)* (electron micrograph; ×316,000). (***B, C,*** *and* ***D*** *courtesy Prof. I. Roberts.)*

preglomerular arterial vessels often exhibit wall hyalinosis and subintimal fibrosis even in patients with only mild arterial hypertension. In longstanding disease, tubulointerstitial inflammation leads to interstitial fibrosis and tubular atrophy in a pattern no different from other progressive glomerular disease. On occasion, IgAN and minimal change nephrotic syndrome coincide (see under Differential Diagnosis), in which case light microscopy is normal, but there are mesangial IgA deposits.

Morphology is of value in predicting prognosis in patients with slowly progressive disease. The Oxford classification of IgAN is now being widely accepted, although it still requires further validation.[18] This classification identifies four features of prognostic value and can be easily scored on light microscopy: mesangial hypercellularity (M1 when present, M0 when absent), endocapillary hypercellularity (E1), segmental sclerosis (S1), and three degrees of tubular atrophy and interstitial fibrosis (T0, T1, T2). Examples of the glomerular features are shown in Figure 23-5.

Two distinct patterns of injury are seen in AKI. There may be tubular occlusion by RBCs with acute tubular epithelial injury in AKI associated with macroscopic hematuria (Fig. 23-6). Alternatively, glomerular injury may be the cause of AKI, with necrotizing GN and cellular crescent formation. Such crescentic IgAN may develop on a histologic background of established chronic renal injury caused by IgAN or may be the first presentation of IgAN. Small numbers of crescents may be seen in hypertensive patients with stable renal function and no other pathologic evidence of severe glomerular inflammation; the term *crescentic IgAN* should not be used for such patients, in whom the prognosis is often favorable.

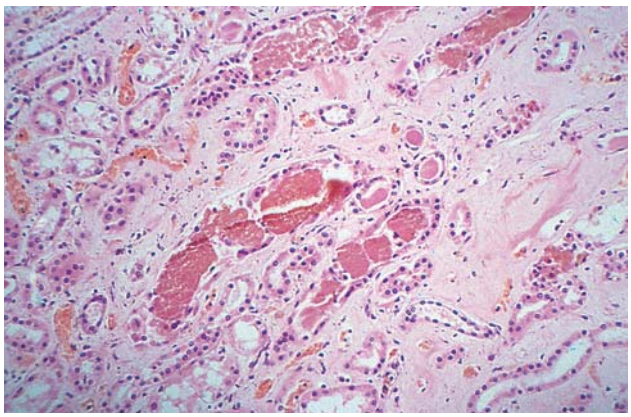


Figure 23-6 Acute kidney injury in IgA nephropathy. Tubular occlusion by red blood cells. This appearance may be associated with only minor glomerular changes. (Hematoxylin-eosin stain; ×300.)

Electron Microscopy

Electron-dense deposits correspond to the mesangial (or capillary loop) IgA (Fig. 23-5, *E*). Typically, electron-dense deposits are confined to mesangial and paramesangial areas, although subepithelial and subendothelial deposits can also be seen. Up to one third of patients will have some focal thinning of the glomerular basement membrane (GBM). On occasion, there will be extensive GBM thinning, suggesting a coincident diagnosis of thin membrane nephropathy (see Chapter 48).

DIFFERENTIAL DIAGNOSIS

The diagnosis of IgAN or HSP nephritis requires identification of mesangial IgA in the glomeruli. Therefore, it cannot be made without a renal biopsy, no matter how suggestive the clinical presentation. Serum IgA is often increased, and there may be IgA in cutaneous

Differential Diagnosis of IgA Nephropathy: Conditions Associated with Mesangial IgA Deposition

- IgA nephropathy
- Henoch-Schönlein nephritis
- Lupus nephritis*
- Alcoholic liver disease
- IgA monoclonal gammopathy
- Schistosomal nephropathy
- IgA-dominant postinfectious glomerulonephritis (usually induced by *Staphylococcus aureus*)

Box 23-1 Differential diagnosis of IgA nephropathy: conditions associated with mesangial IgA deposition. *Distinguishing lupus nephritis (especially International Society of Nephrology/Renal Pathology Society classes II and III) may cause difficulty. The finding of C1q deposition is useful. It indicates classical pathway involvement found in lupus nephritis but not in IgAN.

blood vessels in IgAN and in both affected and unaffected skin in HSP. Neither finding, however, is reliable enough to support the diagnosis without a renal biopsy. Serum complement components are normal.

Mesangial IgA occurs in other conditions and can usually be differentiated by clinical, serologic, and histologic criteria (Box 23-1). None of the light microscopic features alone is diagnostic of IgAN.

An important differential diagnosis is IgA-dominant acute postinfectious glomerulonephritis (APIGN), in which IgA is the dominant immunoglobulin in glomerular deposits. It usually occurs in association with staphylococcal infections. Risk factors particularly include diabetes. Compared with IgAN, patients with IgA-dominant APIGN are more likely to be older and have AKI, documented staphylococcal infection, hypocomplementemia, diffuse glomerular endocapillary hypercellularity with prominent neutrophil infiltration on light microscopy, stronger immunofluorescence staining for C3 than IgA, and the presence of subepithelial humps on electron microscopy.[19]

Hematuria

Nonglomerular causes of hematuria, particularly stones and neoplasia, must be excluded by appropriate investigations (see Chapter 61). In its most characteristic clinical setting—recurrent macroscopic hematuria coinciding with mucosal infection in a man in the second or third decade of life—the diagnosis can be strongly suspected. Such a diagnosis, however, cannot be made without a biopsy because recurrent macroscopic hematuria also occurs in other glomerular diseases, particularly in children and young adults. In young adults, thin basement membrane nephropathy is the most important differential diagnosis for isolated microhematuria.

Nephrotic Syndrome

Patients with IgAN occasionally develop nephrotic syndrome, which is indistinguishable from that in minimal change disease (MCD). There is a sudden onset of nephrosis, with biopsy evidence of glomerular epithelial cell foot process effacement and a prompt complete remission of proteinuria in response to corticosteroids. Only hematuria and mesangial IgA deposits persist after treatment. This pattern occurs particularly in children. These patients are usually regarded as having two separate common glomerular diseases, IgAN and MCD.[20]

Other patients with IgAN may develop nephrotic syndrome with more structural glomerular damage and lack the response to corticosteroids. The clinical differential diagnosis includes common causes of nephrotic syndrome appropriate for the age of the patient (see Chapter 15).

Chronic Kidney Disease: Hypertension, Proteinuria, Renal Impairment

In this context, IgAN will be clinically indistinguishable from many forms of chronic kidney disease (CKD). The renal biopsy may be diagnostic by identifying mesangial IgA, even when structural damage is so advanced on light microscopy that it has the nonspecific features of ESRD.

Acute Kidney Injury

When AKI occurs in a patient known to have IgAN, renal biopsy should be performed unless there is rapid improvement in renal function, after at least 5 days from the onset of kidney function worsening, in response to supportive care and vigorous hydration.[21] Renal biopsy may be required to differentiate the tubular occlusion and acute tubular necrosis that occasionally follow heavy glomerular hematuria from crescentic IgAN or other coincidental causes of AKI (see Fig. 23-6).

Differential Diagnosis of Henoch-Schönlein Purpura

In children, the diagnosis of HSP is usually made on the basis of clinical criteria. Confirmatory evidence of tissue IgA deposition will not be obtained unless persistence of renal disease results in a renal biopsy. In adults, the differential diagnosis is much wider and includes other forms of systemic vasculitis, requiring diagnosis by clinical, serologic, and histologic characteristics (see Chapter 25).

NATURAL HISTORY

IgA Nephropathy

The overall prognosis of IgAN has been reevaluated in recent long-term natural history studies.[22,23] By age 20 years, one fourth of patients will have ESRD, and a further 20% will have progressive impairment of renal function.

Although an active approach to the investigation of microhematuria will increase the size of the cohort of patients found to have IgAN, it will include more with a good prognosis, thus altering the perceived risk of disease progression. Episodes of macrohematuria do not confer a worse prognosis. This may indicate that such episodes occur only early in the natural history of the disease, and that patients doing less well from the point of diagnosis in fact were identified at a later stage in their disease. This is also suggested by the adverse influence on outcome of advancing age at diagnosis.

The risk of ESRD is not uniform. As in any chronic glomerular disease, the presence of hypertension, proteinuria, and reduced glomerular filtration rate (GFR) at presentation, as well as histologic evidence of glomerular and interstitial fibrosis, identifies at the time of diagnosis those with a poor prognosis (Table 23-2). Hyperuricemia, smoking, and increased body mass index are also independent risk factors for progression. However, during follow-up, only hypertension and proteinuria are reliable predictors of risk of progression. Canadian and French studies indicate that risk of progression is

Prognostic Markers at Presentation in IgA Nephropathy	
Clinical	**Histopathologic**
Poor Prognosis	
Hypertension Renal impairment Severity of proteinuria Smoking Hyperuricemia Gross obesity Long duration of preceding symptoms Increasing age	Mesangial hypercellularity Endocapillary proliferation Segmental glomerulosclerosis Tubular atrophy Interstitial fibrosis Capillary loop IgA deposits Crescents (controversial)
Good Prognosis	
Recurrent macroscopic hematuria	
No Impact on Prognosis	
Gender Serum IgA level	Intensity of IgA deposits

Table 23-2 Prognostic markers at presentation in IgA nephropathy. None of the clinical or histopathologic adverse features, except capillary loop IgA deposits, is specific to IgA nephropathy.

negligible when proteinuria remains below 0.2 g/24 h with normal blood pressure.[22,23]

If a renal biopsy documents IgAN in patients with mild disease (i.e., those manifesting with isolated microhematuria, little or no proteinuria, normotension, and normal GFR), the 7- to 10-year prognosis is mostly good.[24,25] However, up to 40% of the patients will develop increasing proteinuria, and up to 5% will lose GFR over this period, implying the need for regular follow-up in such patients. Large studies with long-term follow-up indicate a slow attrition.

Pathologic findings and clinical findings together inform prognosis. The Oxford classification of IgAN has shown that mesangial hypercellularity, endocapillary proliferation, and segmental sclerosis, as well as tubular atrophy and interstitial fibrosis, each add prognostic information even when clinical features (proteinuria, hypertension, GFR) are known at presentation and during follow-up.[18]

Henoch-Schönlein Nephritis

The natural history for HSP is less well defined than for IgAN. Observations are restricted to patients referred for renal biopsy, which excludes the majority of patients with minor transient renal involvement who have an excellent prognosis. The renal prognosis is worse in adults than in children with HSP. In adults, up to 40% will have CKD or ESRD 15 years after biopsy. One series reports an increased mortality from lung and gastrointestinal malignant disease.[16]

TRANSPLANTATION

Recurrent IgA Nephropathy

Transplant registry data show that transplant outcome is not affected for the first 10 years if IgAN is the patient's primary renal disease; thereafter, however, recurrent disease may lead to accelerated graft loss (see also Chapter 108). Mesangial IgA deposits recur in the donor transplant kidney in up to 60% of patients with IgAN.[26] They may occur within days or weeks, but the risk increases with the duration of the transplant. The deposits seem benign in the short term and are not often associated initially with light microscopy changes. In pooled series, recurrent IgAN is 30% in living related transplants versus 23% in cadaveric grafts,[26] but this does not affect graft survival, and living related donation should not be discouraged. However, any urinary abnormality in a potential related donor requires thorough evaluation, including, if necessary, a renal biopsy. Recurrence of crescentic IgAN with rapid graft failure occurs infrequently and is generally resistant to treatment.

In a few unwitting experiments, cadaver kidneys with IgA deposits have been transplanted into recipients without IgAN. In all cases, the IgA rapidly disappeared, supporting the concept that abnormalities in IgAN lie in the IgA immune system and not in the kidney.

Recurrent Henoch-Schönlein Nephritis

Henoch-Schönlein purpura can recur as isolated IgA deposits in the graft (~50% of transplants), as full-blown yet isolated IgAN, or rarely as a full recurrence of systemic involvement including a rash. The characteristics of renal recurrence are apparently similar to those of recurrent primary IgAN.[26] Delay of transplantation once ESRD is reached does not reduce the risk of HSP recurrence.

TREATMENT OVERVIEW

Although specific early treatment intervention might influence the IgA immune system abnormalities that underlie IgAN, the mechanisms of chronic disease progression are unlikely to be unique. Therefore, studies of such IgAN patients likely will provide information applicable to many forms of chronic GN for which IgAN is the paradigm.

The balance of risk against benefit for immunosuppressive therapy is often unfavorable in patients with IgAN, except in the unusual circumstance of crescentic IgAN.

The need for randomized controlled trials (RCTs) of adequate power to answer questions about the prevention of ESRD in IgAN is pressing. It is disappointing, despite the prevalence of IgAN and consensus about its definition and natural history, that there are so few such studies.[27] Patients with HSP have been excluded from almost all treatment studies, so it is uncertain whether any strategies developed for IgAN are applicable to HS nephritis.

TREATMENT OF IgA NEPHROPATHY

Figure 23-7 provides a treatment algorithm for IgAN that is based on the current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[21] The approach distinguishes among the following[27]:

- The "good prognosis" patient, with minor urinary abnormalities, normal GFR, and normotension, who only needs sporadic follow-up for a prolonged period (>10 years)
- The "intermediate prognosis" patient, with significant proteinuria, hypertension, and slow reduction of GFR, who particularly benefits from comprehensive supportive care
- The "poor prognosis" patient, with a rapid loss of GFR, who may require more aggressive immunosuppression

Slowly Progressive IgA Nephropathy ("Intermediate Prognosis")

Minimal evidence exists to suggest the events of progressive glomerular injury are unique to IgAN. Comprehensive supportive therapy following the strategies outlined in Chapter 80 therefore

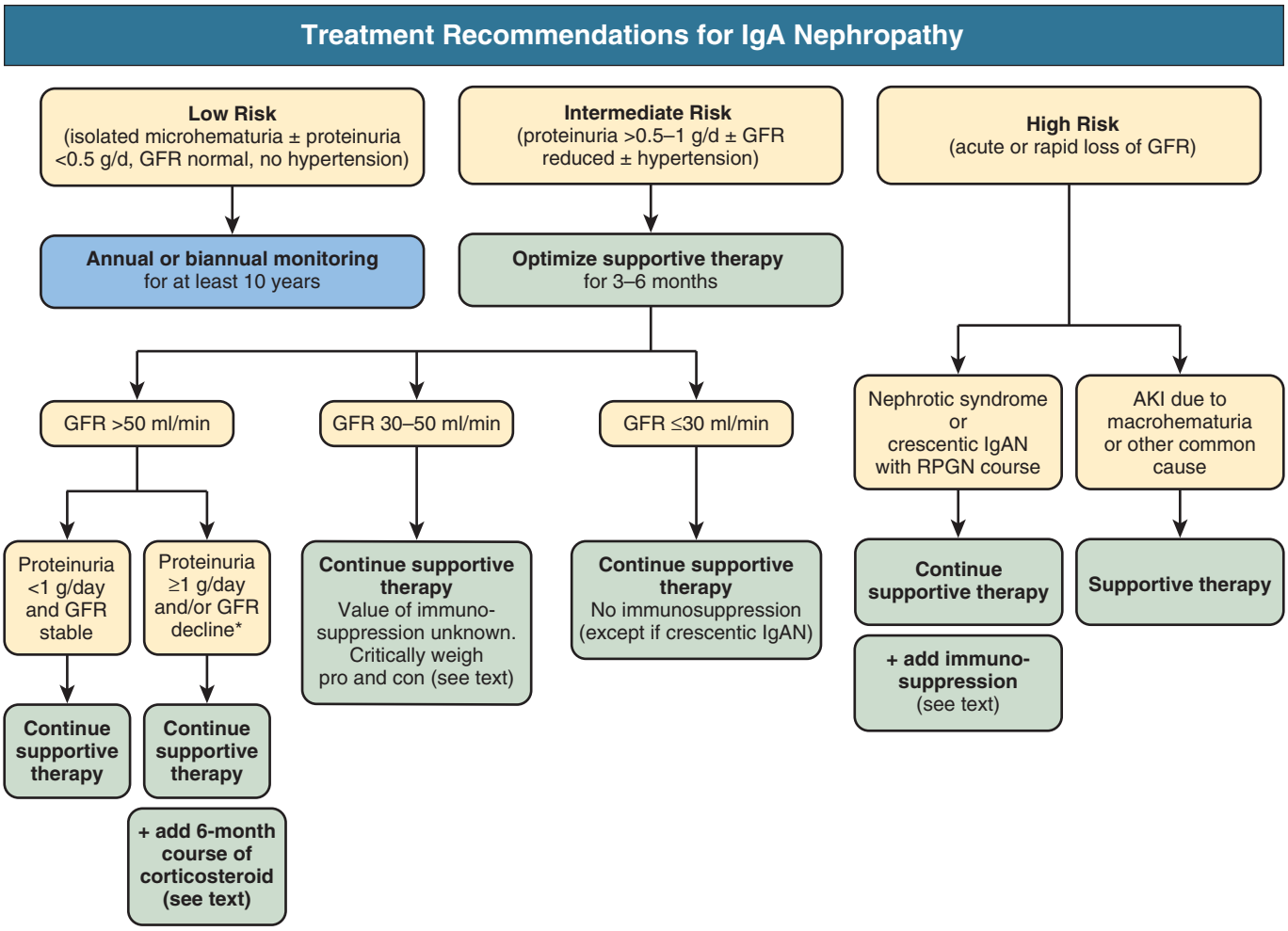


Figure 23-7 Treatment recommendations for IgA nephropathy. *AKI,* Acute kidney injury; *GFR,* glomerular filtration rate; *RPGN,* rapidly progressive glomerulonephritis. *(Modified from reference 27.)*

remains central in the therapeutic approach to patients at risk for progressive IgAN (Fig. 23-7).

Antihypertensives and Proteinuria-Lowering Drugs

There is compelling evidence for the benefit of lowering blood pressure (BP) in the treatment of chronic progressive glomerular disease such as IgAN. In patients with IgAN, there is also evidence that casual clinic BP readings underestimate BP load, as judged by ambulatory BP monitoring and echocardiographic evidence of increased left ventricular mass.[28] Two prospective, controlled trials strongly support the use of angiotensin-converting enzyme (ACE) inhibitors in IgAN patients as first-choice hypotensive agents to lower BP.[29,30] In a randomized study of IgAN, achieving a mean BP of 129/70 mm Hg prevented the decrease in renal function over 3 years seen in patients achieving mean BP of 136/76 mm Hg.[31]

Observational studies indicate that the risk of progression in IgAN decreases significantly if proteinuria can be reduced to less than 1 g/day by any therapeutic maneuver.[23] Another compelling indication for the role of lowering proteinuria in IgAN is based on the superior effectiveness of ACE inhibitors over other antihypertensive agents.[29,30]

Fish Oil

The favorable effects of supplementing the diet with omega-3 fatty acids in the form of fish oil include reductions in eicosanoid and cytokine production, changes in membrane fluidity and rheology, and reduced platelet aggregability. These features should significantly reduce the adverse influence of many mechanisms thought to affect progression of chronic glomerular disease.

The evidence for a beneficial action of fish oil in IgAN is weak; its suggested use in patients at risk in the 2012 KDIGO guidelines is only supported by low-level evidence.[21] However, fish oil treatment does not have the drawbacks associated with immunosuppressive treatment. Fish oil is safe except for a decrease in blood coagulability, which is not usually a practical problem, and an unpleasant taste, with flatulence, which may make compliance difficult. Some fish oil preparations contain significant amounts of cholesterol, necessitating close surveillance if such treatment is initiated. A further confirmatory study of fish oil would be of great value.

Immunosuppressive or Anti-Inflammatory Regimens

Corticosteroids Corticosteroids were given in a short-term RCT in nephrotic adults.[32] Although the trial overall showed no benefit, a small group with minor histologic changes responded rapidly to treatment. Nephrotic syndrome may occur in this setting when MCD and IgAN coincide, in which case the nephrotic syndrome will be fully and promptly corticosteroid responsive. A trial of high-dose corticosteroid therapy is therefore justified in IgAN patients who have nephrotic syndrome associated with minimal glomerular injury.

Five prospective clinical trials have used corticosteroids in nonnephrotic IgAN. Two failed to show any benefit, whereas three found reduced progression of IgAN.[27] Corticosteroid dosage was somewhat lower in the negative versus the positive trials, and several trials did not optimize supportive therapy, in particular ACE inhibitors, or required that such drugs be temporarily halted before the trial. In clinical practice and consistent with the KDIGO guidelines, corticosteroids should only be initiated in high-risk patients if proteinuria remains above 1 g/day after supportive care has been optimized for 3 to 6 months, and only if GFR remains above 50 ml/min. At present, no evidence supports a more intense or complex regimen of intravenous as well as oral corticosteroid therapy over a purely oral prednisolone regimen, starting with 1 mg/kg/day for 2 months, then reduced by 0.2 mg/kg/day/month.[27] At least two large prospective trials of oral corticosterods in IgAN added to optimized supportive care (STOP-IgAN and TESTING) are underway.

Cyclophosphamide and Azathioprine Cyclophosphamide has been used in combination with warfarin and dipyridamole in two RCTs, with inconsistent results. Both showed modest reduction in proteinuria, but only one preserved renal function. Cyclophosphamide followed by azathioprine combined with prednisolone preserved renal function in patients with a poor prognosis, although BP control was suboptimal.[33] Many physicians regard the toxicity of cyclophosphamide as unacceptable in young adults with IgAN.[27] In another recent study, adding azathioprine to corticosteroids in proteinuric IgAN patients with a GFR greater than 50 ml/min had no added benefit and only increased side effects.[34] Neither agent is therefore recommended in "intermediate risk" IgAN patients by the 2012 KDIGO guidelines.[21]

Mycophenolate Mofetil Mycophenolate mofetil (MMF) has been used in several controlled trials in high-risk patients. Two trials in Caucasian patients failed to demonstrate a benefit, whereas a study in Chinese patients noted reduced proteinuria and preservation of GFR.[27] Whether racial effects underlie these discrepant results remains to be clarified. In another Chinese trial, four of 32 IgAN patients receiving MMF plus corticosteroids died of *Pneumocystis* pneumonia.[35] MMF is therefore not recommended in "intermediate risk" IgAN patients by the 2012 KDIGO guidelines.[21]

Dipyridamole and Warfarin Two RCTS with dipyridamole and warfarin showed mutually inconsistent results. There was no benefit in one and preserved renal function in the other. Neither drug is currently recommended in IgAN patients.[21]

Cyclosporine Cyclosporine has been used in one controlled trial in IgAN.[35a] Patients showed a reversible decrease in proteinuria along with a decrease in creatinine clearance, suggesting the changes were a hemodynamic effect of cyclosporine rather than an immunomodulating effect.

Pooled Human Immunoglobulin Pooled human immunoglobulin has given encouraging preliminary results in patients with IgAN who have an aggressive clinical course. Proteinuria was reduced, deterioration of GFR slowed, and histologic activity lessened on repeated renal biopsies.[36] No RCT is available for this approach.

Rapidly Progressive IgA Nephropathy ("Poor Prognosis")

In this uncommon situation of rapidly progressive renal failure associated with crescentic IgAN, the risk-benefit ratio most strongly favors intensive immunosuppressive therapy, because untreated the patient will rapidly progress to ESRD. Treatment has often combined plasma exchange with prednisolone and cyclophosphamide.[37] Early clinical response is favorable, as in other crescentic nephritis. Medium-term results, however, are disappointing; in one half of the reported cases, patients have reached ESRD within 12 months. A subset of patients with circulating IgG-ANCA (antineutrophil cytoplasmic antibody) may have a more favorable response to immunosuppressive therapy similar to that seen in other ANCA-positive crescentic nephritis.[38] With no RCTs of treatment, it is not possible to be certain which elements of the regimen (corticosteroids, cyclophosphamide, or plasma exchange) are mandatory.

Other Therapeutic Approaches to Progressive IgA Nephropathy

Reduction of IgA Production

Tonsillectomy reduces the frequency of episodic hematuria when tonsillitis is the provoking infection. A long-term retrospective study from Japan suggests that tonsillectomy may reduce the risk of renal failure, but this is not supported by studies from Germany, Italy, or China. The lack of controlled trials is particularly important because the natural history is that macrohematuria becomes frequent with time, independent of a specific treatment. Tonsillectomy may be indicated in the occasional patient with recurrent AKI with macroscopic hematuria induced by tonsillitis, but is not routinely recommended[21]; there is no role for prophylactic antibiotics. Dietary gluten restriction, used to reduce mucosal antigen challenge, has not been shown to preserve renal function. A trial evaluating the role of an enteric corticosteroid preparation in "intermediate prognosis" IgAN patients (NEFIGAN) is underway.

Prevention and Removal of IgA Deposits

The ideal treatment of IgAN patients would remove IgA from the glomerulus and prevent further IgA deposition. This remains a remote prospect while the pathogenesis remains incompletely understood.

Transplant Recurrence

There is no evidence that newer immunosuppressive agents have modified the frequency of recurrent IgA deposits or are of value in recurrent disease. There is, however, registry evidence that transplant outcome is improved if corticosteroids are continued long term.[38a] Most clinicians therefore merely optimize supportive care in such patients. When crescentic IgAN recurs with rapidly deteriorating graft function, treatment as for primary crescentic IgAN has been used, although evidence of its success is sparse.

TREATMENT OF HENOCH-SCHÖNLEIN NEPHRITIS

Many patients have transient nephritis during the early phase of HSP, which spontaneously remits and requires no treatment. There are no prospective RCTs to guide the treatment of HS nephritis. Most therapeutic studies of IgAN exclude those with HSP, so it is uncertain whether a number of potential treatments have a role in HS nephritis[21] (Box 23-2).

Rapidly Progressive Chronic Kidney Disease Caused by Crescentic Nephritis

Crescentic nephritis is more common in HS nephritis than in IgAN, particularly early in the course of HSP. There is little specific information on treatment in adults or children, but regimens based on those for other forms of systemic vasculitis are widely used. These have included corticosteroids and cyclophosphamide, with the

Treatment Recommendations for Henoch-Schönlein Nephritis

Crescentic nephritis: regimen as for crescentic IgA nephropathy (see Fig. 23-7)

All other Henoch-Schönlein nephritis (including nephrotic syndrome): regimen as for IgA nephropathy (see Fig. 23-7)

Hypertension: ACE inhibitor and ARB are agents of first choice; target blood pressure: 130/80 mm Hg if proteinuria <1 g/24 h, 125/75 mm Hg if proteinuria >1 g/24 h

Transplantation: cadaveric donor may be preferable to living related donor in children (controversial)

Box 23-2 Treatment recommendations for Henoch-Schönlein nephritis. *ACE,* Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker.

addition of plasma exchange or pulse methylprednisolone in some cases. However, a recent randomized French study in adults with severe HS nephritis failed to detect a benefit of cyclophosphamide plus steroids over steroids alone.[39]

Active Henoch-Schönlein Nephritis Without Renal Failure

There is little information about less aggressive HS nephritis. Corticosteroids alone have never been shown to be beneficial. There is no evidence that early use of corticosteroids in HSP may prevent nephritis.[21] Promising findings with combination therapy of corticosteroids, cyclophosphamide, and antiplatelet agents have been reported in only small, nonrandomized studies.[21] A nonrandomized study reported that prednisolone and azathioprine preserved renal function and improved histologic appearances, but relied on historical controls.[40]

Slowly Progressive Chronic Kidney Disease

Whereas the renal histology and clinical course of slowly progressive HS nephritis and IgAN may be indistinguishable, patients with HS nephritis have not been included in studies of fish oil. Tight BP control with ACE inhibitors or angiotensin receptor blockers (ARBs) is recommended for proteinuric HS nephritis as for IgAN. The 2012 KDIGO guidelines recommend a similar indication for corticosteroids in slowly progressive HS nephritis as in intermediate-risk IgAN patients.[21]

Transplant Recurrence

No treatment is known to reduce the risk of recurrence. There is some evidence that recurrence is more common and more likely to lead to graft loss in children receiving kidneys from living rather than deceased donors, although this is not confirmed in adults.[41,42] If crescentic HS nephritis recurs, intensive immunosuppression may be justified as for primary disease. This, however, has not been thoroughly evaluated.

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CHAPTER 24

Anti–Glomerular Basement Membrane Disease and Goodpasture Disease

Richard G. Phelps and A. Neil Turner

The syndrome of renal failure and lung hemorrhage was associated with the name of Ernest Goodpasture by Stanton and Tange in their description of nine cases in 1958.[1,2] All nine patients presented with lung hemorrhage and acute renal failure and died within hours or days. These features had been prominent in the case of a young man who died during the influenza pandemic of 1919, whose postmortem findings were memorably reported by Goodpasture[1]: "The lungs gave the impression of having been injected with blood through the bronchi so that all the air spaces were filled" (Fig. 24-1).

Several diseases are now recognized as being associated with alveolar hemorrhage and rapidly progressive glomerulonephritis (RPGN). Nevertheless, this remains a striking clinical entity with relatively few causes and few pathogenetic mechanisms.

Because the first recognized mechanism was anti–glomerular basement membrane (anti-GBM) antibody formation and deposition, Goodpasture's name is firmly associated with anti-GBM disease (Goodpasture disease), even though this is responsible for only a proportion of patients with Goodpasture syndrome of lung hemorrhage and RPGN. The terminology used in this chapter is defined in Table 24-1.

ETIOLOGY AND PATHOGENESIS

Autoimmunity to a Component of Glomerular Basement Membrane

Goodpasture disease is caused by autoimmunity to the carboxyl terminal, noncollagenous (NC1) domain of a type IV collagen chain, α3(IV)NC1, also known as the Goodpasture antigen[3,4] (Fig. 24-2). Type IV collagen is an essential constituent of all basement membranes. In most tissues, it is composed of trimers comprising two α1 chains and one α2 chain, but there are also four tissue-specific chains, α3 through α6.[5,6] Three of these, α3 through α5, are found in GBM as well as in the basement membranes of the alveolus, the cochlea, parts of the eye (including corneal basement membrane and Bruch membrane), the choroid plexus of the brain, and some endocrine organs.

All patients with RPGN, lung hemorrhage, and anti-GBM antibodies have antibodies to α3(IV)NC1, usually binding predominantly to a single or a very restricted set of epitopes. Some patients also have antibodies to other basement membrane constituents, including other collagen IV chains, usually in low titer.

Predisposing Factors

Both environmental and genetic factors appear to be important in etiology. There are strong associations between Goodpasture disease and HLA class II alleles, including DRB1*1501 and DR4 alleles, whereas DR1 and DR7 confer strong and dominant protection.[7] Of likely increasing importance, it is now clear that treatment of multiple sclerosis (MS) with alemtuzumab, a monoclonal antibody targeting CD52 on B and T cells, is associated with the development of new autoimmunity, including anti-GBM disease, sometimes as late as 4 years after treatment. Only a handful of cases have been reported during development of the drug for MS, but with wider use, this could become a numerically very significant predisposing factor. It remains to be established whether carriage of DRB1*1501, which is overrepresented in MS, influences the risk of developing anti-GBM disease after alemtuzumab therapy.

Precipitating Factors

The onset of acute disease has long been linked to various precipitating factors. Theories of pathogenesis include factors that alter antigen processing to generate peptides that are usually destroyed or hidden, and to which tolerance is therefore deficient[8,9] and molecular mimicry.[10] None of these is proved. Reports of temporal and geographic clustering of cases suggest an environmental trigger,[11] but no specific infectious agent has been consistently identified. Hydrocarbon exposure has been linked to disease onset in several striking case reports; but in some cases, such exposure may simply trigger lung hemorrhage in patients who already have the disease. Furthermore, exposures of this kind are very common in the modern world. Similarly, cigarette smoking may precipitate lung hemorrhage in patients who already have circulating autoantibodies, but there is no evidence for a role in causation.

In several cases, renal trauma or inflammation has preceded the development of the disease (Box 24-1). These may alter α3(IV)NC1 turnover and metabolism qualitatively or quantitatively, providing an opportunity for self-tolerance to be broken. Qualitative changes in the basement membrane epitopes presented to T cells could be a result of overloading of the usual or recruitment of alternative processing pathways, such as extracellular processing by proteases released into inflamed glomeruli. The quantity of α3(IV)NC1 presented to T cells may be greater where there has been damage to the basement membrane, as occurs in systemic small-vessel vasculitis (see Chapter 25). Some features suggest that an anti-GBM response may be a secondary phenomenon in some patients with vasculitis.[12,13] The association with membranous nephropathy is interesting because the thickened GBM in that disease contains increased amounts of the tissue-specific type IV collagen chains, including the Goodpasture antigen. The same could apply to a recently suggested possible association with longstanding type 1 diabetes mellitus.[14]

Mechanisms of Renal Injury

The α3(IV)NC1 autoantibodies are central in the pathogenesis of Goodpasture disease[15,16] (Fig. 24-3). Antibodies eluted from the kidneys of patients who had died of Goodpasture disease rapidly bind to the GBM and cause glomerulonephritis (GN) when they are

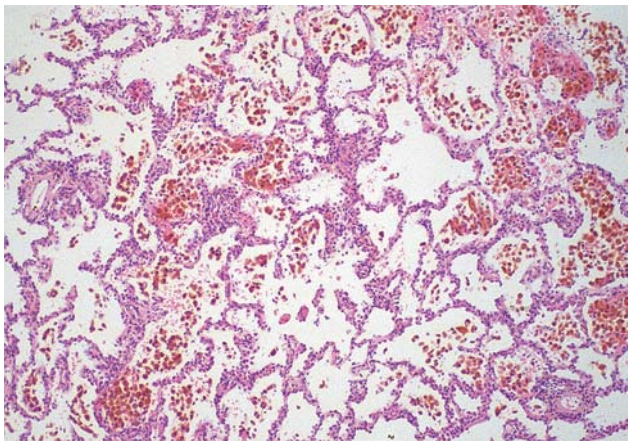

Figure 24-1 Alveolar hemorrhage. Open lung biopsy in a patient with Goodpasture disease shows alveolar hemorrhage. *(Courtesy Dr. E. Mary Thompson, St Mary's Hospital, London.)*

Predisposing Events Associated with Presentation of Goodpasture Disease

Possibly Induce Autoimmune Response and Disease

Systemic small-vessel vasculitis affecting glomeruli
Membranous nephropathy (MN)
Lithotripsy of renal stones
Urinary obstruction
Alemtuzumab therapy for multiple sclerosis

Precipitate Pulmonary Hemorrhage

Cigarette smoke
Hydrocarbon exposure
Pulmonary infection
Fluid overload

Box 24-1 Predisposing events associated with the presentation of Goodpasture disease.

Type IV Collagen Structure

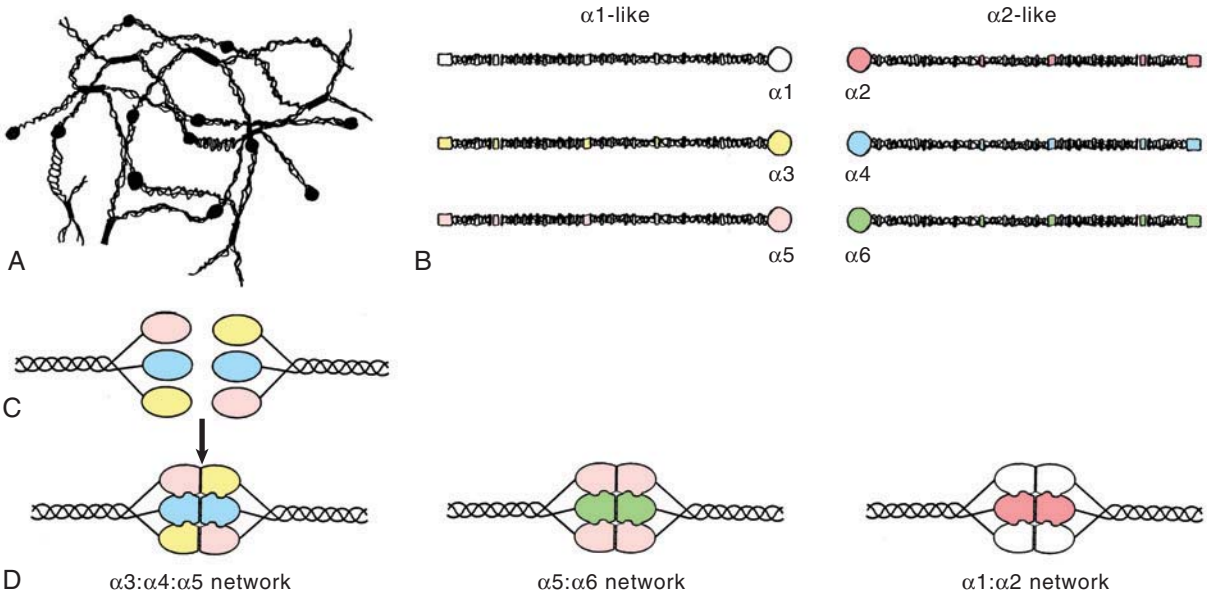

Figure 24-2 Type IV collagen structure. A, The type IV collagen network makes a "chicken wire" structure in the GBM. **B,** Six paired type IV collagen genes, *COL4A1* to *COL4A6,* encode type IV collagen monomers α1 to α6. These associate in two or three defined monomer types per protomer (carboxyl terminal domains of α3:α4:α5 shown in **C,** to form three recognized networks shown in **D,** α1:α2 is present in almost all basement membranes; α3:α4:α5 is the major constituent of GBM and is a significant component of alveolar basement membrane and other locations; and α5:α6 is found in Bowman capsule, skin, esophagus, and other locations.

Anti–Glomerular Basement Membrane (GBM) Terminology

Term	Definition	Pathogenesis
Pulmonary renal syndrome	Renal and respiratory failure	Many causes (see Fig. 24-7)
Goodpasture syndrome	RPGN and alveolar hemorrhage	Several causes (see Box 24-2)
Anti-GBM disease	Disease associated with antibodies specific for (any) components of GBM	Most important are Goodpasture disease and Alport syndrome post-transplant anti-GBM disease
Goodpasture disease	Disease associated with autoantibodies specific for α3(IV)NC1 May include RPGN, lung hemorrhage, or both	Autoimmunity to α3(IV)NC1
Alport syndrome post-transplant anti-GBM disease	Glomerulonephritis associated with anti-GBM antibodies developing after renal transplantation in Alport syndrome patients	Immunity to foreign collagen IV chains not expressed in Alport syndrome patients usually α3 or α5 (IV)NC1

Table 24-1 Definition of terms associated with anti-GBM disease and Goodpasture syndrome. *RPGN,* Rapidly progressive glomerulonephritis.

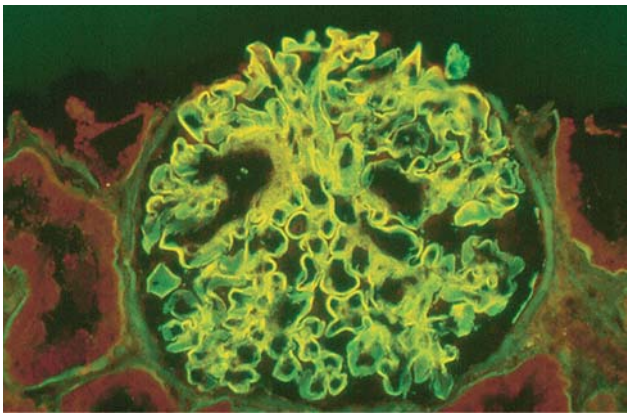

Figure 24-3 Autoantibodies to Goodpasture antigen bound to a normal glomerulus. Direct immunofluorescence of normal kidney with sera from a patient with Goodpasture disease shows the antigen in a patient with lung hemorrhage and hematuria. *(Courtesy Dr. Richard Herriot, Aberdeen Royal Infirmary, UK.)*

injected into monkeys.[17] Furthermore, the deposited antibodies are predominantly IgG1 and are complement fixing. Contributions to renal injury mediated by such antibodies come from complement and from neutrophil and macrophage infiltration. T cells are essential for driving autoantibody production by T cell–dependent B cells, and in experimental renal disease, they are critical in producing glomerular crescents,[15,18] which are a usual feature of Goodpasture disease. Moreover, in mice engineered to express the human susceptibility HLA allele, DRB1*1501, α3(IV)NC1-specific CD4 T cells are sufficient to transfer disease between animals.[19]

Agents that downregulate inflammation by inhibiting interleukin-1 or tumor necrosis factor, or that inhibit recruitment of inflammatory cells by blockade of adhesion molecules or chemoattractants, suppress injury in experimental models of anti-GBM disease. Evidence in humans and in experimental animals supports the severity of renal injury being increased by proinflammatory cytokines or by stimuli likely to elicit them, such as bacteremia.[18] Crescent formation is seen in aggressive inflammatory GN, as described in Chapter 16 (see Fig. 16-8).

Lung Hemorrhage

Lung hemorrhage in Goodpasture disease (but not in small-vessel vasculitis, the other major cause of Goodpasture syndrome) occurs only if there is an additional insult to the lung, which is usually cigarette smoke. However, infection, fluid overload, toxicity from inhaled vapors or other irritants, and the systemic effects of some cytokines are also possibilities. This is probably because the alveolar capillary endothelial cell provides a better barrier between circulating immunoglobulin and the underlying basement membrane than the diaphragm-free fenestrations of the glomerular capillary endothelial cell. In the glomerulus, antibodies have direct access to the GBM because of the fenestrations of glomerular endothelium. Other sites at which the Goodpasture antigen is found are not involved in Goodpasture disease, except possibly the choroid plexus, where the endothelium is again fenestrated, and more rarely the eye.

EPIDEMIOLOGY

Goodpasture disease is rare, with a possibly increasing incidence in Caucasian populations approaching 1 case per 1 million population per year.[14] The incidence in black and South Asian populations appears to be lower. The incidence in other racial groups is uncertain. There is a slight male predominance. Lung hemorrhage is more common in younger patients.

CLINICAL MANIFESTATIONS

Between 50% and 75% of patients present with acute symptoms of lung hemorrhage and are found to be in a state of advanced renal failure. Symptoms are usually confined to the preceding few weeks or months, but rapid progression (during days) or much slower progression (during many months) may occur. A lack of systemic symptoms, other than those related to anemia, is typical, although an apparently minor infection often triggers the clinical presentation.

Lung Hemorrhage

Lung hemorrhage may occur with renal disease or in isolation. Presenting symptoms may include cough and hemoptysis, but hemorrhage into alveolar spaces may result in marked iron deficiency anemia and exertional dyspnea, even in the absence of hemoptysis. Depending on the degree and chronicity of lung hemorrhage, examination findings may include pallor, dry inspiratory crackles, signs of consolidation, or respiratory distress. Recent lung hemorrhage typically is shown on the radiograph as central shadowing that may traverse fissures and give rise to the appearance of an air bronchogram (Fig. 24-4). However, even lung hemorrhage sufficient to reduce the hemoglobin concentration may cause only minor or transient radiographic changes, and these cannot be confidently distinguished radiologically from other causes of alveolar shadowing, notably edema or infection. The most sensitive indicator of recent lung hemorrhage is an increased uptake of inhaled carbon monoxide (DLCO). Patients with lung hemorrhage are usually current cigarette smokers.

In isolated lung disease, progressive alveolar or fibrotic disease or pulmonary hemosiderosis may be suspected, although at least hematuria is usually present. This may continue for months or in rare cases recurrently for years before significant renal disease occurs.

Glomerulonephritis

Patients with GN may notice dark or red urine, but progression to oliguria is sometimes so rapid that this phase, if it occurs, is missed. In one third to half of patients, GN occurs in the absence of lung hemorrhage. In this subgroup, because systemic symptoms are generally not prominent, presentation is often late with renal failure.

Whatever the early pattern of disease, once significant renal impairment has occurred, further deterioration in renal function is usually rapid. Presentation at or shortly after acceleration of the disease process is common, and patients may demonstrate very rapid loss of renal function and life-threatening lung hemorrhage. Urinalysis always reveals hematuria (even in apparently isolated pulmonary disease), usually modest proteinuria, and dysmorphic red blood cells and RBC casts on microscopy. The kidneys are generally of normal size but may be enlarged. Hematuria may be substantial or associated with loin pain in acute disease.

PATHOLOGY

Renal biopsy is essential as it provides diagnostic and prognostic information. Typical appearances are of diffuse proliferative GN with

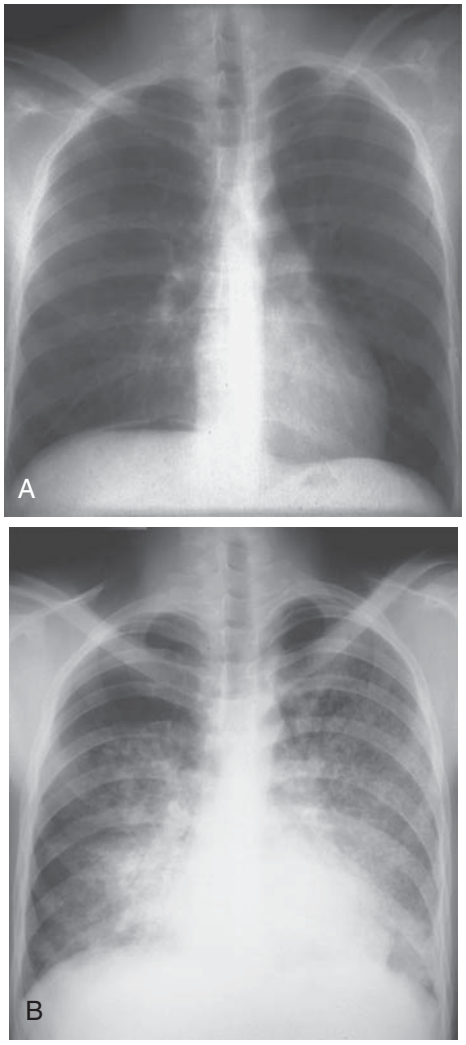

Figure 24-4 Lung hemorrhage. A, Patient with early pulmonary hemorrhage. The chest radiograph still appears normal. **B,** Radiograph taken 4 days later shows the evolution of alveolar shadowing caused by lung hemorrhage.

variable degrees of necrosis, crescent formation, glomerulosclerosis, and tubular loss (Fig. 24-5). The degree of crescent formation and tubular loss correlates with renal prognosis. Characteristically, the crescents all appear to be of similar age and cellularity. When biopsy is performed earlier in the disease, changes may be limited to focal and segmental mesangial expansion, with or without necrosis. This progresses to hypercellularity and then to more general changes, including fractures of the GBM and Bowman capsule, neutrophils in the glomeruli, and glomerular capillary thrombosis.[20]

Immunohistology

In the presence of severe glomerular inflammation, linear deposition of immunoglobulin along the GBM is pathognomonic. The immunoglobulin is usually IgG, sometimes (10% to 15%) with IgA or IgM, but rarely, IgA alone is detected. Linear deposition of C3 is detectable in about 75% of biopsies. Linear immunofluorescence with anti-immunoglobulin reagents is occasionally seen in other conditions, usually without glomerular inflammation (Box 24-2). In most cases, the deposited immunoglobulin is less abundant than in Goodpasture disease and is either nonspecifically deposited or bound to GBM components other than type IV collagen chains.

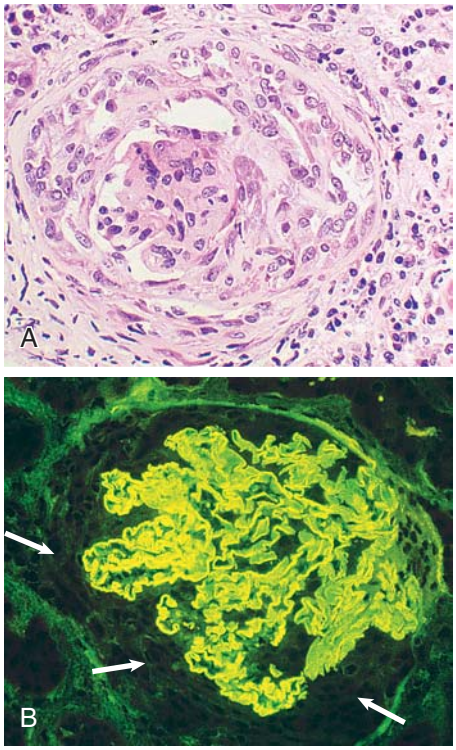

Figure 24-5 Renal biopsy in Goodpasture disease. A, Glomerulus from a patient with Goodpasture disease showing a recent, mostly cellular crescent. **B,** Direct immunofluorescence study showing ribbon-like linear deposition of IgG along the glomerular basement membrane. The glomerular tuft is slightly compressed by cellular proliferation (exhibiting no immunofluorescence), forming a crescent *(arrows). (Courtesy Dr. Richard Herriot, Aberdeen Royal Infirmary, UK.)*

Conditions Associated with Linear Binding of Immunoglobulin to GBM

Specific Binding to GBM
Goodpasture syndrome
Alport syndrome after renal transplantation

Nonspecific Binding to GBM
Diabetes
Cadaver kidneys
Light-chain disease
Fibrillary glomerulopathy
Systemic lupus erythematosus (possibly specific but not considered directly pathogenic)

Box 24-2 Conditions associated with linear binding of immunoglobulin to the glomerular basement membrane (GBM).

Circulating IgG anti-GBM antibodies are almost invariably present, even in the rare instances in which only IgM or IgA is demonstrated on the GBM. Antibodies may be detected and quantified by use of immobilized Goodpasture antigen in an immunoassay. The titer of anti-GBM antibody at presentation correlates with the severity of nephritis. Treatment and relapse are often mirrored by changes in titer.

Pathology in Other Tissues

Pathologic changes in lung tissue can be difficult to interpret because the changes, including immunoglobulin deposition, are often patchy

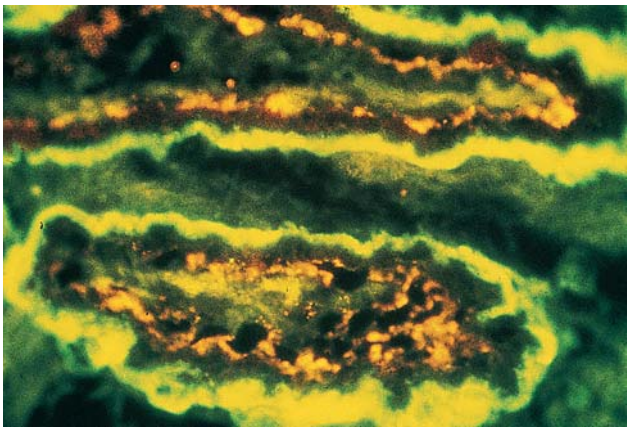

Figure 24-6 IgG binding to choroid plexus. Direct immunofluorescence study showing binding of IgG to the choroid plexus of a patient who died of Goodpasture disease. *(Courtesy Dr. Stephen Cashman, Imperial College, London.)*

and may be missed. Frequently, the only findings are mild, chronic inflammation and hemosiderin-laden macrophages, which are consistent with other more common pathologic diagnoses. This makes negative bronchoscopic or open lung biopsy findings unhelpful in excluding the diagnosis.

Other tissues in which α3(IV)NC1 is expressed are rarely available for pathologic analysis, but even if antibody is deposited in these other sites, it is rarely associated with clinical disease. A number of case reports describe neurologic syndromes, particularly convulsions, that may be related to antibody deposition in the choroid plexus, but may have other explanations in patients with acute kidney injury (Fig. 24-6). Other reports have described retinal detachment, in one case with antibody deposition, but again, this is rare. Placental tissue also contains the Goodpasture antigen and has been reported in a single case to act as a "sink" that binds anti-GBM antibody during pregnancy, resulting in exacerbation of glomerulonephritis following delivery.

DIFFERENTIAL DIAGNOSIS

Diagnosis of Goodpasture disease in patients who present with Goodpasture syndrome does not usually present difficulties once the possibility has been raised, although the urgency is often not appreciated. Direct immunofluorescence on renal tissue and assay for circulating anti-GBM antibodies are the most rapid techniques, and renal biopsy is always indicated. Diagnosis is often delayed when patients present with subacute disease affecting the lung or the kidney in isolation. Patients with subacute lung hemorrhage may never report hemoptysis and may present with diffuse lung disease, which has many causes. Testing for hematuria is important.

Detection of Anti–Glomerular Basement Membrane Antibodies

Direct immunohistology using antibodies that are specific for different Ig classes is very sensitive for detection of anti-GBM antibody production, because the GBM selectively adsorbs and concentrates low levels of circulating antibody. However, in some circumstances, GBM may also adsorb antibody nonspecifically (see Box 24-2). Detection of anti-GBM antibodies in serum requires solid-phase immunoassays based on preparations of human or animal GBM or recombinant antigen. The quality of these assays is variable. Confirmation of the specificity of anti-GBM antibodies may be obtained by Western blotting of serum onto solubilized human GBM or recombinant α3(IV)NC1, usually at a reference laboratory. Indirect immunohistology (putting patient serum onto normal kidney sections) is too insensitive for reliable diagnostic use.

False-positive results may be encountered in sera from patients with inflammatory diseases that often exhibit increased nonspecific binding. This places greater emphasis on the purity of antigen used for anti-GBM assays. False-negative results are usually encountered in patients with low titers of antibodies in association with isolated lung disease or with very early or subacute renal disease. Low titers may also be associated with anti-GBM disease that occurs after renal transplantation in patients with Alport syndrome (see later discussion).

In very advanced disease, linear antibody deposition may not be seen because of extensive destruction of GBM structure. Otherwise, deposited immunoglobulin remains detectable for some months after immunoassays have become negative.

Patients with Anti-GBM Antibodies and Other Diseases

Antineutrophil Cytoplasmic Antibody and Systemic Small-Vessel Vasculitis

Anti-GBM antibodies are sometimes detected in patients with antineutrophil cytoplasmic antibody (ANCA), especially ANCA with specificity for myeloperoxidase (see Chapter 25). Such "double-positive" patients may have a clinical course and response to treatment more typical of vasculitis than of Goodpasture disease and have possibly developed anti-GBM antibodies secondary to vasculitic glomerular damage.[8-11] Anti-GBM titers tend to be lower in ANCA-positive anti-GBM antibody–positive patients than in patients with anti-GBM antibodies alone. Recovery of renal function may be more likely if ANCAs are present, even if patients are dialysis dependent when treatment is started, although newer series have failed to detect the differences described in early reports.

Membranous Nephropathy

Anti-GBM antibodies are occasionally identified in patients with membranous nephropathy (MN), usually coincident with an accelerated decline in renal function and the formation of glomerular crescents.[5,14,21] About two thirds of studies report evidence of evolution from preexisting nephrotic syndrome, and about half report a previous kidney biopsy showed typical MN. Progression to end-stage renal disease (ESRD) has usually been rapid, but the diagnosis has rarely been made at an early enough stage to expect intensive treatment to be successful. Three patients with Goodpasture disease later developed typical MN.

Goodpasture Syndrome

A wide variety of conditions may cause simultaneous pulmonary and renal disease. The term *pulmonary-renal syndrome* implies failure of both organs, the most common cause being fluid overload in a patient with renal failure of any cause. This may resemble Goodpasture syndrome, particularly if there is hematuria and preexisting cardiac dysfunction. However, a number of diseases may mimic Goodpasture syndrome (lung hemorrhage with RPGN) to varying degrees by causing acute kidney injury with acute lung disease (Box 24-3). Diseases associated with the syndrome fall into two pathogenetic classes: those characterized by systemic vasculitis and those associated with anti-GBM antibodies (Goodpasture disease; Box 24-4).

Nonimmune Causes of Pulmonary-Renal Syndrome

With Pulmonary Edema
Acute kidney injury with hypervolemia
Severe cardiac failure

Infective
Severe bacterial pneumonia (e.g., *Legionella*) with renal failure
Hantavirus infection
Opportunistic infections in the immunocompromised patient

Other
Acute respiratory distress syndrome with renal failure in multiorgan failure
Paraquat poisoning
Renal vein/inferior vena cava thrombosis with pulmonary emboli

Box 24-3 Nonimmune causes of pulmonary-renal syndrome.

Causes of Lung Hemorrhage and Rapidly Progressive Glomerulonephritis

Diseases Associated with Antibodies to the GBM (20%-40% of cases)
Goodpasture disease (spontaneous anti-GBM disease)

Diseases Associated with Systemic Vasculitis (60%-80% of cases)
Granulomatosis with polyangiitis (Wegener) (common)
Microscopic polyangiitis
Systemic lupus erythematosus
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
Henoch-Schönlein purpura
Behçet syndrome
Essential mixed cryoglobulinemia
Rheumatoid vasculitis
Drugs: penicillamine, hydralazine, propylthiouracil

Box 24-4 Causes of lung hemorrhage and rapidly progressive glomerulonephritis. *GBM,* Glomerular basement membrane.

These diseases can sometimes be differentiated clinically, but serology and renal biopsy are usually required. Renal biopsy also provides valuable prognostic information.

NATURAL HISTORY

There is some variability in the pattern of early disease. Most patients present acutely with lung hemorrhage or advanced renal failure and report that the illness developed during only weeks or a few months. However, there are several reports of patients presenting with mild respiratory symptoms or incidental microscopic hematuria with disease progressing much more slowly during months or years; some have abruptly developed the full acute syndrome.

Once RPGN has developed, renal function is rapidly and often irretrievably lost. Progression is often much more rapid than in RPGN occurring in other contexts, such as microscopic polyangiitis, perhaps because more glomeruli are simultaneously affected. Consequently, there is a much narrower window of opportunity for effective treatment.

Response to Immunosuppressive Treatment in a Patient with Goodpasture Disease

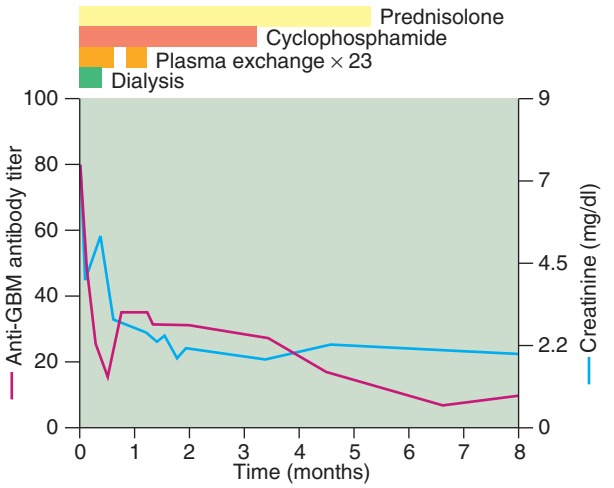

Figure 24-7 Response to immunosuppressive treatment in Goodpasture disease. The patient required dialysis for renal disease but had no lung hemorrhage. The good response to treatment was unusual but not unique. The renal biopsy showed that 85% of glomeruli contained recent (mostly cellular) crescents, suggesting very acute disease, which may be indicative of a more favorable response to treatment.

Although a severe exacerbation of lung disease usually coincides with deterioration of renal function, the natural history of isolated lung disease critically depends on continued exposure to irritants.

TREATMENT

Immunosuppressive Regimens

Before the introduction of immunosuppressive treatment, most patients died shortly after the development of renal impairment or lung hemorrhage.[18] Lung hemorrhage can usually be arrested now within 24 to 48 hours. Renal function can be protected if impairment is mild, and even severe renal impairment can be reversed in some patients. However, dialysis-dependent patients rarely recover kidney function despite immunosuppression and should probably be immunosuppressed only if lung hemorrhage occurs.

Figure 24-7 shows a chart recording the treatment of a patient with Goodpasture disease. Treatment recommendations for acute severe disease were devised to reduce levels of circulating pathogenic antibodies as rapidly as possible, as well as lessen their contribution to rapid glomerular destruction (Table 24-2). However, this regimen is almost certainly effective through a much broader range of mechanisms, including T cell depletion. Once the disease is controlled, immunosuppression can usually be tapered off during 3 months, and subsequent relapse is uncommon. The immune response is self-limited in the absence of immunosuppression, with antibodies disappearing over 1 to 2 years. Spontaneous remissions and effectiveness of relatively brief periods of immunosuppression are in striking contrast to the more prolonged immunosuppression generally required to prevent relapse of vasculitis and suggest a greater capacity for restoration of usual tolerance to α3(IV)NC1[22] than to targets in vasculitis.

In RPGN with no evidence of an infective cause, immunosuppressive therapy should be started immediately, sometimes before the renal biopsy findings are available. If therapy is stopped after a

Treatment Regimen for Acute Goodpasture Disease	
Therapy	**Recommendation**
Prednisolone	1 mg/kg/24 h orally. Reduce at weekly intervals to achieve one sixth of this dose by 8 weeks. For a starting daily dose of 60 mg, use weekly reductions to 45, 30, 25, 20, and 15 mg; then 2 weekly to 12.5 and 10 mg. Maintain this dose to 3 months; then taper to stop by 4 months.
Cyclophosphamide	3 mg/kg/24 h orally, rounded down to the nearest 50 mg. Patients older than 55 years receive a reduced dose of 2.5 mg/kg.
Plasma exchange	Daily exchange of 1 volume of plasma for 5% human albumin for 14 days or until the circulating antibody is suppressed. In the presence of pulmonary hemorrhage or within 48 hours of invasive procedure, 300 to 400 ml of fresh-frozen plasma is given at end of each treatment or according to coagulation tests.
Monitoring	Daily blood count during plasma exchange and while antibody titer remains elevated. At least twice weekly during first month, weekly thereafter. If white blood cell count decreases to $<3.5 \times 10^9$/l, stop cyclophosphamide until the count recovers. Resume at lower dose if cessation has been necessary. Baseline D_{LCO}, with further measurements as indicated. Daily coagulation tests during plasma exchange to monitor for significant depletion of clotting factors. Initially, daily checks of renal and hepatic function, glucose.
Prophylaxis against complications of treatment	Oral antifungal lozenges or rinse; proton pump inhibitor. Cotrimoxazole prophylaxis against *Pneumocystis carinii.* Avoid nonessential lines and catheters.

Table 24-2 Treatment regimen for acute Goodpasture disease.

few days, the patient will have incurred minimal risk (as long as pulse high-dose corticosteroids are avoided) but may have much to gain from earlier treatment.

Plasma Exchange and Immunosuppression

The regimen described in Table 24-2 dramatically improved the outlook for patients when it was introduced in the 1970s. An early randomized trial suggested some additional benefit of plasma exchange, but the interpretation was complicated by the recipient group's less severe disease at presentation.[23] It showed that milder disease can be effectively treated with corticosteroids and cyclophosphamide alone, although the overall outcomes for all patients were not as good as described with more intensive regimens.[23] Historical evidence suggests that treatment with corticosteroids alone, or corticosteroids with azathioprine, is less effective. Plasma exchange is of value only if it is accompanied by adjunctive immunosuppressive therapy. Immunoadsorption to protein A also lowers anti-GBM antibodies rapidly and does not deplete complement components or clotting factors, and a few reports suggest that it is as effective as plasma exchange. Information on the effectiveness of newer immunosuppressive agents such as mycophenolate mofetil (MMF) or anti–B cell antibodies, which tend to have only a slow effect on antibody production but may affect antigen presentation, is lacking. Their use over proven therapy is rarely justifiable in this often rapidly progressive disease. In contrast to advanced renal failure, in which treatment is unlikely to lead to recovery of renal function, even severe lung hemorrhage is likely to respond to treatment with full or almost full recovery of lung function.

Lung hemorrhage occurring alone tends to be relapsing and remitting, so there have been many reports of treatments (e.g., bilateral nephrectomy) that may help. Pulse methylprednisolone has been advocated, but high doses of corticosteroids fail to alter the underlying pathogenetic immune response and put the patient at increased risk of infectious and other complications. We recommend treating seriously ill patients with moderate doses of corticosteroids plus plasma exchange and cyclophosphamide.

In other acute severe diseases, daily administration of cyclophosphamide has often been superseded by pulse administration. We still prefer to use daily oral administration because it is known to work and requires only 3 months of therapy. Patients unable to take the drug orally can be given daily intravenous therapy at the usual oral dose. Dose does not need to be reduced in severe renal failure provided the white blood cell count is monitored closely, but reductions for older patients are important (see Table 24-2), and close monitoring of leukocyte counts is imperative in all patients. If pulsed therapy were chosen, the CYCLOPS regimen would be a reasonable if untested option (see Chapter 25).

Results from all series show that recovery of renal function is unlikely if, at initiation of treatment, the patient is oliguric, has a very high proportion of glomeruli with circumferential crescents, or has a serum creatinine level above 5.5 to 6.5 mg/dl (~500 to 600 µmol/l).[24] This is a notably different experience from that encountered in systemic vasculitis or idiopathic RPGN (see Chapter 25), in which renal disease of apparently similar severity (using histology and serum creatinine) can be salvaged by similar treatment protocols.[25] This has led to the suggestion that immunosuppressive treatment should be withheld from patients with only slight chance of recovery (Table 24-3; also see later).

Supportive Treatment

The most likely cause of death in the first few days is respiratory failure caused by lung hemorrhage. Lung hemorrhage may be precipitated or exacerbated by the following:

- Fluid overload
- Smoking and other pulmonary irritants, possibly including high Fio_2
- Local or distant infection
- Anticoagulation used during dialysis or plasma exchange
- Thrombocytopenia, defibrination, and depletion of clotting factors as a consequence of plasma exchange

It is therefore advisable to ensure correct fluid balance, to prohibit smoking, to use the lowest fractional inspired oxygen concentration (Fio_2) that gives adequate oxygenation, and to minimize the use of heparin.

Plasma exchange should be monitored by daily blood counts, calcium concentration (if regional citrate anticoagulation is used), and coagulation tests. Diminished clotting factor levels should be replenished by administration of fresh-frozen plasma or clotting factor preparations at the end of each plasma exchange session, as required.

After the first few days, the major cause of morbidity and mortality is infection. Infection carries the added risk of potentiating glomerular and lung inflammation and injury, so precautions to reduce

Factors in Decision to Treat Goodpasture Disease Aggressively		
	Factors Favoring Aggressive Treatment	**Factors Against Aggressive Treatment**
Pulmonary hemorrhage	Present	Absent
Oliguria	Absent	Present
Creatinine	<5.5 mg/dl (approximately 500 μmol/l)	>5.5-6.5 mg/dl (approximately 500-600 μmol/l) and ANCA negative Severe damage on kidney biopsy No desire for early kidney transplantation
Other factors	Creatinine >5.5-6.5 mg/dl (~500-600 μmol/l) *but* Rapid and recent progression ANCA positive Glomerular damage less severe than expected Crescents recent, nonfibrous Early renal transplantation desired	
Associated disease	Absent	Unusually high risk from immunosuppression

Table 24-3 Factors influencing decision to treat aggressively or not to treat aggressively in Goodpasture disease. *ANCA,* Antineutrophil cytoplasmic antibody.

risk, such as minimizing indwelling cannulas, are important. If leukopenia below 3.5×10^9/l or neutropenia develops, cyclophosphamide should be discontinued and resumed at a lower dose when the neutrophil count recovers, if necessary with the assistance of granulocyte colony-stimulating factor.

Monitoring Effect of Treatment on Disease Activity

The effect of treatment on the renal disease is monitored by following serum creatinine values. Indicators of recent lung hemorrhage include hemoptysis, decreases in hemoglobin concentration, chest radiograph changes, and increases in the DLCO, the last being the most sensitive. Any worsening of symptoms during treatment may indicate inadequate immunosuppression, but it is frequently a consequence of intercurrent infection exaggerating immunologic injury or fluid overload or other factors precipitating lung hemorrhage.

Monitoring of anti-GBM titers during, and particularly 24 hours after, the last planned plasma exchange treatment is useful for confirming effective suppression of autoantibodies. They should be undetectable within 8 weeks, but even without treatment, autoantibodies generally become undetectable by an average of 14 months.

Duration of Treatment and Relapses

Corticosteroid treatment may be gradually reduced and cyclophosphamide discontinued at 3 months. In contrast to treatment of small-vessel vasculitis, immunosuppression longer than this is usually not necessary. Longer treatment is appropriate for patients who are both anti-GBM antibody positive and ANCA positive (see later discussion). Late increases in anti-GBM level may predict clinical relapse, although antibodies are generally permanently suppressed in patients who have completed the immunosuppressive regimen. If there is recurrence, success has been achieved by treating as at first presentation.

Electing Not to Treat

Advanced renal failure, frequently already established at presentation, is generally not salvaged by any current treatment.[24,26,27] Furthermore, the immunosuppressive regimen outlined carries significant risks, and careful monitoring is required. For these reasons, it may be reasonable not to initiate immunosuppression in patients who present with advanced renal failure without lung hemorrhage. The decision not to treat is strengthened if the renal biopsy specimen shows widespread glomerulosclerosis and tubular loss and the patient is dialysis dependent at presentation (see Table 24-3). The risk for development of late lung hemorrhage in these patients seems to be low but warrants particular care to avoid the major precipitating factors, smoking and pulmonary edema, in at least the first few months. However, patients who are dialysis dependent should usually be treated if the renal histopathologic changes are unexpectedly mild or very recent (highly cellular crescents, even if 100% of glomeruli are involved, or acute tubular necrosis). Several reports describe good outcomes in these patients even after prolonged oliguria.

Treatment of Double-Positive Patients

Patients with both ANCA and anti-GBM antibodies may have other extrarenal disease requiring treatment (see Table 24-3). There is conflicting evidence as to whether their renal prognosis is the same as or better than that of other patients with anti-GBM antibodies. Earlier series suggested a better prognosis, but this was not confirmed in two later reports.[12,13] Because of the risk of serious disease in other organs, double-positive patients should usually receive an immunosuppressive regimen similar to that given for small-vessel vasculitis, with continuing immunosuppression with azathioprine after 3 months of cyclophosphamide (see Chapter 25).

TRANSPLANTATION

Renal transplantation in patients who have had Goodpasture disease carries the additional risk of disease recurrence. Recurrence with consequent loss of the graft has been reported and appears more likely when circulating anti-GBM antibodies are still detectable at transplantation. Therefore, it is reasonable to delay transplantation until circulating anti-GBM antibodies have been undetectable for 6 months, and to monitor graft function, urinary sediment, and circulating anti-GBM antibody levels to detect recurrent disease (see Chapter 108). Biopsies of well-functioning grafts sometimes show linear deposition of immunoglobulin on the GBM without clinical or histologic disease or apparently an adverse prognosis.

ALPORT SYNDROME POST-TRANSPLANT ANTI–GLOMERULAR BASEMENT MEMBRANE DISEASE

Patients with Alport syndrome have mutations in a gene encoding one of the tissue-specific type IV collagen chains, usually α5. Because these chains assemble with each other during biosynthesis, the resulting phenotype in the case of most mutations often has all the tissue-specific chains (α3 through α5) missing from the basement membranes, where they are normally coexpressed. Altered expression may lead to absent or inadequate immunologic tolerance to these proteins and to the preservation of the capacity to mount a powerful (allo)immune response to the type IV collagen chains expressed in a normal donor kidney after renal transplantation. Most Alport syndrome patients accommodate renal transplants with conventional immunosuppression without development of anti-GBM nephritis. However, development of low titers of anti-GBM antibodies is shown by many such patients having linear deposition of IgG on the GBM of the transplanted kidney on direct immunofluorescence, without disease. This alone does not justify treatment.

Up to 5% of Alport patients develop RPGN in the transplanted kidney. It is clinically indistinguishable from Goodpasture syndrome but without lung hemorrhage. This is more likely if the patient has a large gene deletion causing the disease rather than a point mutation, with the inference that the immune system has never been exposed to the mature protein. Typically, graft function is lost despite treatment for presumed acute rejection. Disease is usually encountered some months or longer after a first renal transplant, after weeks in a second, and after days in a third.[26] However, regrafting has been successful in two cases known to us and in two further cases in the literature. If the disease is recognized early, there are sound theoretical reasons for treating with the regimen recommended for Goodpasture syndrome, but there are few data on its effectiveness.[28]

In contrast to spontaneous Goodpasture disease, the specificity of anti-GBM antibodies in Alport post-transplant anti-GBM disease is not always to α3(IV)NC1. In many patients, possibly in most, the autoantibodies are specific for α5(IV)NC1, encoded by the *COL4A5* gene usually implicated in causation of the disease.[29] This is important because immunoassays for anti-GBM antibodies are optimized for detection of the anti-α3(IV)NC1 antibodies of spontaneous Goodpasture disease, and they may have low sensitivity for anti-α5(IV)NC1 antibodies. In the absence of widely available assays for these uncommon antibodies, renal biopsy with immunohistology is the only reliable method of diagnosis.

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CHAPTER 25

Renal and Systemic Vasculitis

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DEFINITION

The kidneys are targets for a variety of systemic vasculitides, especially those that affect small vessels.[1-5] This is not surprising given the large number and variety of renal vessels. Vasculitis involving the kidneys can produce a wide variety of clinical manifestations, depending mainly on the type of renal vessel affected. Vasculitides can be categorized as large-vessel vasculitis, medium-vessel vasculitis, and small-vessel vasculitis (Figs. 25-1 and 25-2). For the purposes of the discussion in this chapter, the 2012 Chapel Hill Consensus Conference definitions are used (Table 25-1).[4]

A number of the vasculitides listed in Figure 25-2 are covered in other chapters and are not reviewed in detail here except in the context of differential diagnosis, for example, cryoglobulinemic vasculitis (Chapter 21), IgA vasculitis (Henoch-Schönlein purpura; Chapter 23), and anti–glomerular basement membrane (anti-GBM) disease (Chapter 24). Nephrologists most often encounter patients with small-vessel vasculitides because these often cause glomerulonephritis (GN). Therefore, small-vessel vasculitis is the primary focus of this chapter.

Small-Vessel Vasculitis

Small-vessel vasculitis is necrotizing polyangiitis that affects predominantly vessels smaller than arteries, including capillaries, venules, and arterioles; however, arteries also may be involved.[4] The most common renal target for small-vessel vasculitis are glomerular capillaries, and therefore the most common renal clinical manifestations are those of GN.

Medium-Vessel Vasculitis

Medium-vessel vasculitis is necrotizing arteritis that affects predominantly major visceral arteries.[4] The interlobar arteries and arcuate arteries are affected most often in the kidneys, although any arteries from the main renal artery to the smallest interlobular arteries may be affected. Inflammation and necrosis of arteries may result in thrombosis or rupture, which causes renal infarction and hemorrhage, respectively.

Large-Vessel Vasculitis

Large-vessel vasculitis is chronic granulomatous arteritis that affects the aorta and its major branches more often than other forms of vasculitis.[4] When there is renal involvement, the ostia of the renal arteries and the main renal arteries are most often affected. The most common clinical renal manifestation is renovascular hypertension.

SMALL-VESSEL PAUCI-IMMUNE VASCULITIS

Small-vessel vasculitis can be divided into *immune complex* small vessel vasculitis with moderate to marked vessel wall deposits of immunoglobulin and *pauci-immune* small-vessel vasculitis with few or no immune deposits in vessel walls.[4] Pauci-immune small-vessel vasculitis often is associated with circulating antineutrophil cytoplasmic autoantibodies (ANCAs).[5] The ANCA-associated vasculitides share an indistinguishable form of necrotizing small-vessel vasculitis that affects capillaries, venules, arterioles, and small arteries.[1-5] Some patients with *ANCA-associated vasculitis* (AAV) have no evidence of involvement of arteries, even though they have involvement of glomerular capillaries, causing GN; pulmonary alveolar capillaries, causing pulmonary hemorrhage; or dermal venules, causing purpura. The clinicopathologic variants of pauci-immune small-vessel vasculitis are categorized on the basis of clinical, laboratory, and pathologic findings, as follows[4]:

- *Microscopic polyangiitis* (MPA) is pauci-immune small-vessel vasculitis occurring in the absence of evidence of necrotizing granulomatous inflammation.
- *Granulomatosis with polyangiitis* (Wegener) (GPA) is pauci-immune vasculitis associated with necrotizing granulomatous inflammation, most often affecting the respiratory tract.
- *Eosinophilic granulomatosis with polyangiitis* (Churg-Strauss) (EGPA) is pauci-immune vasculitis associated with asthma, eosinophilia, and necrotizing granulomatous inflammation.

MPA, GPA, and less frequently EGPA share an indistinguishable pattern of GN that is the expression of the vasculitis in glomerular capillaries.[1,2] In the acute phase, the GN usually has necrosis and crescent formation and an absence or paucity of immunoglobulin deposition and is often designated *pauci-immune crescentic glomerulonephritis*. When occurring in the apparent absence of systemic vasculitis, pauci-immune crescentic GN is sometimes referred to as *renal-limited vasculitis*.

Pathogenesis

Microscopic polyangiitis, GPA, EGPA, and renal-limited pauci-immune crescentic GN are all associated with ANCA.[5-9] The most common antigen specificities of ANCA in patients with vasculitis and GN are for proteinase 3 (PR3) and myeloperoxidase (MPO). Recently, autoantibodies to lysosome-associated membrane protein 2 (LAMP-2) were reported in the circulation of most patients with either MPO-ANCA or PR3-ANCA.[10] LAMP-2 has homology to the bacterial adhesin FimH, and thus autoantibodies to LAMP-2 may arise by molecular mimicry secondary to infection with fimbriated gram-negative bacteria. Further, rats injected with anti–LAMP-2 or immunized with FimH develop pauci-immune focal necrotizing and

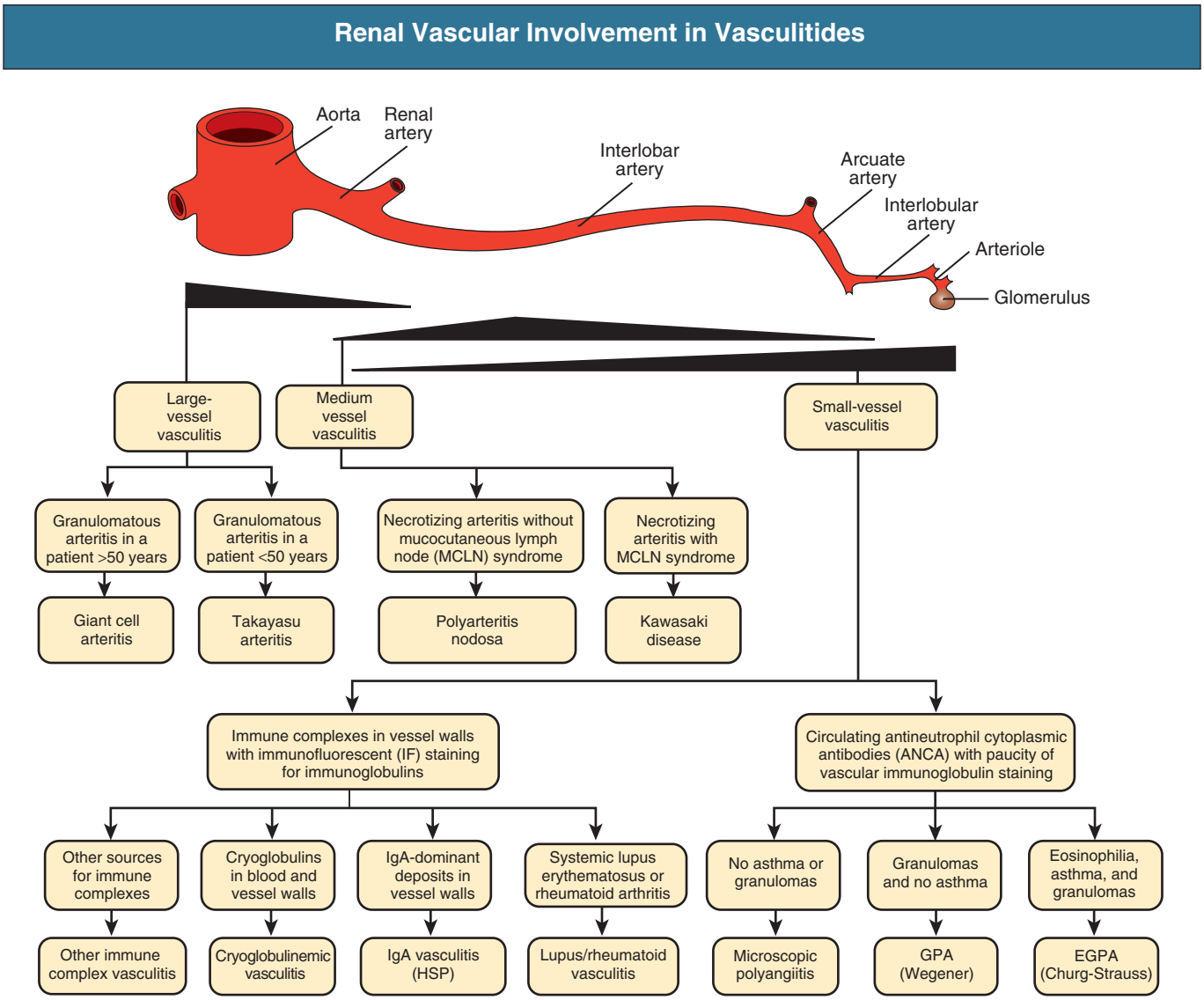

Figure 25-1 Renal vasculitis. Predominant distribution of renal vascular involvement by a variety of vasculitides. The heights of the trapezoids represent the relative frequency of involvement of different portions of the renal vasculature by the three major categories of vasculitis. *EGPA,* Eosinophilic granulomatous polyangiitis; *GPA,* granulomatous polyangiitis; *HSP,* Henoch-Schönlein purpura. *(Modified from reference 3.)*

crescentic GN. At least one research group was not able to reproduce these results.[11] These observations are intriguing but need additional confirmation.

The strong association of ANCA with this distinctive form of small-vessel vasculitis suggests that ANCAs are involved in the pathogenesis.[5-9] The report of a neonate who developed GN and pulmonary hemorrhage possibly caused by transplacental passage of MPO-ANCA IgG is intriguing but has not been substantiated by additional reports.[12] The observation that ANCA titers correlate with disease activity also suggests a pathogenic role; however, this correlation is not strong, and some patients with clinically and pathologically typical MPA, GPA, or renal-limited pauci-immune crescentic GN are negative using conventional serologic testing for ANCA. A recent report explains both these discrepancies, at least in patients with MPO-ANCA, based on a multiplicity of ANCA epitope specificities.[13] The MPO-ANCA epitope specificity determines not only the pathogenicity but also the detectability and clinical predictive value of circulating MPO-ANCA. For example, ANCAs with certain epitope specificities only occur in patients with active disease, whereas other MPO-ANCA epitope specificities occur not only in patients with active disease, but also in patients in remission and even in healthy controls (natural ANCA), although at very low titers. Some AAV patients who are negative by conventional serologic testing have MPO-ANCA with very restricted epitope specificity that can be detected with special unmasking techniques.[13]

The pathogenic potential of ANCA is supported by the observation that administration of certain drugs, such as propylthiouracil, hydralazine, and penicillamine, can induce AAV.[14] Cocaine adulterated with levamisole also can induce AAV associated with high titers of MPO-ANCA, PR3-ANCA, and ANCA specific for another neutrophil granule protein elastase.[15] Levamisole-induced vasculitis has frequent cutaneous leukocytoclastic angiitis and upper respiratory tract involvement, but rarely renal or lung involvement.

A number of *in vitro* observations suggest mechanisms by which ANCA can cause vascular injury.[6,7] Priming of neutrophils by cytokines, as would occur with a viral infection, causes neutrophils to increase expression of ANCA antigens on their surfaces, where they are accessible to interact with ANCA. Cytokine-primed neutrophils that are exposed to ANCA release IgG from granules, release toxic oxygen metabolites, and kill cultured endothelial cells.[6,7,16-18]

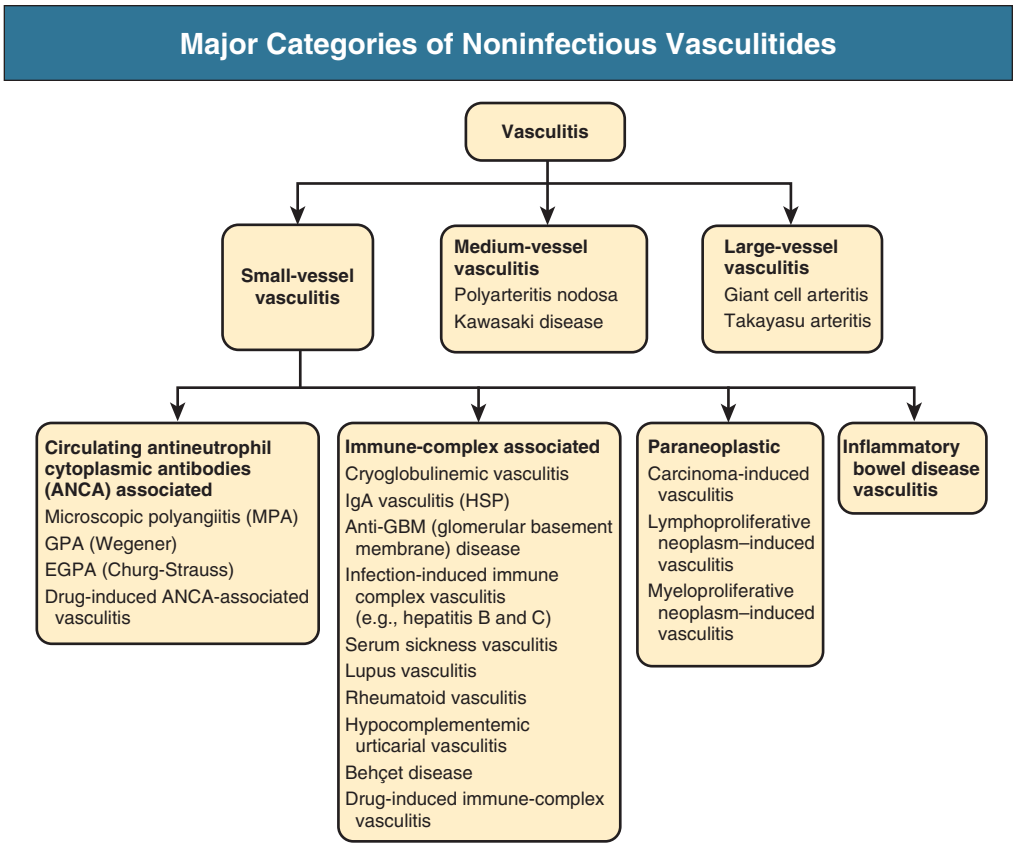

Figure 25-2 Major categories of noninfectious vasculitis. Not included are vasculitides that are known to be caused by direct invasion of vessel walls by infectious pathogens, such as rickettsial vasculitis and neisserial vasculitis. *EGPA,* Eosinophilic granulomatous polyangiitis; *GPA,* granulomatous polyangiitis; *HSP,* Henoch-Schönlein purpura.

ANCA-antigen complexes adsorb onto endothelial cells, where they could participate in *in situ* immune complex formation.[19] ANCA activation of neutrophils is mediated by both $F(ab)'_2$ binding to neutrophils and Fc receptor engagement.[20,21] Neutrophils that have been activated by ANCA adhere to endothelial cells and release mediators of inflammation and cell injury.[17,18] If occurring *in vivo,* these events would lead to vasculitis as a result of neutrophils adhering to, penetrating, and destroying vessel walls (Fig. 25-3).[22]

The ability of ANCA IgG to cause pauci-immune necrotizing and crescentic GN and vasculitis has been demonstrated in multiple animal models induced with MPO-ANCA, although no widely accepted model of PR3-ANCA disease has been developed. Wild-type or immunodeficient mice that receive anti-MPO antibodies intravenously develop pauci-immune focal necrotizing GN with crescents.[23]A rat model of pauci-immune necrotizing and crescentic GN has been developed by immunizing rats with human MPO, resulting in the development of antibodies that cross-react with rat MPO and are able to induce pauci-immune glomerular necrosis and crescents.[24] MPO-ANCA GN in mice is mediated by neutrophil activation, modulated by Fc gamma receptor repertoire, and can be prevented by neutrophil depletion.[6,7,25] Activation of the alternative complement pathway plays a role in amplifying ANCA-induced inflammation.[26] ANCA-activated neutrophils release factors that activate the alternative complement pathway, resulting in the generation of C5a that is strongly chemotactic for neutrophils and primes neutrophils to facilitate further activation by ANCA.[27,28] The relevance of these experimental observations in patients is supported by a report that AAV patients have increased plasma levels of alternative pathway activation markers C3a, C5a, soluble C5b-9, and Bb during active disease but no remission, and that the plasma level of Bb correlated with percentage of cellular crescents in the renal biopsies and with Birmingham Vasculitis Activity Scores.[29]

Thus, the clinical and experimental data indicate that ANCA can activate neutrophils and cause vasculitis, especially if there are concurrent synergistic proinflammatory stimuli. The requirement for a synergistic inflammatory process may be reflected in the frequent association of the onset of ANCA small-vessel vasculitis with an influenza-like syndrome.[30] An influenza-like syndrome is a manifestation of high levels of circulating cytokines that could serve as priming factors for neutrophils, making them more receptive to activation by ANCA.

Epidemiology

Wegener granulomatosis (GPA), MPA, and EGPA usually begin during the fifth, sixth, and seventh decades of life but may occur at any age. There is a slight male predominance. The incidence is disproportionately greater in Caucasians than in African Americans. In Europe, MPA has a prevalence of approximately 2.5 in 100,000; GPA, 2.5 in 100,000; and EGPA, 1 in 100,000 population.[31] GPA is more common in colder than in warmer climates, whereas MPA has the opposite trend. AAV in Asia is much more often associated with MPO-ANCA than PR3-ANCA.[32]

Clinical Manifestations

Generalized nonspecific manifestations of systemic inflammatory disease, such as fever, malaise, anorexia, weight loss, myalgias, and arthralgias, often are present. Many patients with vasculitis trace the onset of their disease to a flu-like illness.[30]

The clinical manifestations of GPA, MPA, and EGPA are extremely varied because they are influenced by the sites of involvement and the activity versus the chronicity of involvement. All three categories of vasculitis share features caused by the small-vessel vasculitis, and

Vasculitis Categories and Definitions	
Category/Name	**Definition**
Large-Vessel Vasculitis	
Takayasu arteritis	Arteritis, often granulomatous, predominantly affecting aorta and/or its major branches. Onset usually in patients younger than 50.
Giant cell arteritis	Arteritis, often granulomatous, usually affecting aorta and/or its major branches, with predilection for branches of carotid and vertebral arteries; often involves temporal artery. Onset usually in patients older than 50 and often associated with polymyalgia rheumatica.
Medium-Vessel Vasculitis	
Polyarteritis nodosa	Necrotizing arteritis of medium or small arteries without glomerulonephritis (GN) or vasculitis in arterioles, capillaries, or venules; and not associated with ANCA.
Kawasaki disease	Arteritis associated with mucocutaneous lymph node syndrome and predominantly affecting medium and small arteries; coronary arteries are often involved; aorta and large arteries may be involved. Usually occurs in infants and young children.
Small-Vessel Vasculitis	
ANCA-Associated Small-Vessel Vasculitis	
	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (capillaries, venules, arterioles, small arteries), associated with MPO-ANCA or PR3-ANCA. Not all patients have ANCA. Add prefix indicating ANCA reactivity, e.g., PR3-ANCA, MPO-ANCA, ANCA-negative.
Microscopic polyangiitis (MPA)	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (capillaries, venules, arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing GN is common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.
Granulomatosis with polyangiitis (Wegener) (GPA)	Necrotizing granulomatous inflammation usually involving upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (capillaries, venules, arterioles, arteries, veins). Necrotizing GN is common.
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more common when GN is present.
Immune Complex Small-Vessel Vasculitis	
	Vasculitis with moderate to marked vessel wall deposits of immunoglobulin and/or complement components predominantly affecting small vessels (capillaries, venules, arterioles, small arteries). GN is common.
Anti–glomerular basement membrane (anti-GBM) disease	Vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with basement membrane deposition of anti–basement membrane autoantibodies. Lung involvement causes pulmonary hemorrhage, and renal involvement causes GN with necrosis and crescents.
Cryoglobulinemic vasculitis	Vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) and associated with cryoglobulins in serum. Skin, glomeruli, and peripheral nerves are often involved.
IgA vasculitis (IgAV) (Henoch-Schönlein purpura)	Vasculitis, with IgA1-dominant immune deposits, affecting small vessels (predominantly capillaries, venules, or arterioles). Often involves skin and gastrointestinal tract and frequently causes arthritis. GN indistinguishable from IgA nephropathy may occur.
Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)	Vasculitis accompanied by urticaria and hypocomplementemia affecting small vessels (capillaries, venules, arterioles), and associated with anti-C1q antibodies. GN, arthritis, obstructive pulmonary disease, and ocular inflammation are common.

Table 25-1 Names and definitions of vasculitis. Adopted by the Chapel Hill Consensus Conference on the nomenclature of systemic vasculitis. Note that all three categories affect arteries, but only small-vessel vasculitis has a predilection for vessels smaller than arteries. *ANCA,* Antineutrophil cytoplasmic antibody. *(Modified from reference 22.)*

patients with GPA and EGPA have the additional features that define each of these syndromes.[3,4,30,33,34]

Renal involvement occurs often in GPA and MPA and less frequently in EGPA (Table 25-2). The most common renal manifestations are caused by glomerular involvement and include hematuria, proteinuria, and renal failure. The renal failure often has the characteristics of rapidly progressive glomerulonephritis (RPGN) in GPA and MPA but usually is less severe in EGPA. Patients with GPA and MPA also can present with a subacute or chronic nephritis. A cohort of more than 300 pauci-immune crescentic GN patients evaluated at renal biopsy had a mean age of 56 ± 20 years (range 2 to 92 years), male-to-female ratio of 1.0:0.9, mean serum creatinine concentration of 6.5 ± 4.0 mg/dl (range 0.8 to 22.1 mg/dl), and proteinuria of 1.9 ± 3.0 g/day (range 0.1 to 18 g/day).[35]

Cutaneous involvement occurs frequently in vasculitis. Purpura is a common manifestation of GPA, MPA, and EGPA (Fig. 25-4). The purpura is most common on the lower extremities and tends to occur as recurrent crops. The purpura may be accompanied by small areas of ulceration. Nodular cutaneous lesions are much more frequent in GPA and EGPA than MPA. Nodules can be caused by dermal or subcutaneous arteritis and the necrotizing granulomatous inflammation.

Upper respiratory tract involvement is most common in GPA and EGPA but also occurs in MPA.[36] In all three categories, patients can have pulmonary hemorrhage caused by hemorrhagic alveolar capillaritis. Patients with GPA and EGPA also can have pulmonary injury caused by necrotizing granulomatous inflammation, which may be detected radiographically as nodular or cavitating lesions. By

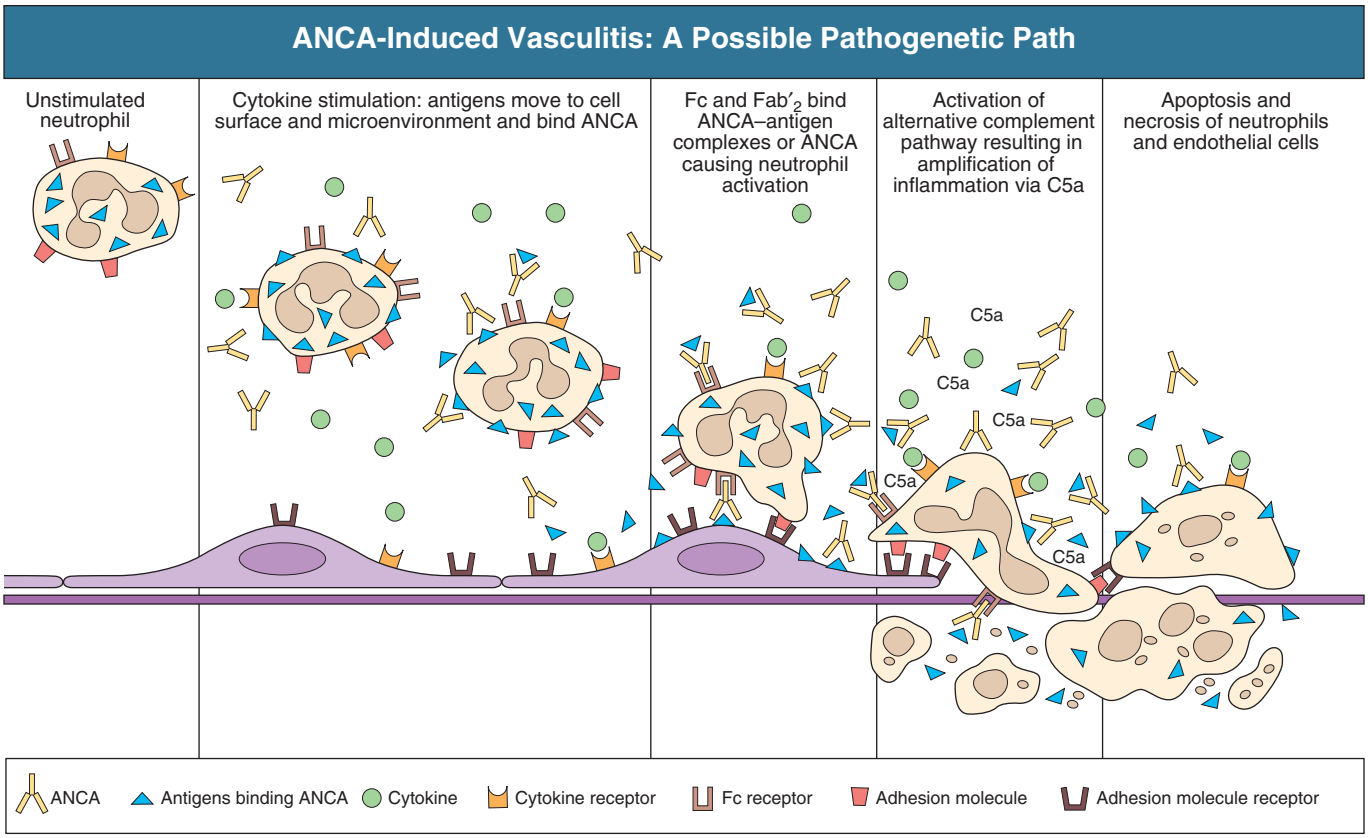

Figure 25-3 Vasculitis induced by antineutrophil cytoplasmic antibody (ANCA). Hypothetical sequence of pathogenetic events. *(Modified from reference 22.)*

Organ System Involvement in Small-Vessel Vasculitis

	Frequency of Involvement (%)				
Organ System	***Microscopic Polyangiitis***	***GPA (Wegener)***	***EGPA (Churg-Strauss)***	***IgA Vasculitis (HSP)***	***Cryoglobulinemic Vasculitis***
Kidney	90	80	45	50	55
Skin/cutaneous	40	40	50	90	90
Lungs	50	90	90	<5	<5
Ear, nose, throat	35	90	50	<5	<5
Musculoskeletal	60	60	50	75	70
Neurologic	30	50	60	10	40
Gastrointestinal	50	50	70	60	30

Table 25-2 Organ system involvement in small-vessel vasculitis. *GPA,* Granulomatosis with polyangiitis; *EGPA,* eosinophilic granulomatosis with polyangiitis; *HSP,* Henoch-Schönlein purpura. *(Modified from reference 2.)*

definition, patients with MPA do not have granulomatous respiratory tract lesions.[4]

Manifestations of upper respiratory tract disease include subglottic stenosis, sinusitis, rhinitis, nasal septal collapse, otitis media, and ocular inflammation. These features are most common in GPA but may occur in EGPA and MPA. The upper respiratory inflammation in MPA is caused by angiitis alone, without granulomatous inflammation. Destruction of bone, for example, resulting in septal perforation and saddle nose, appears to require necrotizing granulomatous inflammation and therefore does not occur in MPA. When patients with saddle nose have ANCA, it is almost always PR3-ANCA.[36]

Cardiac disease is identified in approximately 50% of patients with EGPA but in less than 20% of patients with GPA or MPA. Manifestations range from transient heart block and ventricular hypokinesis that respond to immunosuppressive treatment to infarction and severe life-threatening myocarditis. Pericarditis and endocarditis also may occur.

Peripheral neuropathy, usually with a mononeuritis multiplex pattern, is the most common neurologic manifestation and is most frequent in EGPA. Central nervous system involvement is less common and most often is manifested as vasculitis within the meninges. Gastrointestinal involvement typically causes abdominal

Figure 25-4 Cutaneous vasculitis. Ankle of a patient with small-vessel vasculitis, showing purpura and a few small ulcers.

pain and blood in the stool, with mesenteric ischemia and rarely intestinal perforation. Vasculitis in the pancreas and liver can mimic pancreatitis and hepatitis symptomatically and cause elevated serum pancreatic and liver enzymes.

Antineutrophil Cytoplasmic Autoantibody

Serologic testing for ANCA is a useful diagnostic procedure for pauci-immune small-vessel vasculitis and pauci-immune crescentic GN but should be interpreted in the context of other characteristics of the patient.[37-41] Laboratory testing for ANCA should include both indirect immunofluorescence microscopy assay (IFA) and enzyme immunoassay (EIA).[38] IFA using normal human neutrophils as substrate produces two major staining patterns (Fig. 25-5): cytoplasmic (c-ANCA), in which staining occurs diffusely throughout the cytoplasm, and perinuclear (p-ANCA). By EIA, most c-ANCA have specificity for protease 3 (PR3-ANCA), and most p-ANCA have specificity for myeloperoxidase (MPO-ANCA). For adequate diagnostic accuracy, all serologic testing for ANCA should include an immunochemical analysis for antigen specificity, such as an EIA.[38] Although positive results are rare in completely healthy individuals, approximately one fourth of patients with other inflammatory renal diseases (especially lupus) will have a false-positive IFA result (usually with a p-ANCA pattern), and approximately 5% will have a false-positive EIA result (usually at low titer).[39]

ANCA testing has good sensitivity for AAV (80% to 90%). The specificity and predictive value depend on the population of patients and the quality of the assay.[37,41] Although ANCAs are most frequent in patients with pauci-immune crescentic GN, one fourth to one third of patients with anti-GBM crescentic GN and one fourth of those with idiopathic immune complex crescentic GN with 50% or more crescents are ANCA positive.[35,42] Some of these patients have well-recognized types of immune complex GN complicated by ANCA, such as membranous glomerulopathy and IgA nephropathy, whereas others have nonlupus IgG-dominant immune complex disease that cannot be categorized further. Patients with concurrent ANCA and anti–glomerular basement membrane (anti-GBM) antibodies have a worse prognosis than patients with ANCA alone.

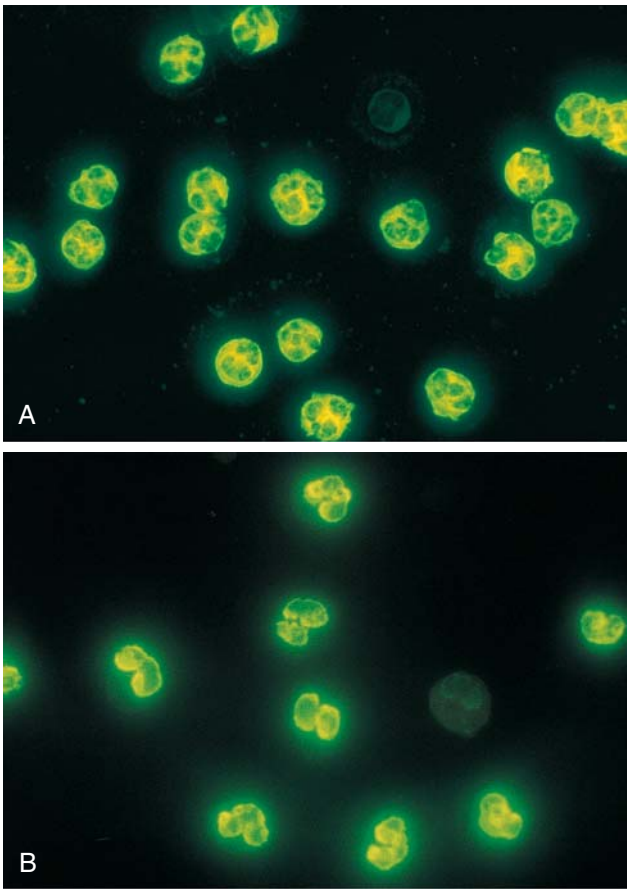

Figure 25-5 Antineutrophil cytoplasmic antibodies (ANCAs). Indirect immunofluorescence staining pattern of alcohol-fixed normal human neutrophils. **A,** Cytoplasmic pattern caused by ANCAs with specificity for proteinase 3. **B,** Perinuclear pattern caused by ANCAs with specificity for myeloperoxidase (anti-IgG). (Original magnification ×250.)

Table 25-3 provides an estimate of the relative frequencies of PR3-ANCA/c-ANCA and MPO-ANCA/p-ANCA in the different clinical phenotypes of AAV. PR3-ANCA/c-ANCA are most prevalent in GPA, and MPO-ANCA/p-ANCA are most prevalent in renal-limited pauci-immune crescentic GN and EGPA. Patients with MPA have a more even distribution of PR3-ANCA/c-ANCA and MPO-ANCA/p-ANCA, although this varies among geographic regions as stated earlier. Patients with EGPA have the lowest overall frequency of ANCA, but the frequency of ANCA is much higher in patients with GN (75%) than in those with no GN (26%).[43] The ANCA specificity correlates with clinical symptoms, with PR3-ANCA having the highest frequency (~90% when ANCA present) in patients who have destructive upper respiratory disease, especially saddle nose.[36]

Changes in ANCA titers over time correlate to a degree with disease activity but are not infallible markers and thus must be interpreted with caution.[39,44] In general, titers decrease with treatment and increase before or at disease recurrence. An increase in ANCA titer should prompt careful evaluation of the patient for corroborating evidence of exacerbation, but most physicians do not modify treatment on the basis of an increase in titer without accompanying clinical signs. A recent report suggests that epitope-specific assays may provide much better correlation with and prediction of disease outcome.[13] MPO-ANCAs with certain epitope specificities occur only in patients with active disease, disappear with remission, and reappear during relapse, whereas MPO-ANCAs with other specificities remain during disease remission.

ANCA in Small-Vessel Vasculitis			
	Frequency (%)		
Disorder	***Proteinase 3 (PR3, usually c-ANCA)***	***Myeloperoxidase (MPO, usually p-ANCA)***	***Negative***
Granulomatosis with polyangiitis (Wegener)	70	25	5
Microscopic polyangiitis	40	50	10
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	5	40	55
Renal-limited pauci-immune crescentic GN	20	70	10

Table 25-3 Antineutrophil cytoplasmic antibody (ANCA) in small-vessel vasculitis. Approximate frequency of ANCA with specificity for proteinase 3 (PR3/c-ANCA) and for myeloperoxidase (MPO/p-ANCA) in patients with different categories of pauci-immune small-vessel vasculitis and crescentic glomerulonephritis. *GN,* Glomerulonephritis.

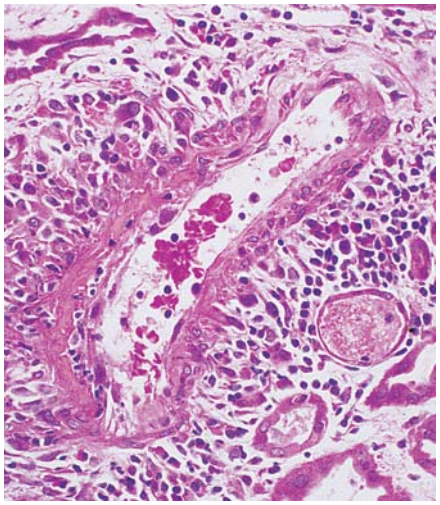

Figure 25-6 Necrotizing arteritis of interlobular artery in patient with ANCA-associated small-vessel vasculitis. There is segmental fibrinoid necrosis with adjacent perivascular leukocyte infiltration. (Hematoxylin-eosin (HE) stain; ×50.)

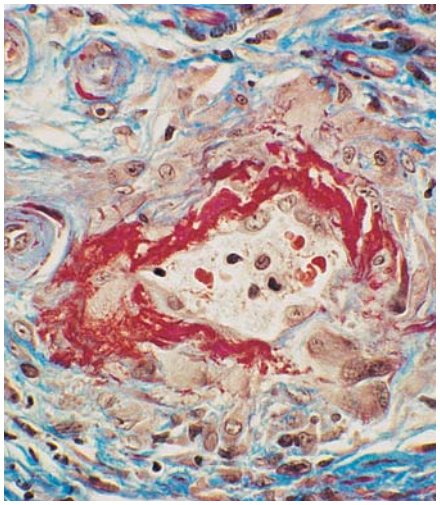

Figure 25-7 Necrotizing arteritis of interlobular artery in patient with ANCA-associated small-vessel vasculitis. The fibrinoid necrosis is indicated by the *red* staining. (Masson trichrome; ×100.)

From 10% to 20% of patients with pauci-immune necrotizing and crescentic GN and pauci-immune small-vessel vasculitis will be ANCA negative. The clinicopathologic and outcome characteristics of these patients are no different from those of ANCA-positive patients.[45] In the same epitope-specific assays previously mentioned, some AAV patients who are negative by current clinical assays have MPO-ANCA with restricted epitope specificity that can be detected with sensitive assays that remove a masking factor.[13]

ANCA may be positive in inflammatory conditions other than vasculitis, including inflammatory bowel disease (IBD), rheumatoid disease, chronic inflammatory liver disease, bacterial endocarditis, and cystic fibrosis. In IBD, specificity of the ANCA may not be against PR3 or MPO but against other neutrophil antigens, including lactoferrin, cathepsin G, and anti–bactericidal/permeability-increasing protein (BPI).

Pathology

The acute vascular lesion of the pauci-immune small-vessel vasculitides is segmental fibrinoid necrosis, often accompanied by leukocyte infiltration and leukocytoclasia[1,2,46-49] (leukocyte fragmentation; Figs. 25-6 and 25-7). The earliest vasculitic lesions have infiltrating neutrophils that are quickly replaced by predominantly mononuclear leukocytes. The acute necrotizing lesions evolve into sclerotic lesions and may be complicated by thrombosis.

These focal necrotizing lesions can affect many different vessels, thus causing many different signs and symptoms. For example, involvement of glomerular capillaries causes nephritis; of alveolar capillaries, pulmonary hemorrhage; of dermal venules, purpura; of upper respiratory mucosal venules, rhinitis and sinusitis; of abdominal visceral arteries, abdominal pain; and of epineural arteries, mononeuritis multiplex.

The shared glomerular lesion of the pauci-immune small-vessel vasculitides is a necrotizing GN, usually with resultant crescent formation.[1,2,46-49] Early mild lesions have segmental fibrinoid necrosis with or without an adjacent small crescent (Fig. 25-8). Severe acute lesions may have essentially global necrosis with large circumferential crescents (Fig. 25-9). In a cohort of 181 renal biopsy specimens from patients with ANCA-associated GN, 90% had glomerular crescents that on average affected 50% of glomeruli, with half having crescents in more than 50% of glomeruli.[27] Non-necrotic segments within segmentally injured glomeruli (see Fig. 25-8) and glomeruli without necrosis typically have slight or no histologic abnormalities.

As mentioned previously, approximately one fourth of patients with anti-GBM crescentic GN and one fourth of patients with immune complex–mediated crescentic GN will be ANCA positive.[35] By contrast, less than 5% of patients with immune complex GN who do not have crescents will be ANCA positive. Therefore, even in patients with immune complex GN, the presence of ANCA is

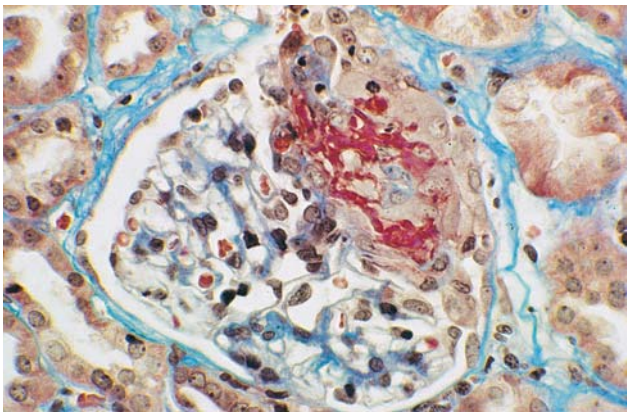

Figure 25-8 Segmental glomerular necrosis and crescent formation in patient with ANCA-associated small-vessel vasculitis. The fibrinoid material is *red*. The uninvolved segments appear normal. (Masson trichrome; ×150.)

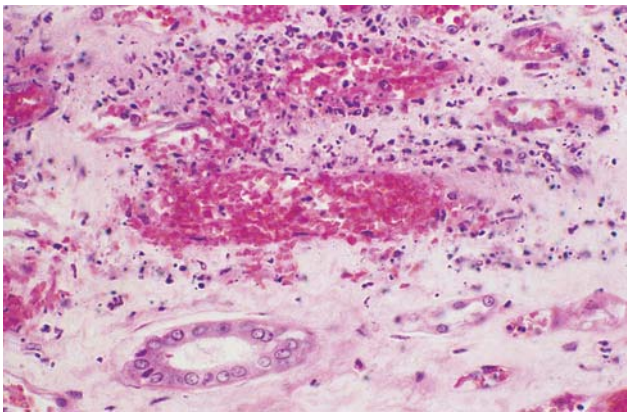

Figure 25-10 Medullary leukocytoclastic angiitis involving vasa recta in patient with granulomatosis with polyangiitis. (HE stain; ×150.)

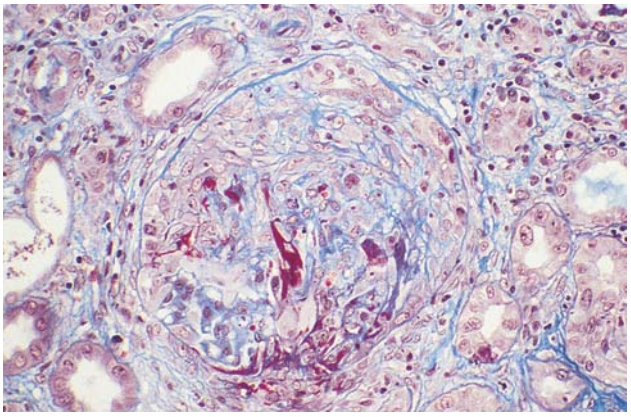

Figure 25-9 Global glomerular necrosis and circumferential crescent formation in a glomerulus from patient with ANCA-associated small-vessel vasculitis. (Masson trichrome; ×150.)

associated with an increased incidence of crescents (and also inflammation in vessels other than glomerular capillaries). A histopathologic classification has been proposed for AAV GN: sclerotic class (≥50% globally sclerotic glomeruli), focal class (≥50% normal glomeruli), crescentic class (≥50% of glomeruli with cellular crescents), or mixed class if none of these features predominated.[49] Renal survival at 5 years was 93% for the focal class, 76% for crescentic class, 61% for mixed class, and 50% for sclerotic class. Validation studies are underway to better understand the utility of this classification.

In addition to GN, patients with AAV also may have renal arteritis, most often affecting interlobular arteries (see Figs. 25-6 and 25-7), and medullary angiitis affecting the vasa recta (Fig. 25-10). The medullary angiitis may be severe enough to cause papillary necrosis, although this is a rare complication.

Patients with GPA and EGPA have pathologic lesions in addition to the necrotizing small-vessel vasculitis.[1-4] The necrotizing granulomatous inflammation of GPA occurs most often in the respiratory tract and is characterized by zones of necrosis surrounded by mixed infiltrates of neutrophils, lymphocytes, monocytes, and macrophages, often including scattered multinucleated giant cells. Varying numbers of eosinophils may be present in the lesions of GPA, but these are more conspicuous in the necrotizing granulomatous inflammation of EGPA. Eosinophils also are typically conspicuous in the vasculitic lesions of EGPA, but this is not a pathognomonic observation because numerous eosinophils may be present in the vasculitic lesions of GPA, MPA, polyarteritis nodosa, and other vasculitides.

Differential Diagnosis

ANCA-associated small-vessel vasculitis must be differentiated from other forms of small-vessel vasculitis that can produce the same signs and symptoms.[2] In addition, an attempt should be made to distinguish MPA, GPA, and EGPA, although in some patients this cannot be accomplished conclusively and is not required for initiation of therapy. Pathologic confirmation of the granulomatous inflammation that is seen in ANCA disease is particularly difficult because small biopsy specimens often show only nonspecific acute and chronic inflammation and necrosis. Thus, findings other than histologic lesions, such as nodular or cavitating lung lesions observed radiographically or destructive bone lesions in the nasal septum, often must be used as markers of necrotizing granulomatous inflammation to categorize patients. Because of the toxicity of the treatment, even in a patient with substantial clinical and serologic evidence of ANCA disease, pathologic confirmation of vasculitis is warranted. This can be accomplished with biopsy of many different involved sites, including skin, muscle, nerve, gut, and kidney. When the patient has substantial renal involvement, renal biopsy findings also can be useful for predicting response to treatment and clinical outcome.[46-49]

All forms of small-vessel vasculitis listed in Figure 25-2 are capable of producing clinically indistinguishable overlapping features of disease, such as nephritis, purpura, peripheral neuropathy, myalgias, arthralgias, and abdominal pain. Table 25-4 lists a number of features that help distinguish several important categories of small-vessel vasculitis.[2] Accurate differentiation is very important for proper patient management because the natural histories and appropriate treatments vary greatly. For example, a patient presenting with nephritis, arthralgias, and abdominal pain could have IgA vasculitis (IgAV, formerly Henoch-Schönlein purpura), MPA, cryoglobulinemic vasculitis, or a number of other small-vessel vasculitides. A number of serologic and pathologic observations are useful for reaching the correct diagnosis (Table 25-4). A positive ANCA assay (confirmed by EIA to be MPO-ANCA or PR3-ANCA) supports a diagnosis of MPA or one of the other pauci-immune small-vessel vasculitides. A negative ANCA assay and positive cryoglobulin assay (especially accompanied by hypocomplementemia and positive hepatitis C serology) support a diagnosis of cryoglobulinemic vasculitis. A negative ANCA assay, negative cryoglobulin assay, and normal

Differential Diagnostic Features of Small-Vessel Vasculitis					
Features	**Microscopic Polyangiitis**	**GPA (Wegener)**	**EGPA (Churg-Strauss)**	**IgA Vasculitis (HSP)**	**Cryoglobulinemic Vasculitis**
Vasculitic signs and symptoms*	+	+	+	+	+
IgA-dominant immune deposits	–	–	–	+	–
Cryoglobulins in blood and vessels	–	–	–	–	+
ANCAs in blood	+	+	+	–	–
Necrotizing granulomas	–	+	+	–	–
Asthma and eosinophilia	–	–	+	–	–

Table 25-4 Differential diagnostic features of select forms of small-vessel vasculitis. *All these vessel vasculitides can manifest any of the shared features of small-vessel vasculitides, such as nephritis, purpura, abdominal pain, peripheral neuropathy, myalgias, and arthralgias. Each is distinguished by the presence and, just as important, by the absence of certain specific features. *ANCAs,* Antineutrophil cytoplasmic antibodies; *GPA,* granulomatosis with polyangiitis; *EGPA,* eosinophilic granulomatosis with polyangiitis; *HSP,* Henoch-Schönlein purpura. *(Modified from reference 2.)*

complement levels support a diagnosis of IgAV, especially in a patient younger than 21 years. The age of a patient influences the likelihood of a specific diagnosis. For example, approximately 80% of children younger than 10 years who have purpura, nephritis, and arthralgias will have IgAV, whereas approximately 80% of adults older than 60 years with the same symptoms will have an AAV. However, each disease can occur at any age.

Exposure to drugs that may provoke AAV must be considered, including penicillamine, hydralazine, and propylthiouracil,[14] as well as cocaine adulterated with levamisole.[15] Cholesterol embolization can also mimic the clinical features of small-vessel vasculitis with lower extremity rash, but ANCA assay is negative. The differential diagnosis of lung hemorrhage and nephritis includes anti-GBM disease, alone or with ANCA disease.

Natural History

Before the advent of immunosuppressive therapy, the survival of patients with MPA and GPA was poor, with most patients dying in less than 1 year. With adequate immunosuppressive therapy, 5-year renal and patient survival is 65% to 75%.[50-52] The likelihood of success of long-term maintenance of renal function is inversely correlated with the serum creatinine concentration when therapy begins, which indicates the importance of early diagnosis and prompt initiation of appropriate treatment. The likelihood of patient survival increases with early treatment of pulmonary hemorrhage and sepsis and avoidance of overimmunosuppression leading to life-threatening infections. Adverse events from therapy, including infections, are the leading cause of death in the year following diagnosis.[50] Older age, higher serum creatinine concentration at presentation, pulmonary hemorrhage, and especially dialysis-dependent renal failure correlate with an overall poor outcome. However, even dialysis-dependent renal failure may resolve with aggressive early therapy. Respiratory tract disease and PR3-ANCA are predictors of higher relapse rates.[52] Pathologic features that correlate with renal outcome include histologically normal glomeruli, glomerular sclerosis, interstitial leukocyte infiltration, tubular necrosis, and tubular atrophy.[48,49] Increased numbers of histologically normal glomeruli or glomeruli with cellular crescents correlated with a better prognosis than higher proportions of globally sclerotic glomeruli, suggesting that active inflammatory lesions may be suppressed if not reversed by treatment, whereas chronic injury at initiation of treatment may be irreversible.

When severe GN is present, the renal prognosis is similar for patients with MPA, GPA, or EGPA, and renal-limited pauci-immune crescentic GN. Renal involvement, however, is less common and usually less severe in patients with EGPA. Cardiac involvement is the most frequent cause of death in patients with EGPA, but only rarely causes mortality in MPA or GPA. GPA has a broad spectrum of clinical manifestations, from localized indolent disease to fulminant multisystem disease. For example, some patients have disease limited to the upper respiratory tract or to the upper and lower respiratory tract. Such limited disease may have a more benign natural history than systemic disease with substantial renal involvement and may warrant less aggressive treatment.

Patients with MPO-ANCA have a slightly better renal outcome than those with PR3-ANCA, even though they have more renal impairment and more chronic renal pathologic changes at presentation. Patients with PR3-ANCA have more extrarenal organ manifestations (especially respiratory tract disease), higher chance for relapse, and higher mortality than MPO-ANCA patients. Regardless of the category of ANCA disease, the best clinical predictor of renal outcome is the glomerular filtration rate (GFR) at diagnosis.

Treatment

This section focuses on patients with ANCA-associated small-vessel vasculitis affecting the kidneys. The goal should be not to overtreat mild disease and not to undertreat severe disease. Glomerulonephritis that is severe enough to cause renal impairment is an indication for immunosuppressive treatment in patients with GPA, MPA, EGPA, and renal-limited pauci-immune crescentic GN. Patients with AAV who have concurrent anti-GBM disease or concurrent immune complex disease should be treated similarly to patients with AAV alone. Treatment involves three phases: induction of remission, maintenance of remission, and treatment of relapse[53] (Fig. 25-11).

Induction Therapy

The consensus is that corticosteroids alone are not as effective for induction therapy as corticosteroids combined with a cytotoxic agent such as cyclophosphamide.[54-61] Combined treatment with corticosteroid and cyclophosphamide induces remission in approximately 75% of patients at 3 months and 90% at 6 months. The specifics of combined induction regimens vary with respect to agents, doses, route of administration, and duration. One induction approach is to begin with 7 mg/kg/day intravenous (IV) methylprednisolone for 3 days followed by oral prednisone 1 mg/kg/day, tapering to an alternate-day regimen and discontinuing within 3 to 4 months.[54] Alternatively, the corticosteroids can be administered as 1 mg/kg/day prednisolone tapered to 0.25 mg/kg/day by 3 months.[58] The corticosteroid treatment is combined with 2 mg/kg/day oral cyclophosphamide or IV cyclophosphamide at 0.5 g/m^2 per month adjusted upward to

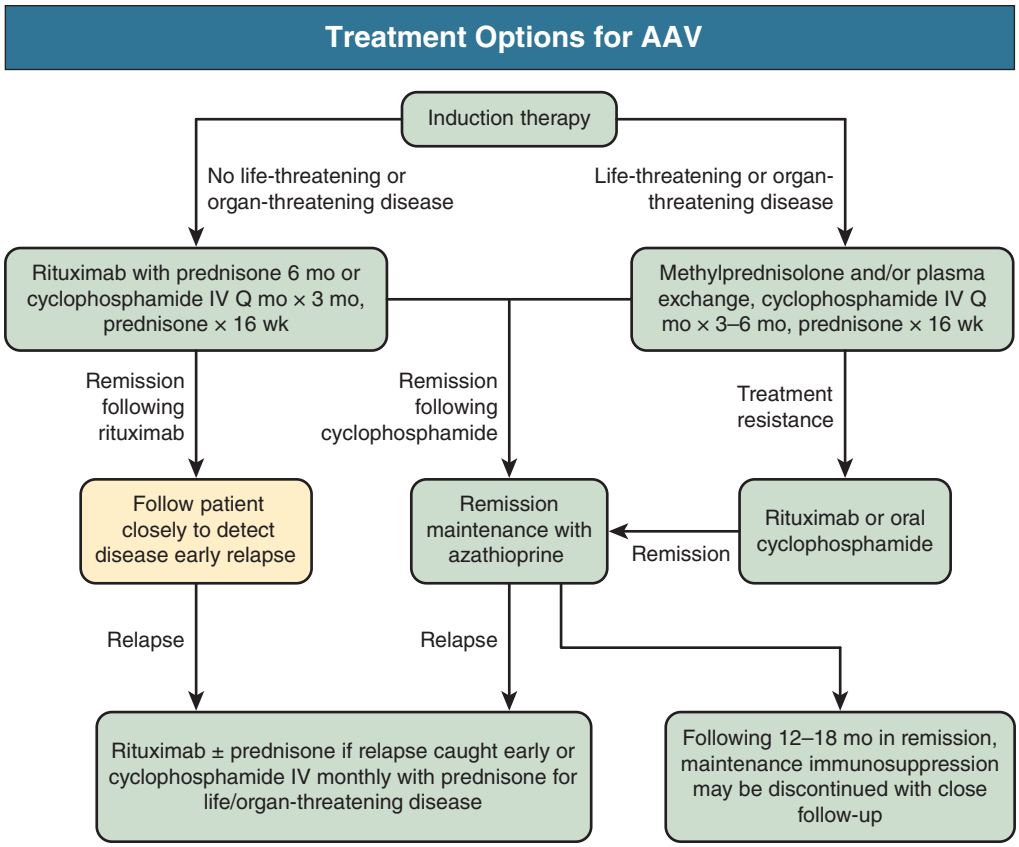

Figure 25-11 **Algorithm of recommended treatment for ANCA-associated vasculitis.**

1 g/m^2 on the basis of the leukocyte count after 2 weeks with a target nadir of 3000 cells/mm^3. The dose of oral cyclophosphamide can be reduced by 25 mg for patients older than 60.[58] A comparison by the European Vasculitis Study Group (CYCLOPS trial) indicated that IV cyclophosphamide results in the same remission rates as oral cyclophosphamide while reducing the total dose of cyclophosphamide.[62]

The U.S. Food and Drug Administration (FDA) has approved rituximab for use as induction therapy for AAV based on the results of two randomized controlled trials (RCTs) noting that rituximab-based cyclophosphamide-sparing strategies were comparable to traditional cyclophosphamide induction protocols.[60,61] The Rituximab for ANCA-associated Vasculitis (RAVE) trial noted no difference in remission off all therapy in 6 months between patients treated with four infusions of 375 mg/m^2 rituximab plus prednisone and those receiving oral cyclophosphamide with prednisone (64% in rituximab arm, 55% in cyclophosphamide arm). The RITUXVAS trial compared 6 to 10 infusions of cyclophosphamide followed by maintenance therapy with azathioprine to four infusions of 375 mg/m^2 rituximab in combination with two infusions of cyclophosphamide without maintenance therapy. There was no difference in remission rates at 12 months between the groups. In both RAVE and RITUXVAS, enthusiasm is tempered by higher adverse event rates, which may signify no improvement in safety over cyclophosphamide. This is somewhat disappointing because there was hope that targeted B cell therapy would have less adverse events than broader-spectrum immunosuppression.

Plasma exchange may be of benefit in patients with life-threatening pulmonary hemorrhage[63] and patients who have dialysis-dependent renal failure at presentation.[64] With pulmonary hemorrhage, 20 of 20 patients treated with early plasma exchange had resolution of pulmonary bleeding compared with a 50% mortality in historical controls.[63] A trial by the European Vasculitis Study Group (MEPEX) evaluated the efficacy of IV methylprednisolone as induction therapy or plasma exchange in patients who had a serum creatinine of more than 500 µmol/l.[64] Results from this study suggest that plasma exchange compared with pulse methylprednisolone in this population increases the rate of recovery from renal failure. Patient survival and adverse events were similar in patients who did or did not receive plasma exchange. Plasma exchange was associated with a 24% reduced risk of progression to end-stage renal disease (ESRD), from 43% to 19% at 1 year.

Maintenance Therapy

The duration of induction therapy and the intensity of maintenance therapy should be decreased as much as possible to reduce toxic side effects. This is a difficult challenge because of the tendency of AAV to recur. A number of approaches have been used to reduce the cyclophosphamide dose, such as giving less cyclophosphamide through IV rather than oral schedules,[54] substituting a less toxic maintenance drug after 3 to 6 months,[58] and discontinuing therapy earlier in patients with lower risk of relapse. IV cyclophosphamide regimens afford one-third to one-half the total dose of cyclophosphamide given in oral regimens. Long-term follow up, however, notes longer time to relapse in the oral cyclophosphamide treated group, at the cost of increased leukopenia.[65] Another approach to reducing cyclophosphamide dose is to substitute azathioprine after 3 to 6 months of therapy.[49,58] In the European Vasculitis Study Group CYCAZAREM trial, cyclophosphamide was replaced with 2 mg/kg/day azathioprine after 3 to 6 months with no change in the relapse rate at the end of the study.[58] Azathioprine (2 mg/kg/day) has been compared to mycophenolate mofetil (MMF 2 g/day) in a randomized control fashion, noting that relapses were more common in the

MMF group compared to the azathioprine group (unadjusted HR for MMF 1.69; 95% CI 1.06 to 2.70). Adverse events, disease activity score, GFR, and proteinuria did not differ between the groups.[66]

Cyclophosphamide dose also could be reduced by alternative induction therapies. The French Vasculitis Study Group examined methotrexate compared with azathioprine as maintenance therapy in patients with GPA and MPA.[67] In this study, methotrexate was as effective as azathioprine for maintenance of remission, but methotrexate did not have fewer side effects. Of special note to nephrologists, methotrexate should not be used in patients with low GFR. An attractive alternative is to stop induction therapy at 6 to 12 months if the patient is in full remission, especially if the patient is at lower risk of relapse.[52]

Although there are proponents of reinfusion strategies every 4 to 6 months with rituximab,[68,69] enthusiasm is substantially diminished for repetitive use of rituximab for remission maintenance for at least four reasons. First, the 18-month data from the RAVE trial suggest equal efficacy and also equal numbers of adverse events when compared with 6 months of oral cyclophosphamide and 12 months of azathioprine. Thus, the rituximab approach is not without significant adverse events. Second, a number of patients, especially those with MPO-ANCA, may not need remission maintenance therapy. Rather, they need careful supportive care. Third, rituximab has a significant amount of immunogenic mouse protein as part of its structure, so a growing number of patients have become sensitized to this biologic agent, and some have developed serum sickness–like disease. Thus, when these patients need rituximab for clinical disease activity, it may not be an option. Fourth, the expense of rituximab may become prohibitive for some patients.

The role of antimicrobial agents such as trimethoprim-sulfamethoxazole in maintenance of remission is controversial. Some studies have suggested a benefit, but others have not because of an increased likelihood of relapse.[70,71] TMP-SMX may be useful adjunct therapy, especially in patients with upper respiratory disease, but should not be used in the absence of immunosuppressive drugs with more proven efficacy (e.g., cyclophosphamide, azathioprine) for induction or maintenance therapy for systemic vasculitis or GN.

Relapse Therapy

Approximately one fourth to one half of patients with AAV will experience a relapse within several years. Relapses are diagnosed on the basis of clinical and pathologic evidence of recurrent disease, not by an increase in ANCA titer alone.[44] However, an increase in ANCA titer increases the likelihood of a relapse, and some advocate preemptive immunosuppressive therapy if the ANCA titer increases by at least fourfold.[44] We prefer to identify clear-cut clinical or pathologic evidence of relapse before increasing immunosuppressive therapy.[54]

Observational data suggest that the best treatment for relapses may be rituximab. There is mounting evidence that use of rituximab for relapse is superior to cyclophosphamide.[60] Reinstitution of treatment similar to an induction regimen is used most often, but less intensive or less toxic therapy may be adequate.[46,54,55] In addition to rituximab or cyclophosphamide, a number of therapies can be used in the treatment of relapse, including azathioprine, MMF, methotrexate, or combinations of these drugs tailored to the individual patient with recalcitrant disease.

In some individuals, long-term therapy may not be required, especially if there is a very low risk of relapse. In prospective observational studies from the Glomerular Disease Collaborative Network, the relative risk of relapse was increased in those individuals who had PR3-ANCA and respiratory tract disease.[52] Patients had more than a threefold risk of relapse compared with those individuals with MPO-ANCA and without lung or ear, nose, and throat disease. In a follow-up study, this model of relapsing disease was investigated in a separate registry in France, in which PR3-ANCA and lung disease was the most important predictive marker.[72] Thus, in those who have a much smaller risk of relapse, all therapy may be stopped, provided the patient and physician pursue a monitoring course in which the risk of early relapse is detected (e.g., home urinary dipstick testing to monitor for recurrence of hematuria). The risk of relapse is about 10% to 15% even with remission maintenance therapy.

Transplantation

Renal transplantation is not contraindicated in patients with ESRD caused by AAV. In a multicenter experience, the vasculitis relapse rate was 0.02 per patient-year[73] (see Chapter 108). A positive ANCA titer at the time of transplantation does not increase the risk of recurrent disease in the transplant.[74,75] Recurrent ANCA GN in a renal transplant responds similarly to recurrent disease in native kidneys.[64] As with native kidney disease, an increase in ANCA titer and an active urine sediment should suggest recurrent GN, but the diagnosis requires pathologic confirmation.

POLYARTERITIS NODOSA

Polyarteritis nodosa is a systemic necrotizing arteritis that affects predominantly main visceral arteries and their intraparenchymal branches.[1,4,5,76] The Chapel Hill nomenclature system limits the diagnosis of polyarteritis nodosa to patients who have only arteritis.[4] The presence of vasculitis in vessels other than arteries, such as capillaries, venules, or arterioles, excludes a diagnosis of polyarteritis nodosa and indicates some form of small-vessel vasculitis. Thus, GN excludes a diagnosis of polyarteritis nodosa. When polyarteritis nodosa is distinguished from MPA by this approach, the two categories of vasculitis have not only different pathologic characteristics but also different clinical features and natural histories, which justifies the nosologic distinction between polyarteritis nodosa and MPA.[76-80]

Pathogenesis

The etiology and pathogenesis of polyarteritis nodosa are unknown. When polyarteritis nodosa is separated from MPA, the latter but not the former is associated with ANCA. An immune complex trigger for polyarteritis nodosa has been proposed but has not been confirmed as the major pathogenetic process. A minority of patients have hepatitis B virus (HBV) infection, suggesting that the HBV infection is producing immune complexes that are localizing in arterial walls and inducing inflammation.[80] However, the evidence that HBV infection is causing vascular immune complex deposition is stronger in certain forms of GN and small-vessel vasculitis than in polyarteritis nodosa.

Epidemiology

When defined by the Chapel Hill nomenclature system, polyarteritis nodosa had a prevalence of approximately 3 in 100,000 population in a study of an urban area in France.[31] This is a higher prevalence for polyarteritis nodosa than for the ANCA-associated vasculitides than has been reported in other studies, perhaps influenced by environmental factors. Polyarteritis nodosa affects males and females equally and is found in all races. Onset occurs most frequently between ages 40 and 60 years.

Clinical Manifestations

The usual clinical presentation of polyarteritis nodosa includes nonspecific constitutional symptoms, such as fever, malaise, arthralgias, myalgias, and weight loss, as well as manifestations of arteritis.[76-80] Peripheral neuropathy, typically in the form of a mononeuritis multiplex, is a common manifestation. This is caused by inflammation of small epineural arteries and is clinically indistinguishable from the peripheral neuropathy caused by other forms of vasculitis that can affect epineural arteries, such as MPA, GPA, and EGPA. Gastrointestinal involvement occurs in about half of patients, usually manifesting as abdominal pain and blood in the stool. Bowel infarction is uncommon and perforation rare. Renal involvement produces infarction and hemorrhage, as indicated by flank pain and hematuria. Rupture of an arterial aneurysm with retroperitoneal or peritoneal hemorrhage is an uncommon but potentially lethal renal complication. Approximately one third of patients develop hypertension, which rarely reaches the malignant range. Red, tender inflammatory nodules are the most common cutaneous manifestation. Infarction, ulceration, and livedo reticularis may be present.

Arterial aneurysms may be detected by angiography in patients with polyarteritis nodosa (Fig. 25-12). This is not a completely specific determination because any necrotizing arteritis that affects arteries large enough to be seen by angiography can produce this finding.

Pathology

Any artery in the kidney can be affected by polyarteritis nodosa, from the main renal artery to the interlobular arteries, although the interlobar and arcuate arteries are affected most often.[1] Nodular inflammatory lesions and aneurysms (pseudoaneurysms) can be observed grossly when medium-sized arteries are involved. Inflammation in small arteries can be observed only by microscopy.

The characteristic acute lesion is segmental transmural fibrinoid necrosis of arteries, usually accompanied by infiltrating leukocytes with leukocytoclasia[3] (Fig. 25-13). The earliest lesions have numerous neutrophils, and later lesions have predominantly mononuclear leukocytes. Acute lesions may be complicated by thrombosis or hemorrhage. Older lesions develop fibrosis and endarterial remodeling. The aneurysms of necrotizing arteritis are not true aneurysms but rather inflammatory pseudoaneurysms. That is, the walls of the arteries are not dilated but rather have been eaten away by the necrotizing inflammation, which then erodes into the surrounding perivascular tissue to create an enlarged lumen at the site of inflammation. This explains the propensity for such lesions to induce thrombosis or to undergo rupture.

The necrotizing arteritis of polyarteritis nodosa cannot be distinguished by light microscopy from arteritis caused by other necrotizing vasculitides affecting arteries.[1,2] For example, necrotizing arteritis in a skeletal muscle biopsy specimen or a peripheral nerve biopsy specimen is histologically identical whether caused by polyarteritis nodosa, MPA, GPA, or EGPA. For these vasculitides to be distinguished, additional clinical and serologic information is required.

Differential Diagnosis

Clinical features may assist in distinguishing polyarteritis nodosa from other forms of vasculitis, especially other forms of necrotizing vasculitis that can affect arteries, such as MPA[79] (Table 25-5). A

Polyarteritis Nodosa and Microscopic Polyangiitis: Distinguishing Features

Clinical Feature	Polyarteritis Nodosa	Microscopic Polyangiitis
Microaneurysms by angiography	Yes	No (rare)
Rapidly progressive nephritis	No	Yes (very common)
Pulmonary hemorrhage	No	Yes
Renovascular hypertension	Yes (10%-33%)	No
Peripheral neuropathy	Yes (50%-80%)	Yes (10%-20%)
Positive hepatitis B serology	Uncommon	No
Positive ANCA	Rare	Frequent
Relapses	Rare	Frequent

Table 25-5 Clinical differences between polyarteritis nodosa and microscopic polyangiitis. *(Modified from reference 34.)*

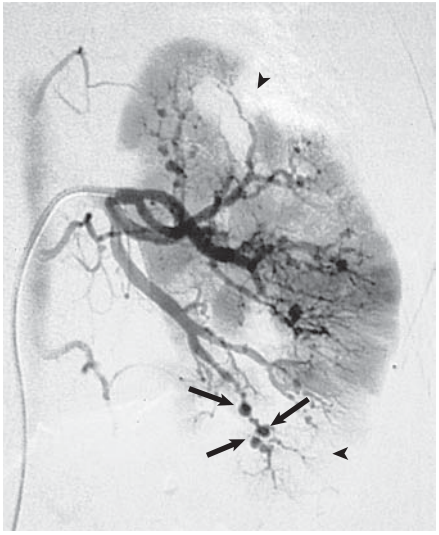

Figure 25-12 Renal angiogram in polyarteritis nodosa. Angiogram shows patchy renal perfusion defects *(arrowheads)* and aneurysms *(arrows)*.

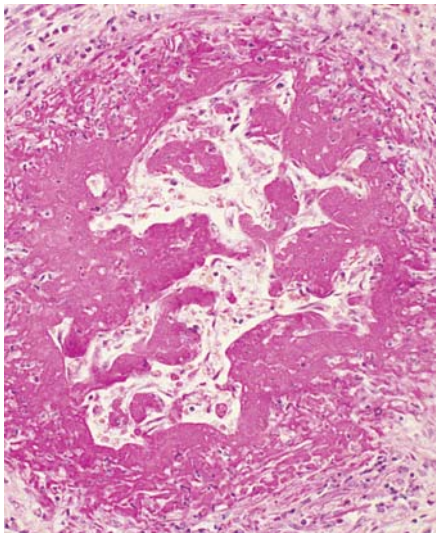

Figure 25-13 Necrotizing arteritis in arcuate artery of patient with polyarteritis nodosa. The lumen is partially occluded by thrombotic material that is continuous with the fibrinoid material that has replaced the entire wall of the artery. (HE stain; ×50.)

positive ANCA test result supports the diagnosis of one of the ANCA-associated small-vessel vasculitides rather than polyarteritis nodosa. The presence of GN indicates some form of small-vessel vasculitis rather than polyarteritis nodosa. Vasculitic pulmonary disease is rare in polyarteritis nodosa but common in MPA, GPA, and EGPA. Peripheral neuropathy or muscle tenderness with arteritis in epineural or skeletal muscle arteries is not a useful differentiating feature because it often occurs in polyarteritis nodosa as well as in the ANCA-associated small-vessel vasculitides. Kawasaki disease causes necrotizing arteritis but is distinguished from polyarteritis nodosa by the presence of the mucocutaneous lymph node syndrome.

Natural History

The natural history of polyarteritis nodosa is difficult to determine because most of the early studies of outcome grouped polyarteritis nodosa with MPA. Polyarteritis nodosa with multisystem involvement has a poor prognosis without therapy. The patient with polyarteritis nodosa usually is treated with corticosteroids and cytotoxic drugs such as cyclophosphamide.[78] The 10-year survival with appropriate treatment is approximately 80%. Approximately 15% of patients who enter remission develop a relapse, which is much less frequent than with MPA. Relapse is more likely if treatment is delayed.

Treatment

Polyarteritis nodosa in patients with no evidence of HBV infection is treated with corticosteroids and cytotoxic drugs, usually cyclophosphamide.[55,76-79] The regimens vary and include treatment approaches similar to those described earlier for MPA and GPA. However, in patients with no risk factors for poor outcome (e.g., age >50; cardiac, gut, or renal involvement), corticosteroids alone may be adequate and are less toxic therapy than corticosteroids combined with cytotoxic agents.

Aggressive immunosuppressive therapy without initial antiviral therapy is contraindicated in patients with HBV-associated polyarteritis nodosa because of potential adverse effects on the outcome of the HBV infection. Short-term corticosteroid treatment combined with antiviral agents and possibly plasma exchange should precede more extensive immunosuppression in such patients.[77,80] The European League Against Rheumatism (EULAR) recommends initial treatment with high-dose corticosteroids, then tapered over 2 weeks, followed by antiviral treatment.[55] The addition of plasma exchange may increase the likelihood of remission.

KAWASAKI DISEASE

Definition

Kawasaki disease is an acute febrile illness that usually occurs in young children, often under 1 year, and is characterized by the mucocutaneous lymph node (MCLN) syndrome (see later discussion).[4,81-83] Necrotizing arteritis is a complication of Kawasaki disease that is present in some but not all patients. Clinically significant renal involvement is very rare; therefore, Kawasaki disease is rarely encountered by nephrologists.

Pathogenesis

The occasional occurrence of Kawasaki disease as an endemic or epidemic disease suggests that the cause may be an infectious agent or an environmental toxin. Both cell-mediated and antibody-mediated mechanisms have been incriminated, including a possible role for antiendothelial antibodies.[83] At present, the etiology and pathogenesis of Kawasaki disease are unproven.

Epidemiology

Kawasaki disease usually occurs in children younger than 5 years and has a peak incidence in the first year of life. It was first described in Japan, but it occurs worldwide. The disease is more common in Asians and Polynesians than in Caucasians and blacks. In Japan, the incidence is 50 in 100,000 children younger than 5 years, with 50% of the children younger than 2.[84] Kawasaki disease occasionally occurs in an endemic or epidemic pattern but usually is sporadic.

Clinical Manifestations

The MCLN syndrome is the characteristic clinical manifestation of Kawasaki disease.[4,83] This includes fever (temperature of usually 38° to 40° C), mucosal inflammation, swollen red tongue (strawberry tongue), polymorphous erythematous rash, indurative edema of the extremities, erythema of palms and soles, desquamation from the tips of digits, conjunctival injection, and enlarged lymph nodes. The frequency of active arteritic lesions peaks during the first week of the illness and is greatly reduced after 1 month. Arteritis most often is manifested as cardiac disease. Thrombosis of inflamed coronary arteries in patients with Kawasaki disease is the most common cause of childhood myocardial infarction. Clinically significant renal disease is uncommon. This is somewhat surprising because autopsy reveals arteritis in renal vessels in up to three fourths of patients.[81]

Pathology

The arteritis of Kawasaki disease involves small and medium-sized arteries. The acute histologic lesion is necrotizing inflammation with less fibrinoid necrosis and more edema than usually observed with polyarteritis nodosa[81] (Fig. 25-14). Aneurysm (pseudoaneurysm) formation and thrombosis may occur. The most frequent site of arteritis is the coronary arteries, followed by the renal arteries.[81] Arteritis most often affects interlobar arteries, occasionally arcuate arteries, and only rarely interlobular arteries.

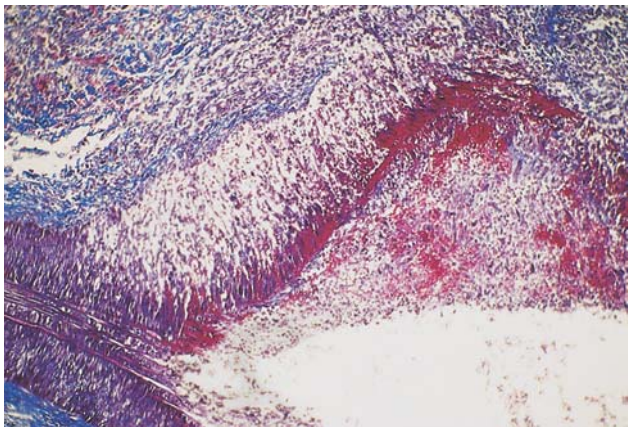

Figure 25-14 Kawasaki disease arteritis affecting renal interlobar artery in young child. The artery wall is intact on the far left. The remainder of the wall has extensive edema, infiltration by mononuclear leukocytes, and a band of fuchsinophilic *(red)* fibrinoid material roughly at the junction between the inflamed intima and muscularis. (Masson trichrome; ×25.)

Differential Diagnosis

Kawasaki disease has sometimes been misdiagnosed as childhood polyarteritis nodosa. The differentiation of Kawasaki disease from polyarteritis nodosa is important because corticosteroid treatment may increase the risk of coronary artery aneurysms in Kawasaki disease. Arteritis in a child younger than 5 years should always raise the possibility of Kawasaki disease. The presence or absence of the MCLN syndrome is the basis for distinguishing between Kawasaki disease and other forms of arteritis.[4]

Natural History

Kawasaki disease usually is self-limited, with an uneventful recovery if treated promptly with intravenous gamma globulins.[82,83] Recurrence is rare. Only about 1% of patients develop severe arteritic complications, usually affecting the coronary arteries.

Treatment

Aspirin and IV gamma globulin are the standard therapy for Kawasaki disease.[82,83] Corticosteroid treatment may increase the risk of adverse coronary artery complications, although the data supporting this are limited.

TAKAYASU ARTERITIS AND GIANT CELL ARTERITIS

Takayasu arteritis and giant cell arteritis affect predominantly the aorta and its major branches.[4,85] Giant cell arteritis has a predilection for the extracranial branches of the carotid artery but can affect arteries in almost any organ. Takayasu arteritis has a predilection for major arteries supplying the extremities. Both diseases cause chronic vascular inflammation, often with a granulomatous appearance that may include multinucleated giant cells. Giant cell arteritis, but not Takayasu arteritis, is associated with polymyalgia rheumatica.

Pathogenesis

The etiology and pathogenesis of giant cell arteritis and Takayasu arteritis are unknown. Because of the histologic changes and the nature of the infiltrating leukocytes, cell-mediated immune mechanisms are incriminated. The inciting antigen or autoantigen has not been identified.

Epidemiology

Takayasu arteritis is seen most frequently in Asia. Giant cell arteritis occurs most often in individuals of northern European ancestry. Takayasu arteritis has a female-to-male ratio of approximately 9:1, and giant cell arteritis, 4:1. Takayasu arteritis usually is diagnosed in those between ages 10 and 20 years and is rare after age 50. Giant cell arteritis is rare before age 50.

Clinical Manifestations

In addition to nonspecific constitutional symptoms, such as fever, arthralgias, and weight loss, the major clinical manifestations of Takayasu arteritis and giant cell arteritis are caused by arterial narrowing and resultant ischemia.[74] The major clinical manifestations of Takayasu arteritis are reduced pulses (95% of patients), vascular bruits, claudication, and renovascular hypertension. Renovascular hypertension is a major cause of morbidity and mortality and results from renal ischemia caused by renal artery stenosis or aortic coarctation.[85,86] Reduced aortic elasticity and impairment of carotid artery baroreceptors also may play a role in some patients. EULAR recommends thorough imaging assessment of the entire major arterial tree when a diagnosis of Takayasu arteritis is suspected.[87]

Headache is the most common presenting symptom in patients with giant cell arteritis. Temporal artery tenderness, nodularity, or decreased pulsation is present in about half of patients. Additional common symptoms include blindness, deafness, jaw claudication, tongue dysfunction, extremity claudication, and reduced pulses. More than half of patients with giant cell arteritis have polymyalgia rheumatica, characterized by stiffness and aching in the neck and the proximal muscles of the shoulders and hips. Clinically significant renal disease is much rarer in giant cell arteritis than in Takayasu arteritis. There are case reports of necrotizing and crescentic GN associated with giant cell arteritis, but these may represent examples of GPA or MPA with temporal artery involvement.

Pathology

The aortitis and arteritis of Takayasu arteritis and giant cell arteritis cannot be confidently differentiated by pathologic examination.[4] Both are characterized in the active phase by inflammation with a predominance of mononuclear leukocytes, often with scattered multinucleated giant cells (Fig. 25-15). The chronic phase is characterized by progressive fibrosis that may cause severe narrowing of vessels, with resultant ischemia. Major renal arteries are often found to be involved at autopsy in both Takayasu arteritis and giant cell arteritis patients. However, clinically significant renal disease is relatively common in Takayasu arteritis but rare in giant cell arteritis. A glomerular lesion characterized by nodular mesangial matrix expansion and mesangiolysis may occasionally be a component of Takayasu arteritis.[88]

Differential Diagnosis

There is a great deal of overlap between the clinical manifestations and pathologic features of Takayasu arteritis and giant cell arteritis. Patient age and presence or absence of polymyalgia rheumatica are the best factors for discriminating between these two vasculitides. Giant cell arteritis also has been called "temporal arteritis," but this is misleading because not all patients have temporal artery involvement, and patients with other types of vasculitis (polyarteritis nodosa, GPA, MPA) can have involvement of the temporal arteries.

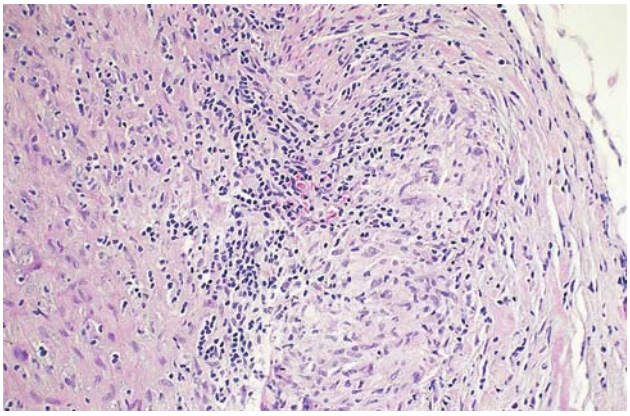

Figure 25-15 Severe giant cell arteritis affecting a main renal artery. This caused marked renal atrophy and renovascular hypertension. (HE stain; ×50.)

Some of the reported examples of necrotizing GN associated with temporal arteritis probably represent GPA or MPA with temporal artery involvement.

Treatment

Corticosteroids are the usual treatment of giant cell arteritis and Takayasu arteritis.[87] EULAR recommends initial daily therapy with prednisolone (1 mg/kg) for 1 month followed by tapering over several months.[87] More prolonged treatment may be dictated by persistent disease activity. Cytotoxic agents such as cyclophosphamide may be required in patients with recalcitrant disease. Patients with giant cell arteritis also should receive low-dose aspirin to protect against thrombotic vascular events.[87]

Management of renal disease is not an issue with typical giant cell arteritis, although rare patients have ischemic renal manifestations. Renovascular hypertension is the major renal problem caused by Takayasu arteritis.[85,86] When bilateral renal artery involvement occurs, angiotensin-converting enzyme (ACE) inhibitors may precipitate renal failure in patients with Takayasu arteritis.[89] When medical management fails, the renovascular hypertension in patients with Takayasu arteritis may be controlled by bypass surgery or angioplasty.[86] Reconstructive vascular surgery should be performed during a quiescent phase of the disease.[87] The management of renovascular hypertension is covered in Chapter 39.

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CHAPTER 26

Lupus Nephritis

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DEFINITION

Lupus nephritis (LN) is an immune complex glomerulonephritis that is a common and serious feature of systemic lupus erythematosus (SLE), which itself is defined by a combination of clinical and laboratory features.[1,2] The American College of Rheumatology (ACR) criteria for the diagnosis of SLE have been widely used in both epidemiologic and treatment studies (Box 26-1). However, many patients with "lupus-like" conditions and others who meet fewer than four ACR criteria should still be recognized as requiring therapy.

EPIDEMIOLOGY

The incidence and prevalence of lupus and LN are influenced by age, gender, ethnicity, geographic region, diagnostic criteria used, and method of ascertainment, but across populations, clinically important kidney disease will occur in 40% of patients[3-7] (Table 26-1). The peak incidence of lupus is age 15 to 45 years, with women outnumbering men by 10:1. This gender predominance is less pronounced in children and older individuals. Among lupus patients, LN affects both genders equally and is more severe in children and men and less so in older adults. Both lupus and LN are three to four times more common in blacks, Asians, and Hispanics than in Caucasians. Additional risk factors for LN include younger age, lower socioeconomic status, more ACR criteria for SLE, longer disease duration, family history of SLE, and hypertension.

ETIOLOGY AND PATHOGENESIS

Genetics, Environment, and Animal Models

Multiple genes predispose to lupus.[8] This is supported by the clustering in families, racial differences in susceptibility, concordance of SLE in more than 25% of identical twins but only in 5% of fraternal twins, and frequency of positive autoantibodies and other autoimmune disorders in family members of SLE patients. Homozygous deficiency of complement components (C1q, C2, C4) carries a high risk for development of SLE; this is also true for certain FcγRIII receptor polymorphisms. Genome-wide association studies have identified 17 loci associated with an increased risk of SLE that involve genes associated with B cell signaling, Toll-like receptors, and neutrophil function.[8] Environmental factors also play a role in the onset and exacerbation of SLE and LN.[9] Hormonal factors are suggested by the strong female predisposition, the exacerbations during or shortly after pregnancy, and the role of hormonal treatment and ablation in animal models of LN. Whereas exposure to certain medications can produce SLE or a lupus-like syndrome, LN occurs infrequently in these patients. Conclusive evidence for a viral pathogenesis of SLE or LN has yet to be produced. Spontaneous and inducible models of SLE in mice include the NZB B/W F1 hybrid, the BXSB, and the MRL/lpr mice. Some of these models have defective apoptosis that lead to defective clonal deletion and B cell proliferation. SLE can be induced in animals by injection of autoantibodies against DNA, phospholipids, or peptides derived from the Smith antigen.

Autoimmunity in Systemic Lupus Erythematosus

Patients with SLE typically develop a wide range of autoantibodies.[10] Early stages of disease evolution include the defective clearance of apoptotic cells and release of autoantigens from these cells, stimulating interferon-α (IFN-α) and proinflammatory cytokine production. This results in a breakdown of self-tolerance, autoantibody production, and immune complex deposition. Many autoantibodies are directed against nucleic acids and proteins concerned with transcriptional and translational machinery, such as nucleosomes (DNA-histone), chromatin antigens, and small nuclear and cytoplasmic ribonuclear proteins. Polyclonal hyperactivity of B cells along with defective autoregulation of T cells is thought to underlie autoantibody production.[10,11]

A number of mechanisms may contribute to SLE, including failure to remove or to silence autoreactive B and T cells, abnormal exposure to or presentation of self antigens, T cell hyperactivity, increased B cell–stimulating cytokines, and B cell hyperactivity.[10] The failure of apoptotic mechanisms to delete or to silence autoreactive cells (tolerance) may allow clonal expansion of such cells later in life, leading to autoantibody production. Abnormal exposure to self antigen may occur through nuclear autoantigens clustering on the blebs of apoptotic cells, which may be associated with germ-line mutations that lead to clonal expansion of autoreactive cells. Likewise, "antigen mimicry" may occur if exposure to viral or bacterial peptides containing sequences similar to native antigens leads to a similar induction of autoantibody-producing cell lines. The nature of antigen presentation may also be important, with certain nuclear antigens capable of triggering an immunogenic response through interactions with a variety of intracellular Toll-like receptors. In SLE, there is evidence that T cell hyperactivity and failure of T cell tolerance may allow autoreactive T cells to drive B cell proliferation and the production of autoantibodies. Also, proliferation of autoreactive B cells may occur through a variety of disturbances of positive and negative regulatory mechanisms (e.g., stimulation by superantigens) in addition to the mechanisms mentioned. The end result is the loss of tolerance and production of a wide array of autoantibodies.[10,11]

PATHOGENESIS OF LUPUS NEPHRITIS

Autoantibodies are crucial to the pathogenesis of both SLE and LN. In SLE, some autoantibodies, such as those causing autoimmune hemolytic anemia, are directly pathogenic. Other autoantibodies

ACR Criteria for Diagnosis of Lupus

The presence of four or more of the following criteria gives 96% sensitivity and specificity for the diagnosis of lupus:

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Nonerosive arthritis
6. Pleuropericarditis
7. Renal disease (proteinuria and/or cellular casts)
8. Neurologic disorder (seizures or psychosis in the absence of precipitating circumstances)
9. Hematologic disorder (hemolytic anemia, leukopenia/lymphopenia, thrombocytopenia)
10. Positive LE cell preparation, raised anti-DNA antibody, anti-Sm present, false-positive antitreponemal test
11. Positive fluorescent antinuclear antibody test

Box 26-1 American College of Rheumatology (ACR) criteria for the diagnosis of lupus.

Renal Manifestations in Patients with Lupus

Manifestation	Prevalence (%)
Proteinuria	100
• Nephrotic syndrome	45-65
Hematuria	
• Microhematuria	80
• Red blood cell casts	10
• Macrohematuria	1-2
Cellular casts	30
Reduced renal function	40-80
• Rapidly progressive glomerulonephritis	10-20
• Acute kidney injury	1-2
Hypertension	15-50
Hyperkalemia	15

Table 26-1 Frequency of kidney manifestations in lupus patients with renal involvement.

combine with antigen to produce immune complexes that if not adequately cleared may deposit in various organs, inciting inflammatory responses.[1] Complement components aid apoptotic clearance and removal of immune complexes, but they are also activated by immune complexes and contribute to the inflammatory cascade. A hallmark of glomerular involvement in LN is the accumulation of immune complexes. Patients with LN have autoantibodies against double-stranded DNA (dsDNA), Sm antigen, C1q, nucleosomes, and other antigens, and there is evidence both for direct binding of anti-DNA antibodies to the glomerular basement membrane (GBM) and for cross-linking of positively charged nucleosome components such as chromatin between autoantibodies and GBM.[12-14] In proliferative LN, DNA and high-affinity complement-fixing antibodies are found in the subendothelial space, and this may be facilitated by cationic histones binding to the negatively charged GBM. In general, mesangial and subendothelial immune deposits are derived from deposition of circulating immune complexes, whereas subepithelial immune complexes may include those formed *in situ*. However, whether deposition of circulating complexes or *in situ* formation is the predominant pathogenic pathway in a given patient is not always clear. The localization of immune complexes within the glomerulus is influenced by size, charge, specificity, and avidity as well as by the clearing ability of the mesangium and local hemodynamics.[12-16] The localization of immune complexes in the glomerulus leads to complement activation and complement-mediated damage, activation of procoagulant factors, leukocyte Fc receptor activation driving leukocyte infiltration into the kidneys with release of their proteolytic enzymes, and activation of cytokines associated with cellular proliferation and matrix formation. Nucleosomes can also activate resident dendritic cells (see later) through binding to Toll-like receptors 2 and 9. Intraglomerular hypertension and activation of coagulation cascades may contribute to the glomerular injury, especially in patients with antiphospholipid antibodies (aPLAs, APA).

The obligatory role of autoantibodies and immune complexes in the pathogenesis of LN has been challenged. In a mouse model of SLE in which B cell secretion of antibodies is prevented, LN still developed, although the glomerular histology was not as inflammatory as in wild-type mice.[17] Also renal biopsies from lupus patients without clinical LN still show immune deposits.[18,19] It is thus unclear why all patients with SLE do not develop LN, and this suggests renal immune complexes may be necessary but not sufficient for the development of the full clinical phenotypes of LN.

T cell subsets appear to contribute to the progression of LN. T helper type 17 (Th17) cells have been observed in human renal biopsies, and by producing interleukin-17 (IL-17) locally, may drive the expression of inflammatory cytokines and chemokines by renal parenchymal cells, recruiting and activating neutrophils and monocytes. Th17 cells in the kidney may reflect a shift away from T regulatory cells ($CD4^+CD25^{hi}FoxP3^+$), which inhibit immune responses and autoantibody production.[20]

There has been increasing recognition of the role of neutrophils in SLE and LN. Neutrophils undergo a novel form of cell death called NETosis in which a chromatin meshwork (a NET) is released.[21] These NETs (neutrophil nets) are a source of autoantigens and are not degraded properly in lupus patients. In addition, lupus patients have an increased number of low-density granulocytes that are more susceptible to NETosis. NET material has been found in LN biopsies, and SLE patients who are nondegraders often had LN.[22,23] The NETs induce production of IFN-α by plasmacytoid dendritic cells, which are also found in LN kidneys.[24,25] IFN-α appears to have a central role in SLE and LN. IFN-α drives dendritic cell maturation to antigen-presenting cells, B cell differentiation to antibody-producing plasma cells, and development of effector and memory T cells.[26-29]

Within the kidney interstitium, T and B cells may associate and in some cases develop germinal centers.[30] These B cells show clonal expansion and somatic hypermutation, suggesting intrarenal autoantibody production, potentially against specific renal antigens. These interactions likely contribute to interstitial inflammation in LN, which is a major determinant of long-term renal survival.[30]

CLINICAL MANIFESTATIONS

Systemic lupus erythematosus can affect virtually any organ of the body. The disease course is characterized by episodes of illness (flares) followed by periods of relative quiescence (remissions). Nonhealing damage is a consequence of inflammation and is a strong predictor of outcome. A number of reliable and reproducible scoring systems have been devised to follow the activity and development of damage of an individual patient with SLE. These include the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), the British Isles Lupus Assessment Group (BILAG), the Systemic Lupus Activity

Measure (SLAM), and the Systemic Lupus International Collaborating Clinic–American College of Rheumatology (SLICC-ACR) damage score. SLE often results in profound disturbance of quality of life and disruption of economic and reproductive activity.

Renal Manifestations

Renal involvement is usually manifested by proteinuria, active urinary sediment with microhematuria, dysmorphic erythrocytes and erythrocyte casts, and hypertension. In many cases with major renal involvement, the nephritic syndrome develops in association with proliferative glomerulonephritis (GN) and a decline in glomerular filtration rate (GFR). Clinical findings correlate well with histologic glomerular findings (see later discussion). Infrequently, renal disease in SLE presents with tubular disorders such as distal renal tubular acidosis with hypokalemia (type 1 RTA) or hyperkalemia (type 4 RTA) (see Chapter 12), thrombotic disorders associated with a secondary antiphospholipid antibody syndrome (see later and Chapter 28), and fibrillary GN (see Chapter 27).

Extrarenal Manifestations

Patients with active SLE often present with nonspecific complaints of malaise, low-grade fever, poor appetite, and weight loss. Other common features include patchy alopecia; oral or nasal ulcerations; arthralgias and nondeforming arthritis; and a variety of dermal findings, including photosensitivity, Raynaud's phenomenon, and the classic "butterfly" facial rash. Livedo reticularis is seen in up to 15% of cases and may be associated with miscarriages, thrombocytopenia, and APA.[31] Neuropsychiatric involvement presents with headache, nerve palsies, frank coma, and psychoses. Serositis, in the form of pleuritis or pericarditis, affects up to 40% of patients. Pulmonary hypertension can develop silently as a result of multiple pulmonary emboli or intravascular coagulation in association with APA or may be caused by nonthrombotic pulmonary arterial disease. Libman-Sacks endocarditis and much more common mitral valve prolapse can be detected with clinical findings or by echocardiography. Splenomegaly and lymphadenopathy are present in about one fourth of patients. Hematologic abnormalities in SLE include anemia caused by impaired erythropoiesis, autoimmune hemolysis, and bleeding. Thrombocytopenia and leukopenia may be part of the disease process or may result from complications of therapy. Thrombotic events should prompt a search for APA and other procoagulant abnormalities.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Whereas the diagnosis of lupus may be obvious in a young female with classic manifestations and serologic markers, less typical presentations can result in multiple physician consultations and diagnostic delay. This is partly a result of the varied features of the disease and the evolution of signs and symptoms over time. Some patients, especially those with membranous LN, may present with renal disease as their initial manifestation. The presence of four or more ACR criteria carries a 96% sensitivity and specificity for lupus (see Box 26-1). However, the ACR diagnostic criteria were developed for clinical studies and do not always prove useful in an individual patient. Other diseases mimicking SLE include fibromyalgia, Sjögren's syndrome, hematologic diseases such as the thrombotic microangiopathies, primary antiphospholipid syndrome, dermatomyositis, and systemic sclerosis (see Chapters 28 and 29). However, SLE may also present with overlapping features of other multisystem or organ-limited autoimmune syndromes. Nephritis has been reported in patients with mixed connective tissue disease associated with the presence of anti-Ro and anti-La antibodies and the absence of anti-dsDNA antibodies. Rheumatoid arthritis can be associated with mesangial proliferative glomerulonephritis or renal disease due to AA (secondary) amyloidosis. Older lupus patients may present with joint deformities typical of rheumatoid arthritis.

Several common forms of glomerulonephritis must be distinguished from LN, since they may have some clinical features in common. These include Henoch-Schönlein purpura, antineutrophil cytoplasmic antibody (ANCA)–associated glomerulonephritis (see Chapter 24), bacterial endocarditis, and cryoglobulinemia. ANCAs of uncertain significance are detected in 20% of LN patients.

Immunologic Tests in Lupus

Antinuclear antibody (ANA), found in more than 90% of untreated patients, is a highly sensitive screen for SLE patients; however, ANAs are nonspecific and found in other rheumatologic and nonrheumatologic diseases as well. Some lupus-like patients with negative ANA test results have APA, and one third of SLE patients will have APA.[32-34] The pattern of ANA (e.g., diffuse, speckled) is not reliable in distinguishing lupus from other rheumatologic diseases. Autoantibodies against dsDNA are more specific, being present in 75% of untreated lupus patients, but are a less sensitive marker. Whereas high titers of anti-dsDNA antibodies correlate with the presence of SLE and are often used to follow the course of LN, antibodies to single-stranded DNA (ssDNA) are found in many rheumatologic conditions and do not correlate with the course of LN. Sm antibodies are strongly associated with the diagnosis of lupus and the presence of nephritis but are present in only about 25% to 30% of patients. Antibodies to C1q (anti-C1q) have been more closely associated with the activity of LN than anti-dsDNA antibodies and may have a prognostic role in the follow-up of patients with LN.[35]

Serum levels of total hemolytic complement and complement components C3 and C4 are often depressed in untreated SLE and especially LN patients. Either both C3 and C4 are depressed or C4 is preferentially depressed in lupus patients, usually reflecting preferential activation of the classical complement pathway. In patients with postinfectious glomerulonephritis (PIGN), C3 glomerulopathies and some idiopathic membranoproliferative GN, C3 is preferentially depressed (see Chapters 21 and 22). Alternatively, low C4 with normal C3 may reflect genetic C4 deficiency in lupus patients or the presence of cryoglobulins.

PATHOLOGY

Although LN may affect all structures of the kidney, glomerular involvement has been the best studied component and correlates well with the presentation, course, and treatment. The systematic classification systems for LN are based on glomerular involvement. The currently used International Society of Nephrology (ISN)/Renal Pathology Society (RPS) classification refines and clarifies some of the deficiencies of the previous WHO classification,[36] and has improved interobserver reproducibility and the predictive value of LN biopsies[37,38] (Table 26-2).

Classification of Lupus Nephritis

Class I of the ISN/RPS classification for LN denotes normal glomeruli by light microscopy but with mesangial immune deposits (Fig. 26-1). All higher classes of LN show mesangial immune deposits in

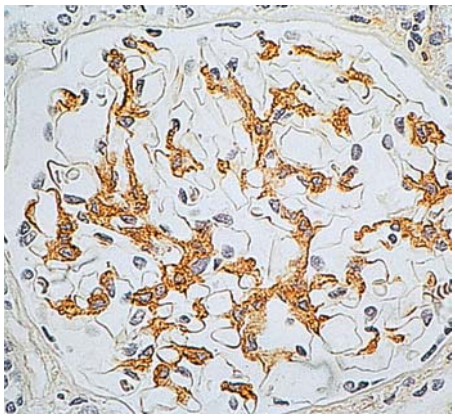

Figure 26-1 ISN/RPS class I: minimal mesangial lupus nephritis. Light microscopy is normal, but immunoperoxidase shows C1q localization (associated with IgG and C3) throughout the mesangial area.

ISN/RPS Classification of Lupus Nephritis

ISN/RPS (2004)	
Class	***Definition***
I	Minimal mesangial LN Normal glomeruli by LM, but mesangial immune deposits by IF
II	Mesangial proliferative LN Mesangial hypercellularity with mesangial immune deposits
III	Focal LN III (A): Purely active lesions: focal proliferative LN III (A/C): Active and chronic lesions: focal proliferative and sclerosing LN III (C): Chronic inactive lesions with glomerular scars: focal sclerosing LN
IV	Diffuse LN IV-S (A) or IV-G (A): Purely active lesions: diffuse segmental (S) or global (G) proliferative LN IV-S (A/C) or IV-G (A/C): Active and chronic lesions: diffuse segmental or global proliferative and sclerosing LN IV-S (C) or IV-G (C): Inactive with glomerular scars: diffuse segmental or global sclerosing LN
V	Membranous LN
VI	Advanced sclerosing LN ≥90% of glomeruli globally sclerosed without residual activity

Table 26-2 Classification of lupus nephritis (LN) using the ISN/RPS classification (2004). In the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification, the distribution of hypercellularity is assessed as mesangial, endocapillary, or extracapillary (crescentic) and as focal (with <50% glomerular involvement) versus diffuse (with ≥50% glomeruli affected). The distribution of immune deposits by immunofluorescence *(IF)* and electron microscopy *(EM)* is judged as mesangial, subepithelial, or subendothelial; *LM,* light microscopy.

addition to their specific differentiating features. *Class II,* mesangial proliferative LN, is defined as pure mesangial hypercellularity (more than three mesangial cells in areas away from the vascular pole in 3-μm-thick histologic sections) by light microscopy with mesangial immune deposits (Fig. 26-2). *Class III,* focal LN, is defined as focal segmental or global endocapillary or extracapillary glomerulonephritis affecting less than 50% of the total glomeruli sampled (Fig. 26-3). *Class IV,* diffuse LN, has diffuse segmental or global endocapillary or extracapillary GN affecting 50% or more of glomeruli (Fig. 26-4). Both class III and class IV have subendothelial immune deposits. Class IV is subdivided into diffuse segmental (IV-S) proliferation (i.e., >50% of affected glomeruli have segmental lesions) and diffuse global (IV-G) proliferation (i.e., >50% of affected glomeruli have global lesions). Both class III and class IV may have active (proliferative), inactive (sclerosing), or combined active and inactive lesions, subclassified as A, C, and A/C, respectively. *Class V,* membranous LN, is defined by subepithelial immune deposits (Fig. 26-5). The membranous alterations may be present alone or on a background of mesangial hypercellularity and mesangial immune deposits. Patients with additional true focal or diffuse proliferative lesions and subendothelial immune complex deposits are classified as V + III and V + IV under the ISN/RPS classification (see Table 26-2). *Class VI,* advanced sclerosing LN, is defined by global glomerular sclerosis affecting 90% or more of glomeruli.

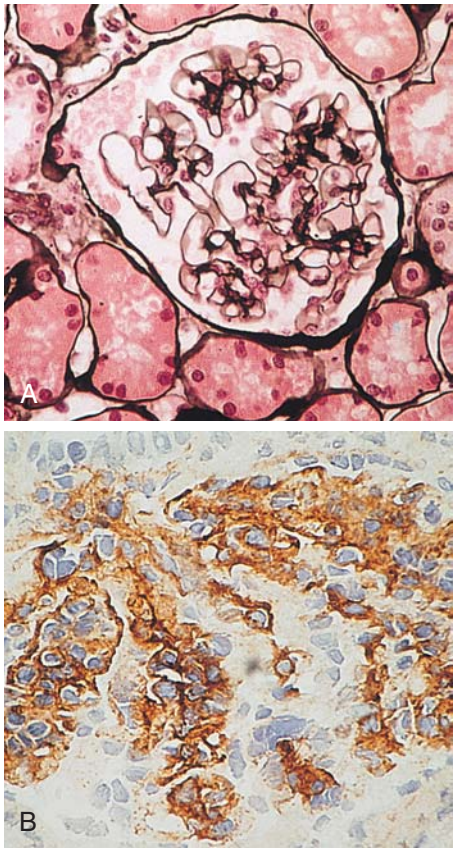

Figure 26-2 ISN/RPS class II: lupus nephritis (mesangial disease). A, Mesangial expansion but little increase in tuft cellularity, and the peripheral capillary walls are normal. (Silver methenamine stain.) **B,** Extensive mesangial IgG deposits shown by immunoperoxidase; the aggregates are just beginning to invade peripheral capillary walls.

On immunofluorescence (IF), IgG is almost always the dominant immunoglobulin, and early complement components such as C4 and especially C1q are usually present along with C3. The presence of all three immunoglobulins, IgG, IgA, and IgM, along with the two complement components, C1q and C3, so called "full-house" staining, is highly suggestive of LN, as is strong C1q staining. Fibrin is often present in the glomerular tuft and especially in crescents.

On electron microscopy (EM) the distribution of immune deposits corresponds to that of IF. Some electron-dense deposits have an organized substructure known as *fingerprinting,* corresponding to the presence of curvilinear microtubular or fibrillar structures

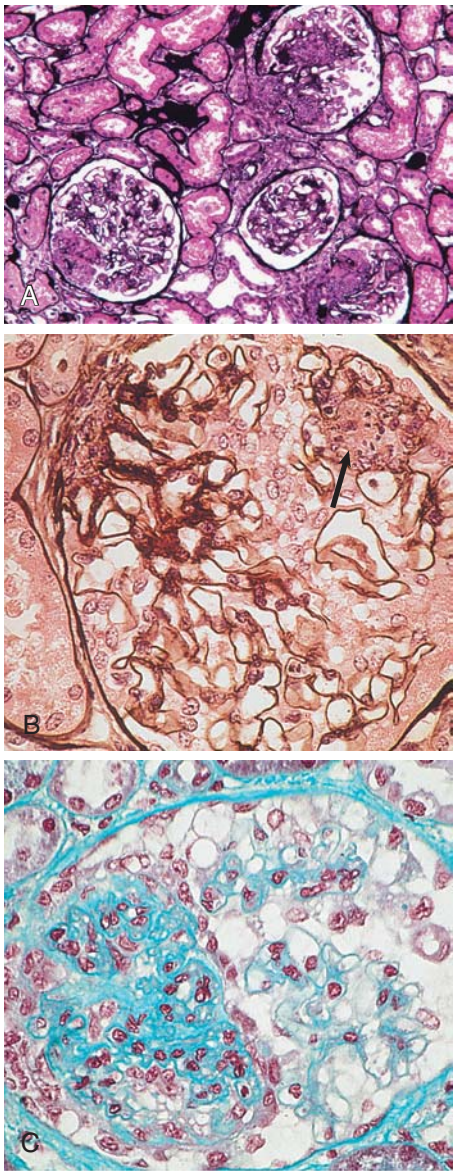

Figure 26-3 ISN/RPS class III: focal proliferative lupus nephritis. A, Low-power magnification shows focal and segmental proliferative lesion–active (class IIIA) with less than 50% of glomeruli affected. (Hematoxylin-eosin [HE] stain.) **B,** Area of focal necrosis containing cellular debris, karyorrhexis (*arrow*), is surrounded by an area of cellular proliferation. (Silver methenamine/HE.) **C,** Major focal and segmental proliferative lesion is affecting almost half the glomerular capillary tuft. (Hematoxylin/lissamine green.)

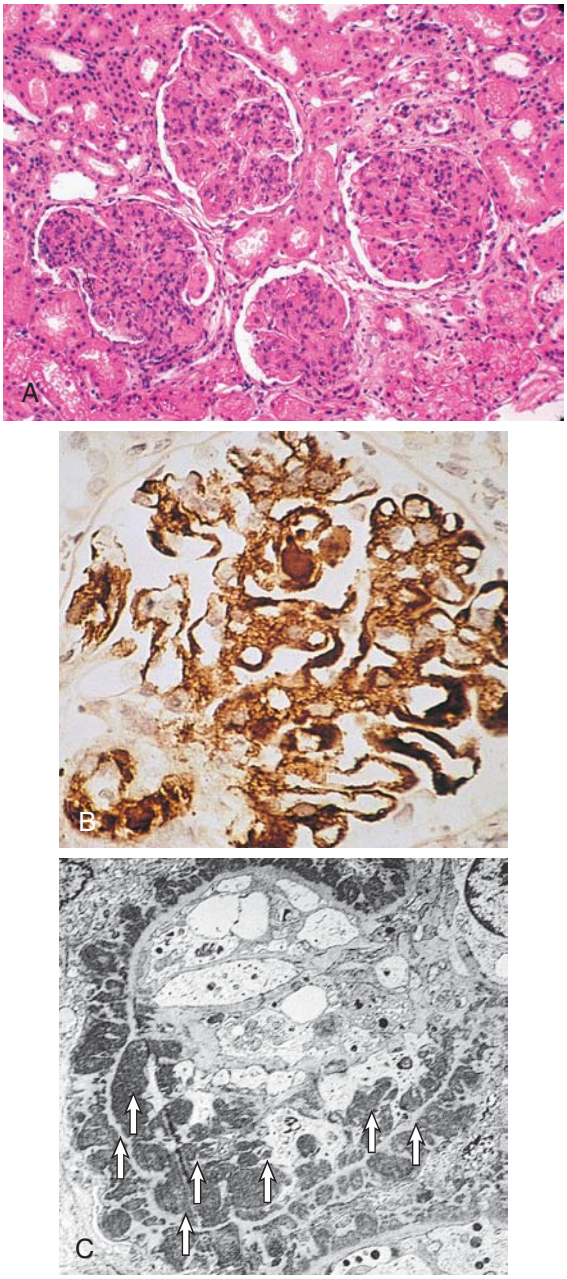

Figure 26-4 ISN/RPS class IV: lupus nephritis. A, Active, diffuse proliferative lupus nephritis. **B,** Immunoperoxidase staining shows dense, irregular aggregates of IgG along the peripheral capillary walls. **C,** Electron microscopy reveals the immune aggregates as electron-dense deposits *(arrows),* predominantly in the subendothelial location.

composed of bands ranging from 10 to 15 nm in diameter. Tubuloreticular inclusions, 24-nm interanastomosing tubular structures located in the dilated cisternae of endoplasmic reticulum of renal endothelial cells, are often found in biopsy specimens of LN patients and are thought to reflect increased interferon expression.

Tubulointerstitial and Vascular Disease

Although LN classification is based on the degree of glomerular involvement, histologic and clinical involvement of other renal compartments is seen in lupus patients.[39,40] This is a deficit of the ISN/RPS system, because interstitial and vascular injury are predictors of kidney outcomes.[41] In about 50% of patients with LN, predominantly those with proliferative glomerular lesions, immune aggregates are found along the tubular basement membranes. Interstitial infiltrates of $CD4^+$ and $CD8^+$ T lymphocytes and monocytes are frequently found. More than half of patients have significant T cell–B cell aggregates in the renal interstitium, and a small percentage have typical-appearing germinal centers.[30] In active disease, infiltration and invasion of the tubules (tubulitis) is found (Fig. 26-6). In chronic disease, the interstitium is expanded by fibrosis and sparser infiltrates. Interstitial inflammation has been correlated with renal dysfunction and hypertension, whereas immune deposition along the tubular basement membranes correlates better with the presence of high anti-dsDNA and depressed serum complement levels. Infrequently, tubulointerstitial nephritis is seen in the absence of glomerular disease and may produce acute kidney injury or RTA.

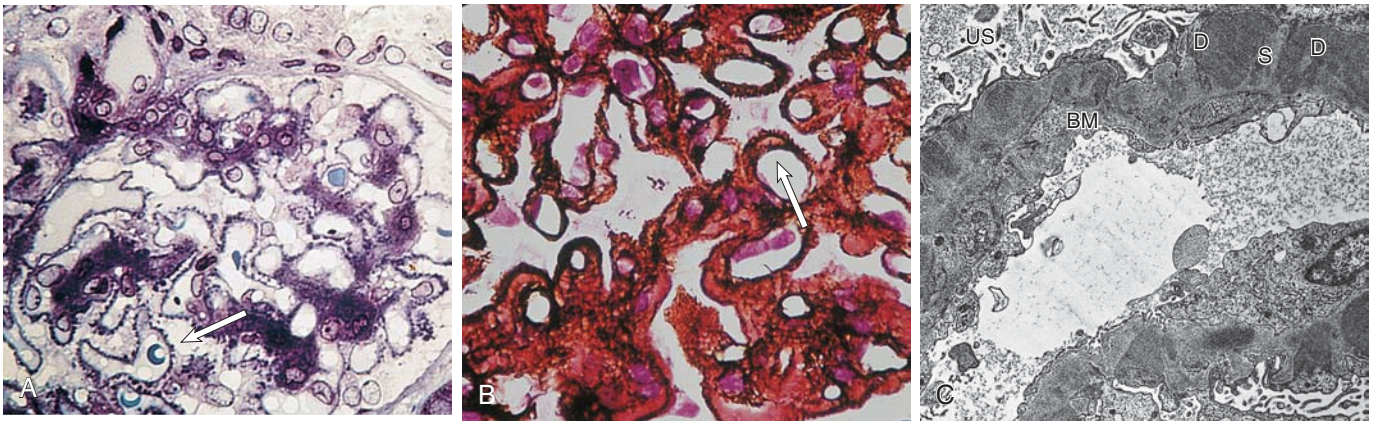

Figure 26-5 ISN/RPS class V: membranous lupus. A, Thick (~0.5 mm) araldite-embedded section stained with toluidine blue shows not only the extramembranous material in dark blue (*arrow*) but also the presence of mesangial deposits, which are common in lupus membranous nephropathy. **B,** Silver methenamine–stained section shows some double contouring of the silver-positive basement membrane *(arrow)* and subendothelium-deposited material as well as the characteristic silver-positive spikes of basement membrane–like material. **C,** Electron micrograph shows the predominantly subepithelial electron-dense deposits *(D)* separated by protrusions of basement membrane material (spikes, *S*); *BM*, basement membrane; *US*, urinary space.

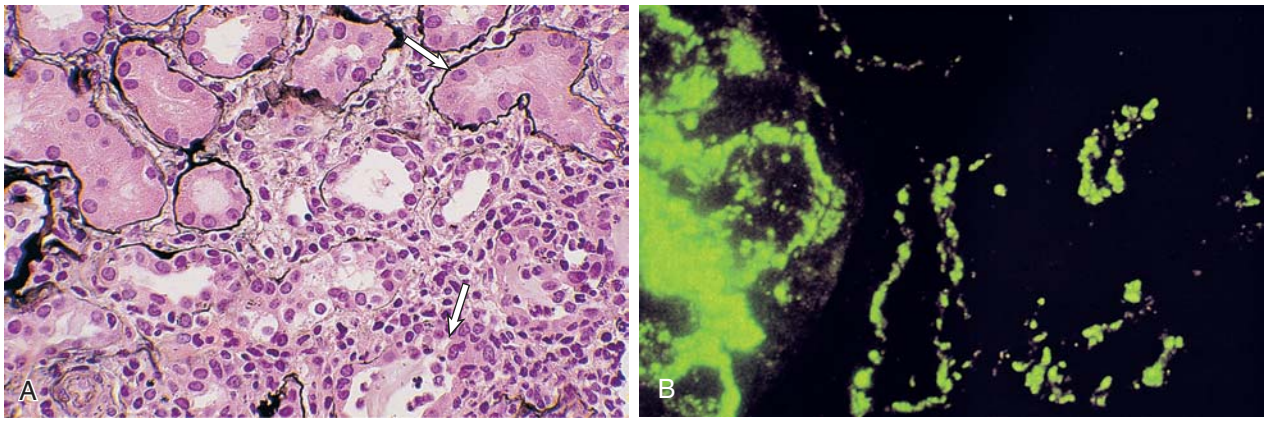

Figure 26-6 Interstitial lupus nephritis. A, Interstitial infiltrate invading and destroying tubules (tubulitis). Tubular basement membranes, which stain black with silver, are digested in the areas of tubulitis *(arrow)*. **B,** Immunofluorescence shows aggregates of C3 in the tubular basement membrane *(right)* as well as within the glomerulus *(left)*. Such tubular basement membrane aggregates are common in lupus nephritis, being found in 60% to 65% of biopsy specimens overall and with increasing frequency from class II (20%) to class IV (75%).

A number of vascular lesions may be seen in lupus patients[40] (Fig. 26-7). True vasculitis is extremely rare. More often, there are vascular immune deposits seen on IF or EM, or a fibrinoid noninflammatory necrotizing lesion of the vessels in patients with severe proliferative nephritis, or a thrombotic microangiopathy. Thrombotic microangiopathy is most often found in patients who are APA positive with prior evidence of coagulation events and may occur in conjunction with a proliferative GN.[32-34]

Transformation of Histologic Appearance and "Silent" Lupus Nephritis

Serial biopsy specimens often show transformation from one to another histologic glomerular class.[42] Some patients with increased clinical activity will transform from a more benign or less proliferative class (ISN class II or V) to a more active proliferative lesion (ISN class III or IV). This is often heralded by increasing proteinuria and active urinary sediment. With successful treatment, other patients will transform from a proliferative class (ISN class III or IV) to a more predominant membranous pattern (ISN class V).

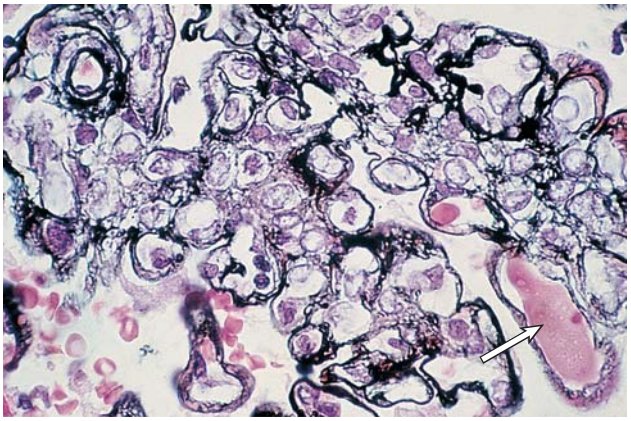

Figure 26-7 Vascular damage in lupus nephritis. Thrombus *(arrow)* occludes a glomerular capillary loop in this class IV biopsy specimen. Such a thrombus contains platelets and cross-linked fibrin as well as immunoglobulins and thus has some characteristics of true thrombus. (Silver methenamine/hematoxylin stain.)

Extremely uncommon are patients who have active proliferative LN on biopsy but no clinical or urinary sediment changes to indicate active disease, with normal anti-dsDNA and serum complement levels, so-called silent LN. If the urine sediment is carefully checked, most patients with proliferative lesions will have microhematuria and often erythrocyte casts.

Clinical and Histopathologic Correlations and Other Correlates of Outcome

Patients with ISN class I biopsies usually have no evidence of clinical renal disease. Likewise, patients with ISN class II may have elevated anti-dsDNA or low complement levels, but in general, their urinary sediment is inactive, hypertension is infrequent, the GFR is preserved, and proteinuria is rarely above 1 g/24 h. Patients with class I and class II biopsy findings have an excellent renal prognosis unless they transform to another pattern. However, patients with LN (especially classes I and II) may be more susceptible to non–immune complex podocyte injury (lupus podocytopathy) that shows a histologic pattern of minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGN), and is often accompanied by nephrotic-range proteinuria.[43]

Patients with active ISN class IIIA or IIIA/C often have microhematuria, hypertension, low complement levels, and proteinuria. From one fourth to one third of patients will have the nephrotic syndrome, and up to one in four will have an elevated serum creatinine concentration at renal biopsy. Patients with focal glomerular scarring (ISN class IIIC) usually have hypertension and reduced renal function but without active urinary sediment. Patients with mild proliferation in only a few glomeruli generally respond well to therapy, with less than 5% progressing to renal failure during 5 years of follow-up. Others with more glomerular involvement or with necrotizing features and crescent formation have a prognosis similar to that of class IVA patients. Although some have suggested patients with "severe" focal segmental proliferative class III have a worse prognosis than do those with diffuse proliferative class IV lesions, this has not been supported by most investigators.[44]

Patients with ISN class IVA typically have high serologic activity (low serum complement and high anti-dsDNA–binding activity) along with active urinary sediment, hypertension, heavy proteinuria, and reduced GFR. Class IV diffuse proliferative disease carries the worst renal prognosis in most series, although this is greatly influenced by prognostic features such as racial background, socioeconomic factors, and renal features at presentation. Patients with segmental diffuse proliferative class IV-S may fare worse than those with diffuse global involvement class IV-G, although this remains controversial.[37]

Patients with ISN class V typically present with proteinuria and features of the nephrotic syndrome. At biopsy, however, up to 40% will have subnephrotic proteinuria, and up to 20% will have less than 1 g/24 h of proteinuria. Patients with ISN class V typically have less clinical renal and serologic activity. Some develop what appears to be idiopathic nephrotic syndrome before developing other features of lupus. Nephrotic ISN class V patients are predisposed to thrombotic complications, such as renal vein thrombosis and pulmonary emboli. Ten-year renal survival rates are 75% to 85%.

Advanced sclerotic LN, ISN class VI, is usually the result of "burnt-out" class III or class IV LN. Many patients will nevertheless have persistent microhematuria and some proteinuria along with hypertension and a decreased GFR.

Other Histologic Prognostic Factors

Features of reversible (active) or irreversible (chronic) damage on biopsy may be able to predict the course of LN patients. Some investigators have found that patients with a higher *activity index* or *chronicity index* are more likely to progress to renal failure[45,46] (Table 26-3). Similar to other types of GN, the renal prognosis is poor if biopsy specimens show extensive glomerulosclerosis or interstitial fibrosis.[41] Whereas there is disagreement about the value of the individual activity index or chronicity index, patients with high degrees of both activity and chronicity on biopsy (activity index >7 plus chronicity index >3) fare poorly, as do those with the combination of cellular crescents and interstitial fibrosis on biopsy. Persisting inflammation with subendothelial and mesangial deposits on repeated renal biopsy, especially with cellular crescents or macrophages in the tubular lumina, is more strongly predictive for the development of renal failure.[47]

NATURAL HISTORY

The natural history of LN in the modern era is unknown because patients with severe renal involvement receive therapy directed at their renal lesions. Fifty years ago, few patients with severe LN survived more than a few years, and half of those with even less severe forms of LN died within 5 years. Most patients now have a gratifying response to early treatment, followed by relatively quiescent disease under continuing immunosuppression that eventually can be tapered (Table 26-4). Some patients will continue to have no disease activity; others will relapse with time. The frequency of relapse depends not only on the underlying disease severity, but also on the intensity and duration of continued immunosuppression.

Point System in Calculating Lupus Nephritis Biopsy Activity and Chronicity

	Lesions Contributing to Activity Index						Lesions Contributing to Chronicity Index			
Semiquantitative Lesion Score*	***Cellular Crescents***	***Glomerular Necrosis-Karyorrhexis***	***Glomerular Neutrophils***		***Large Subendothelial Immune Deposits***	***Interstitial Inflammation***	***Glomerular Sclerosis***	***Fibrous Crescent***	***Tubular Atrophy***	***Interstitial Fibrosis***
None	0	0	0	0	0	0	0	0	0	0
Mild	2	2	1	1	1	1	1	1	1	1
Moderate	4	4	2	2	2	2	2	2	2	2
Severe	6	6	3	3	3	3	3	3	3	3

Table 26-3 The point system used to calculate lupus nephritis biopsy activity and chronicity indices. *Maximum activity index is 24; maximum chronicity index is 12.

Survival in Lupus and Lupus Nephritis			
	5-Year Survival (%)*		
Period	*All Lupus*	*Lupus Nephritis*	*Class IV Nephritis*
1953-1969	49	44	17
1970-1979	82	67	55
1980-1989	86	82	80
1990-1995	92	82	82
2000-2010	95-100	95-100	90-95

Table 26-4 Survival in lupus and lupus nephritis. Five-year actuarial survival for lupus, lupus nephritis, and World Health Organization class IV nephritis during the periods shown. *Weighted mean of published series. *(Data from references 62, 80, and 105.)*

End-stage renal disease (ESRD) now affects 8% to 15% of patients with LN.[5] Rare patients with progressive LN leading to dialysis may regain enough renal function to terminate dialysis. A renal biopsy is often useful to determine whether the disease is still active and potentially treatable or all chronic and irreversibly scarred.

In patients with active LN, fatal infections, often associated with persistent extrarenal disease activity, are the most common cause of death. Studies confirm that almost half of all lupus deaths are the result of excess cardiovascular mortality, often later in the course of the disease and particularly from premature myocardial ischemia.

Multiple factors have been associated with outcomes in LN. Epidemiologic predictors include race, with blacks and Hispanics having worse outcomes.[48-51] Persons of Southeast Asian descent have more severe disease than other Asians or Caucasians. Male gender, younger age (<24 years), and lower socioeconomic status, independent of race, are associated with a worse renal outcome.[50,51] Laboratory outcome predictors include the histologic features previously discussed, higher baseline serum creatinine concentration or greater baseline proteinuria, hypertension, severe anemia, thrombocytopenia, and hypocomplementemia with elevated anti-dsDNA levels. Across several prospective and retrospective trials, the most consistent predictor of poor long-term renal prognosis was an elevated serum creatinine at diagnosis. Adverse clinical management predictors include delay in the onset of therapy, prolonged disease course, failure to reduce proteinuria with treatment, and LN relapses.

TREATMENT

It is useful to divide the treatment of patients with active proliferative LN into an initial phase and a maintenance phase. The *initial phase* deals with acute life- or organ-threatening disease. The *maintenance phase* focuses on the long-term management of chronic, more indolent disease, protection from the side effects of therapy, prevention of flares and slowing or preventing progressive renal failure.

The ISN/RPS biopsy classification should guide initial therapy[52] (see Table 26-2). In general, patients assigned to ISN class I and class II need no therapy directed at the kidney. The majority will have a benign long-term kidney outcome, and the potential toxicity of any immunosuppressive regimen will negatively alter the risk/benefit ratio of treatment. Extrarenal manifestations should be treated with immunosuppression if indicated. An exception is the group of lupus patients with lupus podocyte injury, who often respond to a short course of high-dose corticosteroids similar to patients with MCD or FSGN.[43,53] It is in patients with active focal proliferative LN (ISN class IIIA and IIIA/C), active diffuse proliferative LN (ISN class IVA and IVA/C), and membranous lupus (ISN class V) that combination corticosteroid and immunosuppressive therapy is most widely used.

Although the goal of initial therapy is to induce a complete renal remission, this only occurs in 30% to 40% of LN patients by 12 months. Studies have varied in their definition of remission, but this typically requires a reduction in proteinuria below 0.5 g/24 h or urine protein-creatinine ratio below 0.5 g/g, absence of glomerular hematuria or red blood cell (RBC) casts, and normalization or stabilization of GFR. Subsequent flares are defined as *proteinuric* by an isolated increase in proteinuria, typically at least a doubling and to more than 1 g/24 h; or as *nephritic*, by a reproducible increase in serum creatinine of at least 30% (or a decrease in GFR by at least 10%) and an active urine sediment with an increase in glomerular hematuria of 10 or more RBCs per high-power field regardless of changes in proteinuria.[52]

Evidence in support of different therapeutic agents and regimens has emerged from clinical trials conducted during the last 30 years. It is important to treat many of these conclusions with caution, however, because of small study size and uncontrolled or nonblinded methods and a heterogeneous LN presentation and response to therapy. Therapeutic toxicity is a major contributing factor to mortality and morbidity; thus, claims of efficacy must be carefully balanced against adverse events. Other factors, such as ethnicity, referral practice, center experience, and use of concomitant medications, vary between studies and over time, which reduces the generalizability of some study results. Consensus statements have addressed the methodology and terminology used in clinical studies of LN.[52,54,55]

In addition to the immunosuppressive regimens discussed next, the renoprotective measures outlined in Chapter 80 should be used as appropriate. In addition, unless contraindicated, all LN patients should be treated with hydroxychloroquine.

Proliferative Lupus Nephritis: Initial Phase

Corticosteroids

Corticosteroids used in conjunction with other immunosuppressives are commenced at high dose, either prednisone (or prednisolone) at 0.5 to 1 mg/kg/day ideal body weight (no more than 80 mg/day), then tapered stepwise to approximately 10 mg/day by 3 to 6 months. In severe disease, oral corticosteroids may be preceded by intravenous (IV) methylprednisolone infusions (0.5 to 1.0 g daily for 1 to 3 days). Cosmetic effects, risk of gastrointestinal ulceration, risk of osteonecrosis, hypertension, psychoses, and enhanced risk of infectious complications have led to attempts to minimize prolonged courses of high-dose corticosteroid therapy in lupus patients. For example, a randomized comparison of 1.0 versus 0.5 mg/kg/day of prednisone, both with enteric mycophenolic acid, found a nonsignificant increase in partial responses, but almost a doubling of severe adverse events with the higher prednisone dose. A study using cyclophosphamide as initial therapy, but without high-dose corticosteroids, in a Caucasian population with mild-moderate disease showed complete and partial remission rates at 2 years comparable to patients treated with cyclophosphamide and high-dose corticosteroids.[56] Preliminary results of a pilot trial using anti–B cell therapy plus two doses of IV methylprednisolone followed by mycophenolate mofetil (MMF) alone have been encouraging and suggest that virtually steroid-free regimens for LN may be possible.[57]

Immunosuppressives

Although corticosteroids are effective in controlling proliferative LN, a landmark study showed that over the long term, kidney function

was better preserved and there were fewer LN relapses if corticosteroids are combined with cyclophosphamide during initial therapy.[58] Importantly, this outcome was not apparent for 3 to 5 years, highlighting the need for long-term follow-up in assessing initial LN therapies. Both daily oral and IV pulses of cyclophosphamide are effective in LN. However, IV cyclophosphamide given as six monthly pulses (0.5 to 1 g/m^2) has been the accepted standard of care for several years.[59] Early oral cyclophosphamide regimens exposed patients to high cumulative doses and serious toxicity; a lower-dose, shorter-duration oral regimen has shown efficacy, dose exposure, and tolerability comparable to IV cyclophosphamide.[60] A true low-dose cyclophosphamide protocol of 500 mg given intravenously every 2 weeks for 3 months (six pulses) followed by azathioprine had similar efficacy in a Northern European cohort as a standard regimen of six monthly pulses of cyclophosphamide followed by quarterly infusions.[61] The low-dose regimen, known as the "Eurolupus protocol" (Euro-Lupus Nephritis Trial), had less toxicity with fewer infections. Subsequent reports after 5 and 10 years continued to find no differences in outcome between treatment groups, but with a much lower cumulative dose of the alkylating agent with the Eurolupus regimen.[62] Although this regimen was initially tested in a mainly Caucasian population, a recently completed trial showed that remission induction with low-dose cyclophosphamide was similar in Caucasians, African Americans, and Hispanics.[62a]

Several randomized clinical trials involving multiethnic cohorts showed that oral MMF plus corticosteroids for 6 months, followed by maintenance therapy (see later), is at least as effective and in some cases more effective than six monthly pulses of cyclophosphamide plus corticosteroids followed by maintenance therapy.[63-65] No benefit on mortality or severe infection rates has been seen with MMF, although the risk of amenorrhea is lower and gastrointestinal toxicity is more frequent. Longer-term follow-up of the randomized trials has found no differences in renal outcome, but one study of 227 patients found a non-significant increase in renal flares with MMF as compared to cyclophosphamide induction.[66] Differences in response between ethnic and geographic subgroups have been suggested but not confirmed, including better responses to MMF in American blacks and worse responses to MMF in Chinese.[67] This latter observation is in line with a retrospective analysis of a Korean cohort, where remissions were similar for MMF and cyclophosphamide, but more relapses and ESRD were seen in the MMF group.[68] Patients presenting with marked renal impairment are at high risk of progressing to ESRD and for infective comorbidity; no convincing differences in outcome between MMF and cyclophosphamide induction have been seen for this subgroup. The optimal MMF dosing and adjustments for different patient subgroups remains unclear, but there is increasing evidence for mycophenolic acid monitoring in guiding MMF dosing.

Three organizations recently developed evidence-based guidelines for LN therapy.[52,54,55] Although the groups were independent, their recommended guidelines were fairly consistent. The guidelines are synthesized in the treatment algorithm presented in Figure 26-8.

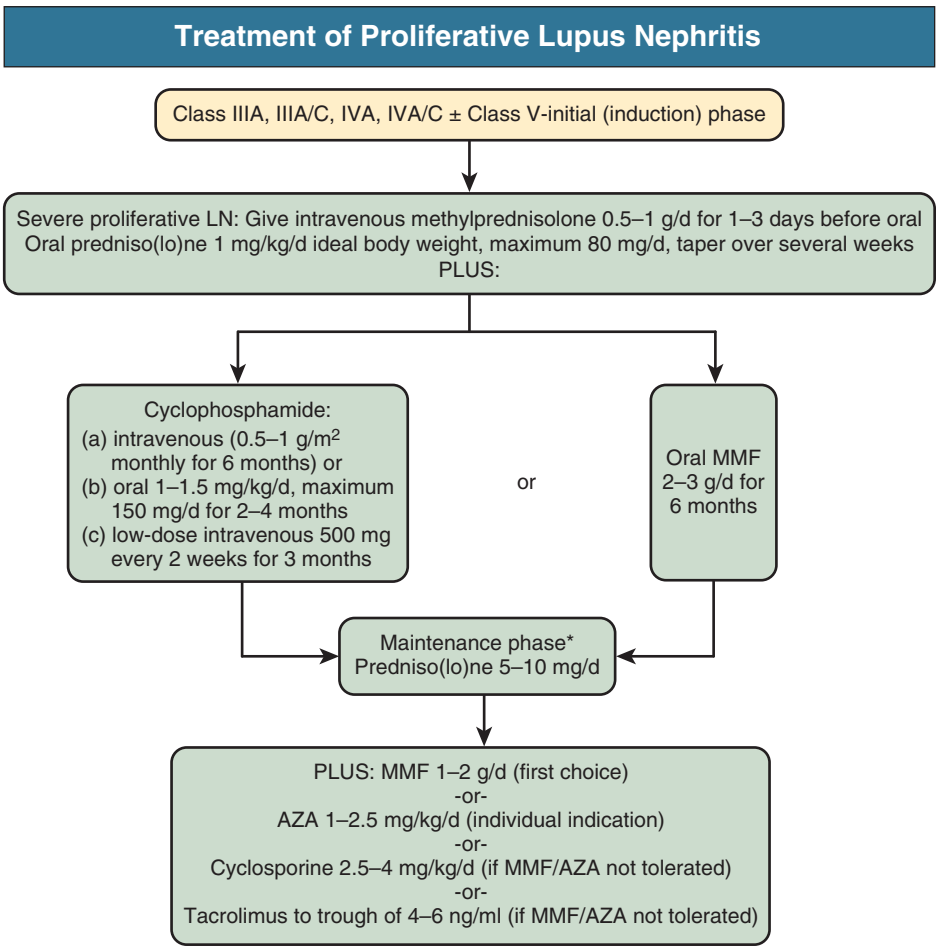

Figure 26-8 Treatment of proliferative lupus nephritis. *AZA,* Azathioprine; *MMF,* mycophenolate mofetil.

Other Immunosuppressive Strategies

Azathioprine (AZA) and calcineurin inhibitors (CNIs) have been used in combination with corticosteroids for the induction of remission in proliferative LN. A randomized trial comparing AZA with cyclophosphamide found no difference in eventual outcome but more relapses and more patients doubling their serum creatinine concentration in the AZA group.[69] Although AZA has not been recommended as first-line therapy by the major LN guidelines, it remains an option when MMF or cyclophosphamide are unavailable or contraindicated. Similarly, the CNIs tacrolimus and cyclosporine tested as alternatives to cyclophosphamide for the initial treatment of proliferative LN have compared favorably in short-term responses.[70,71] Larger and longer-term prospective trials of CNIs in proliferative LN are warranted.

Biologic Agents

Rituximab, an anti-CD20 monoclonal antibody that depletes B cells, has led to improved disease control in LN patients with relapsing or refractory disease in retrospective or nonrandomized trials. However, in a large randomized, prospective trial, when added to MMF and corticosteroids for induction of remission, rituximab did no better than placebo.[72] Of note, no safety concerns with rituximab were seen in this trial. The position of rituximab in LN therapy is currently uncertain, and it may be considered when other therapies have failed.

Abatacept, a fusion protein of CTLA4 and the immunoglobulin heavy chain, blocks T and B cell costimulation, but in combination with MMF and corticosteroids was no better than placebo. However, a retrospective analysis of the abatacept data using different definitions of remission suggested that the drug may have been effective with somewhat less stringent criteria.[73]

Other pathogenic mediators currently being targeted in SLE or LN with monoclonal antibodies are the B cell–stimulating cytokine BAFF, IFN-α, IL-6, and TWEAK, a proinflammatory cytokine and member of the tumor necrosis factor superfamily.

Resistant Proliferative Lupus Nephritis

There is no uniformly accepted definition of resistant or refractory LN. One retrospective analysis of a large randomized clinical trial suggested that success at 6 months was more likely if at 2 months, patients showed a decline in proteinuria by at least 25% and normalization of serum complement levels if low at the start of therapy.[74] Figure 26-9 outlines therapies that have been attempted for "refractory disease." Most of the studies were uncontrolled, small, and retrospective. Rituximab has had some success in this population with refractory disease.[75]

Although no benefit was seen after the addition of plasma exchange for routine remission induction in LN, the removal of circulating antibodies and other immune reactants may be considered for patients with high serologic activity and progressive refractory nephritis. Intravenous immunoglobulin and CNIs have shown benefit in small series of patients with resistant LN.[76,77] For patients with life-threatening resistant disease, small pilot studies have used total lymphoid irradiation and immunoablation by high-dose cyclophosphamide and antithymocyte globulin, with or without reconstitution with autologous stem cells. These approaches have led to sustained treatment-free remissions but are toxic and have treatment-related mortality, and their role in SLE remains to be seen.[78]

Renal Response to Initial Therapy

Achieving a remission of LN predicts an improved long-term outcome. In one study, the 5-year patient and 5-year renal survival were 95% and 94%, respectively, for the group achieving remission and only 69% and 45%, respectively, for the group not achieving a remission.[79] Partial remission was also associated with improved outcomes. Predictors of remission included lower baseline serum creatinine concentration, lower baseline urinary protein excretion, better renal histologic class, lower chronicity index, stable GFR after 4 weeks of therapy, and Caucasian race.

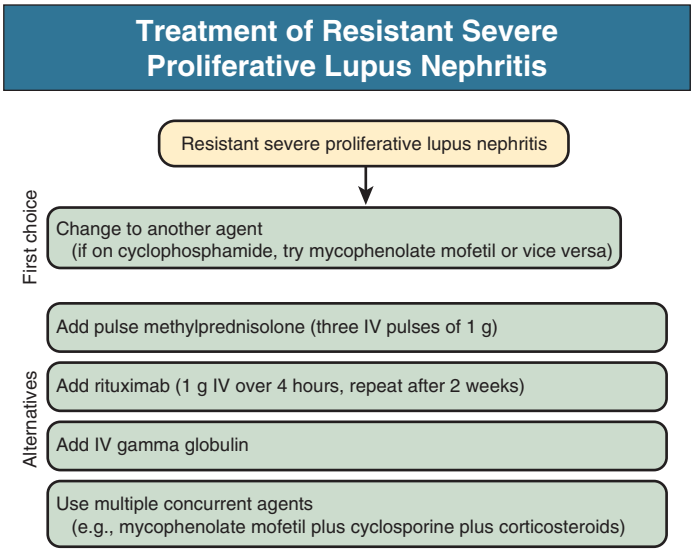

Figure 26-9 Treatment of resistant proliferative lupus nephritis.

Multiethnic studies showed that complete and partial renal responses to MMF or cyclophosphamide ranged from 18% to 85% at 6 months and 32% to 85% at 12 months.* Because the definition of "complete remission" often includes total absence of abnormal proteinuria or hematuria, looking at data after 1 year or longer is often a more reliable predictor of outcome. In general, about half of treated LN patients achieve a complete or partial response by 1 year, and an additional 25% by 2 years.† Thus, even with the best current therapies, time to remission is long, and remission rates are suboptimal, leaving room for improvement with add-on drugs or novel alternative therapies.

Proliferative Lupus Nephritis: Maintenance Therapy

After the initial treatment of proliferative LN, maintenance therapy continues for the long term to prevent renal flares and the development of chronic kidney disease. Early investigations showed maintenance cyclophosphamide was superior to corticosteroids alone.[58,84] Subsequent work demonstrated that less intense maintenance immunosuppression with AZA or MMF was as effective and significantly improved patient morbidity and survival.[59] Because it often takes several months for proteinuria and serum creatinine to decline to baseline levels following initial therapy,[60] the early clinical importance of maintenance therapy is to consolidate renal responses into complete and partial remissions using drugs with a lower side effect profile.

Corticosteroids tapered from the initial treatment period are generally continued during the maintenance period, but the dose is limited (e.g., prednisone 5 to 15 mg/day) (see Fig. 26-8). Both daily and alternate-day regimens have been used. There is no consensus on the optimal duration of corticosteroid therapy.

*References 45, 59-61, 63, 64, 69, 80, 81.
†References 60, 61, 64, 69, 82, 83.

Two randomized clinical trials recently compared AZA (2 mg/kg/day) and MMF (2 g/day) as maintenance drugs. In a trial of 227 multiethnic patients, MMF was significantly better than AZA at preventing renal flares and ESRD and preserving renal function over 3 years after initial therapy with cyclophosphamide or MMF.[66] In a study of 105 patients, mainly European Caucasian, AZA and MMF were as effective at preventing renal flares over 4 years from initial treatment as low-dose cyclophosphamide.[85] Although MMF appears to be the maintenance drug of choice for most LN patients, therapy should be individualized. In some patients, AZA may be appropriate, such as for the patient in complete remission who wants to become pregnant. Two randomized trials compared the CNIs tacrolimus and cyclosporine to AZA for maintenance.[86,87] Although both trials were underpowered, and the tacrolimus trial had only 6 months of follow-up, both demonstrated the CNIs were as effective as AZA in preventing renal flares. Given less data for tacrolimus and cyclosporine, CNIs should probably be reserved for patients who cannot take MMF or AZA. Maintenance therapy should be continued for a minimum of 3 to 4 years unless there is a contraindication.

Figure 26-8 summarizes disease-specific treatment recommendations for both induction and maintenance phases of proliferative LN therapy. General renoprotective measures should follow the agents outlined in Chapter 80. Many believe that an antimalarial agent such as hydroxychloroquine should be used in all lupus patients unless a contraindication exists. Aside from the antimalarials,[88] other agents used to treat extrarenal findings in lupus patients (e.g., NSAIDs, androgens, fish oil) have not shown benefit in patients with LN.

Membranous Lupus Nephropathy

The treatment of pure ISN/RPS class V LN remains controversial. For patients with subnephrotic proteinuria, renoprotective and antiproteinuric therapies should be used. Some patients with subnephrotic proteinuria will benefit from immunosuppressives, but these should be considered for all patients with nephrotic syndrome or renal impairment. The only small, randomized controlled trial in patients with class V LN compared cyclophosphamide or cyclosporine to corticosteroids alone.[89] The patients had preserved GFR but a mean proteinuria of almost 6 g daily. At last follow-up, there were more complete and partial remissions in the cyclophosphamide and cyclosporine groups than in the prednisone group. Remissions occurred more quickly in the cyclosporine group, but there were fewer relapses in the cyclophosphamide group. Patients who relapsed or failed to respond to cyclosporine could subsequently be brought into remission with IV cyclophosphamide. Two recent trials of MMF versus IV cyclophosphamide as initial therapy of LN included 84 patients with pure membranous nephropathy among the 510 patients enrolled.[90] Remissions, relapses, and courses were similar in the patients treated with oral MMF and IV cyclophosphamide. Azathioprine along with corticosteroids has also been successful in some patients with membranous LN, but these studies have all been observational or retrospective.[91]

Membranous nephropathy is often diagnosed in association with proliferative forms of LN. In these patients, treatment is directed at the proliferative component. An alternative approach for the treatment of ISN class V + class III or class IV LN, called multitargeted therapy, combines low doses of corticosteroids, MMF, and a CNI[82] and has shown success in an Asian cohort.

Thus, for patients with membranous nephropathy who have subnephrotic levels of proteinuria and a preserved GFR, we recommend either conservative therapy with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and statins, or a short course of corticosteroids or a CNI. For fully nephrotic patients and those at higher risk for progressive disease, MMF, AZA, or a CNI is preferred, with cyclophosphamide reserved for refractory cases (Fig. 26-10).

Long-Term Monitoring of Lupus Nephritis Patients

The relapse rate for LN ranges from 35% to 60%, depending on the population studied, the criteria for relapse, and the maintenance therapy used.[92-94] An increase in anti-dsDNA antibody levels and a fall in serum C3 and C4 may predict an impending LN flare in some patients, but better biomarkers to predict flare are needed.[95] Treating positive serology in the absence of clinical lupus activity is not recommended. However, a normal anti-dsDNA level suggests a lower risk of relapse after treatment reduction or withdrawal in the chronic phase of maintenance therapy.[96] A stable GFR and no proteinuria also predict successful discontinuation of immunosuppressives.

Patients with SLE who have had LN should have blood pressure, GFR/serum creatinine, proteinuria, and urinary sediment monitored quarterly.[54] Serologies such as C3 and C4 levels and anti-dsDNA should also be monitored quarterly or biannually, respectively. Surveillance kidney biopsies are not generally done, but a repeat biopsy at the time of a suspected LN flare will confirm the diagnosis of increased activity and will identify changes in histologic class. A repeat biopsy for persisting proteinuria or a declining GFR not clearly caused by a flare will identify whether there are active lesions potentially modifiable by restarting, changing, or increasing immunosuppressive therapy, or if the abnormalities are caused by chronic scarring that requires only renoprotective therapies (see Chapter 80).

ANTIPHOSPHOLIPID ANTIBODY SYNDROME, ATHEROSCLEROSIS, AND PREGNANCY IN LUPUS NEPHRITIS

Intrarenal clotting caused by the antiphospholipid antibody syndrome is found in 30% of patients with SLE and may occur in the presence or absence of LN.[32,33] Most such patients have a lupus anticoagulant or anticardiolipin antibody, but up to 15% of patients have neither.[34] The risk of thrombotic episodes is highest with lupus anticoagulant and somewhat lower with anti–β_2-glycoprotein 1 and anticardiolipin antibodies. The exact mechanisms for the thrombotic tendency remain unclear but may include abnormal endothelial function, enhanced platelet aggregation, reduced production of prostacyclin and other endothelial anticoagulant factors, and activation of plasminogen. The clinical manifestations and treatment of patients with APS are discussed further in Chapter 28, but the mainstay of treatment is not immunosuppression as for LN, but rather anticoagulation and hydroxychloroquine.

Patients with lupus have increased risk of atherosclerotic complications compared with age-matched controls and greater atherosclerotic plaque burden, which contribute significantly to morbidity and mortality in SLE.[97,98] Young women with SLE have a risk of heart attack that is 50 times greater than that of healthy women, and even older women with SLE have 2.5 to 4 times the risk of myocardial infarction (MI).[99] After adjustment for all traditional cardiovascular risk factors, SLE patients have a 7- to 10-fold higher risk of nonfatal MI and a 17-fold higher risk of fatal MI.[100] Chronic kidney disease, a frequent outcome of LN, is also a nontraditional cardiovascular risk factor.[101] Reduction of atherosclerotic risk should be focused on control of blood pressure (goal of 130/80 mm Hg), the use of statins and antimalarials to correct lipid abnormalities,[102] and the reduction of inflammatory disease activity.

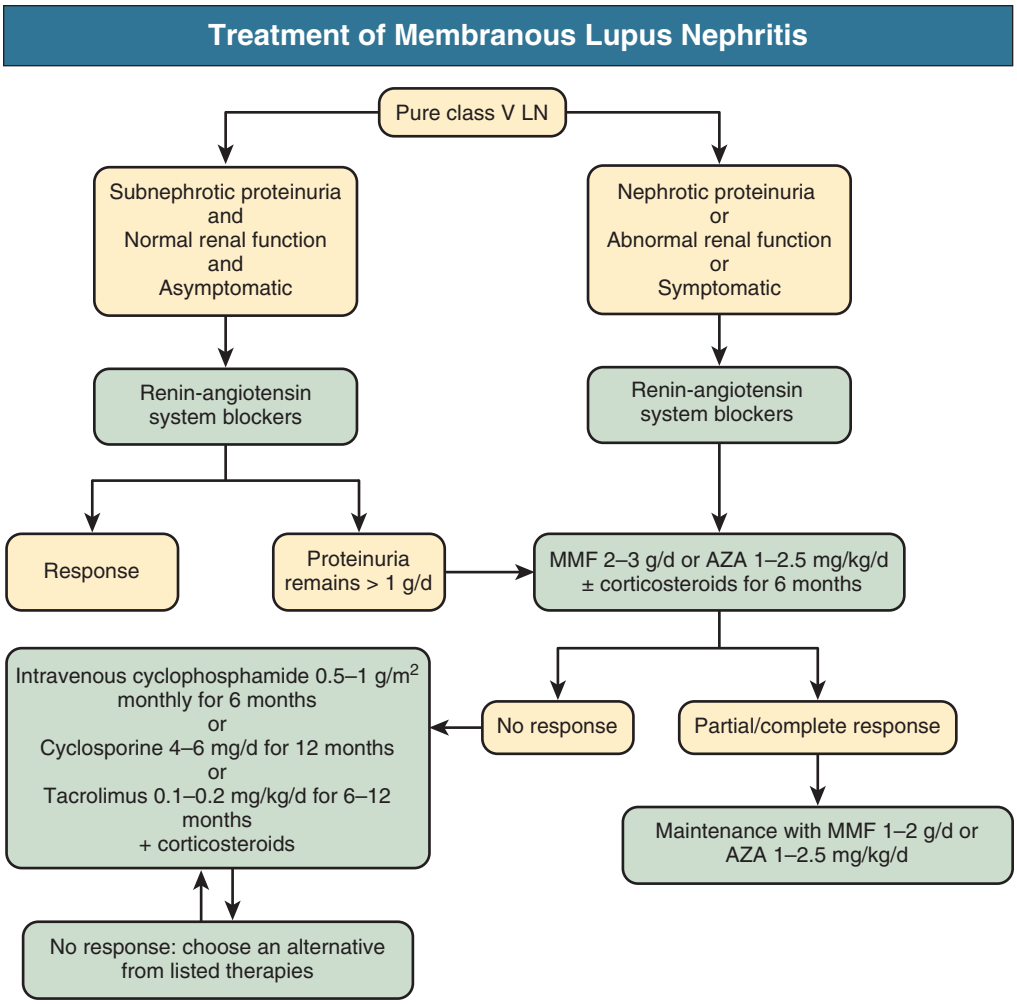

Figure 26-10 Treatment of membranous lupus nephritis. *AZA,* Azathioprine; *MMF,* mycophenolate mofetil.

The effects of SLE and LN on pregnancy and fetal outcomes, and the effects of pregnancy on LN activity, are discussed in Chapter 45.

END-STAGE RENAL DISEASE AND RENAL TRANSPLANTATION

About 10% to 15% of lupus patients develop ESRD, and lupus represents only 1% to 2% of patients with ESRD.[103] Extrarenal lupus will be inactive in many patients by the time they reach ESRD, but some may still have active extrarenal disease that requires immunosuppression while receiving renal replacement therapy. Survival of lupus patients on dialysis is comparable to that of other primary renal diseases.[103]

Transplantation of lupus patients can be performed with only a few extra precautions. Most centers defer transplantation until lupus activity is quiescent for 6 months. For patients who are clinically inactive but retain serologic activity with elevated anti-DNA antibody levels, starting transplant immunosuppressives prophylactically several weeks to 1 month before living donor transplantation may suppress the serologic activity. Allograft thrombosis (arterial, venous, or intraglomerular) may occur after transplantation, especially in patients with APA. APA-positive patients with a prior thrombotic event should be anticoagulated shortly after transplantation. Outcomes in SLE patients undergoing transplantation are similar to those of patients with other diseases.[104] Recurrent LN occurs in 2% to 11% of transplanted kidneys (see Chapter 108).

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CHAPTER 27

Renal Amyloidosis and Glomerular Diseases with Monoclonal Immunoglobulin Deposition

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The glomerular capillaries are a favorite site for the deposition of abnormal proteins. In most patients, the resulting diseases are caused by a monoclonal immunoglobulin or subunit thereof and can be classified into two categories by electron microscopy (Table 27-1). The first category includes diseases with fibril formation, mainly amyloidosis, and diseases with microtubule formation, including cryoglobulinemic glomerulonephritis (see Chapter 21) and immunotactoid glomerulonephritis. The second disease category is characterized by nonorganized electron-dense granular deposits. These deposits are localized along basement membranes in most tissues, especially in the kidney, and define a disease now termed *monoclonal immunoglobulin deposition disease* (MIDD). In some cases, monotypic immune complex–like deposits are observed in the setting of proliferative glomerulonephritis.

RENAL AMYLOIDOSIS

General Characteristics of Amyloidosis

Definition

Amyloidosis is a generic term for a family of diseases defined by morphologic criteria. The diseases are characterized by the deposition in extracellular spaces of a proteinaceous material. Amyloid deposits are composed of a felt-like array of 7.5- to 10-nm-wide rigid, linear, nonbranching, aggregated fibrils of indefinite length.[1] One amyloid fibril is made of two twisted 3-nm-wide filaments, each displaying the typical "cross-β" structure,[1] where antiparallel β-sheets are perpendicular to the filament axis.

Amyloid Precursor–Based Classification

Amyloidoses are classified by the type of precursor protein that composes the main component of fibrils[2] (Table 27-2). The amyloidogenic propensity is related to the ability of this precursor to form intermolecular β-sheets. Besides these structural properties, which may relate to genetically transmitted mutations, the amyloidogenic potential is enhanced by overproduction or impaired clearance of the precursor.

Renal amyloidoses mostly include immunoglobulin light-chain (AL) and systemic secondary (AA) amyloidoses. Other precursors, such as transthyretin, fibrinogen, apolipoprotein A-I, and lysozyme, are responsible for rare familial cases.

Other Components of All Amyloid Fibrils

Glycosaminoglycans (GAGs) are tightly associated with amyloid fibrils. GAGs are polysaccharide chains made of repeating hyaluronic acid–hexosamine units normally linked to a protein core, thus forming proteoglycans. Proteoglycans, mostly of the heparan sulfate type, appear to induce and to stabilize the β-pleated amyloid structure.

Another constituent of all amyloid deposits is serum amyloid P component (SAP). SAP is resistant to proteolytic digestion, and coating of amyloid fibrils with SAP could result in their protection from catabolism. The high affinity of SAP toward amyloid was exploited for scintigraphy with [^{123}I]-SAP. CPHPC (R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid) is a proline-derived small compound that specifically binds to SAP and allows rapid decreases in serum SAP levels.[3] The combination of CPHPC with an SAP-antibody targets amyloid deposits and enables their elimination by recruiting phagocytic cells in a mouse model of AA amyloidosis. A clinical trial using CPHPC combined with an anti-SAP antibody is underway.[4]

General Mechanisms of Fibrillogenesis

Amyloidogenesis involves a nucleation-dependent polymerization process. Formation of an ordered nucleus is the initial and thermodynamically limiting step, followed by addition of monomers and elongation of the fibrils.[5] Fibrillogenesis may involve several mechanisms of processing of the amyloid precursor, including partial proteolysis and conformational modifications. Conformational changes lead to a soluble, partially folded intermediate, whose subsequent ordered self-assembly results in fibril formation. Macrophages have a central role in AA amyloidosis by providing the intralysosomal processing of the precursor. In AL amyloidosis, the variable domain of the light chain V_L is the main component, which suggests a role of partial proteolysis of the light-chain precursor.

Pathology

On light microscopy, the deposits are extracellular, eosinophilic, and metachromatic, inducing a change in color of dyes (e.g., crystal violet). After Congo red staining, the deposits appear faintly red (Fig. 27-1, *A*) and show characteristic apple-green birefringence under polarized light (Fig. 27-1, *B*). Metachromasia is also observed with crystal violet, which stains the deposits red.

The earliest lesions are located in the mesangium (Fig. 27-1, *A*), along the glomerular basement membrane (GBM), and in the blood vessels. Mesangial deposits are primarily in the mesangial matrix and spread from lobule to lobule until eventually the whole mesangial area is replaced. Amyloid deposits may also infiltrate the GBM or may be localized on both its sides. When subepithelial deposits predominate, spikes similar to those seen in membranous nephropathy may be observed. Advanced amyloid typically produces a nonproliferative, noninflammatory glomerulopathy and marked enlargement of the kidney. The amyloid deposits replace the normal glomerular architecture, resulting in loss of cellularity. When glomeruli become massively sclerotic, the deposits may be difficult to demonstrate by Congo red staining. In this case, electron microscopy (EM) may be helpful, as well as in the very early stages, which may not be detected by light microscopy examination in patients presenting with the

nephrotic syndrome. Amyloid deposits are characterized by randomly oriented, nonbranching fibrils with an 8- to 15-nm diameter (Fig. 27-2).

Except for fibrinogen amyloidosis, which characteristically does not affect renal vessels, the media of the blood vessels is prominently involved at early stages. Vascular involvement may predominate and occasionally occurs alone, particularly in AL amyloidosis. Deposits may also affect the tubules and the interstitium, leading to atrophy and disappearance of the tubular structures and to interstitial fibrosis.

Given the heterogeneity of amyloidoses, immunohistology should be routinely performed (Fig. 27-1, *C*). Immunohistochemical classification of amyloid type is possible in most cases. Immunohistology with antibodies specific for immunoglobulin chains may be more difficult to interpret than that with anti-AA antiserum, perhaps because of the absence or inaccessibility of light-chain epitopes. Alternative techniques such as immuno-EM[6] and mass spectrometry–based proteomic analysis of deposits after laser microdissection, which are still used only at highly specialized centers, will likely decrease the percentage of nontypeable amyloidosis.[7,8] A genetic cause should be sought by DNA sequencing in all patients with amyloidosis in whom confirmation of the amyloid precursor cannot be obtained by other techniques.[9]

Glomerular Diseases with Tissue Deposition or Precipitation of Monoclonal Immunoglobulin Components

Immunoglobulin Deposits	Glomerular Disease
Organized	
Fibrillar	Amyloidosis (AL, AH)
Microtubular	Cryoglobulinemia; immunotactoid glomerulonephritis
Nonorganized: Granular	
	Monoclonal immunoglobulin deposition disease: light-chain, heavy-chain, and light-plus-heavy-chain deposition diseases Immune complex–like proliferative glomerulonephritis

Table 27-1 Glomerular diseases with tissue deposition or precipitation of monoclonal immunoglobulin components.

Immunoglobulin-Associated Amyloidosis (AL Amyloidosis)

Free immunoglobulin subunits, mostly light chains, secreted by a single clone of B cells, are the cause of the most frequent and severe amyloidosis affecting the kidney. Studies on the mechanisms of AL amyloidogenesis are made particularly difficult by the unique structural heterogeneity of the precursor: each monoclonal light chain is different from all others, so each patient is unique. The involvement of an immunoglobulin heavy chain in amyloidosis (AH and AHL amyloidosis) remains extremely rare, and its diagnosis

Classification of Amyloidoses

Amyloid Protein*	Precursor	Distribution	Type	Syndrome or Main Involved Tissues
AA	Serum amyloid A	Systemic	Acquired	Secondary amyloidosis, reactive to chronic infection or inflammation, including hereditary periodic fever (FMF, TRAPS, HIDS, FCU, and MWS)
AApoAI	Apolipoprotein A-I	Systemic	Hereditary	Liver, kidney, heart, skin, larynx
AApoAII	Apolipoprotein A-II	Systemic	Hereditary	Kidney, liver, adrenal glands, spleen, skin
Aβ	Aβ protein precursor	Localized Localized	Acquired Hereditary	Sporadic Alzheimer disease, aging Prototypic hereditary cerebral amyloid angiopathy, Dutch type
Aβ2M	β2-Microglobulin	Systemic	Acquired	Chronic hemodialysis
ABri	Abri protein precursor	Localized or systemic?	Hereditary	British familial dementia
ACys	Cystatin C	Systemic	Hereditary	Icelandic hereditary cerebral amyloid angiopathy
AFib	Fibrinogen Aα chain	Systemic	Hereditary	Kidney
AGel	Gelsolin	Systemic	Hereditary	Finnish hereditary amyloidosis
AH	Immunoglobulin heavy chain	Systemic or localized	Acquired	Primary amyloidosis, myeloma associated
AL	Immunoglobulin light chain	Systemic or localized	Acquired	Primary amyloidosis, myeloma associated
ALECT2	Leukocyte chemotactic factor 2	Systemic	Acquired?	Kidney, liver, adrenal glands
ALys	Lysozyme	Systemic	Hereditary	Kidney, liver, spleen, adrenal glands
APrP	Prion protein	Localized Localized	Acquired Hereditary	Sporadic (iatrogenic CJD, new variant CJD) (alimentary?) Familial CJD, GSSD, FFI
ATTR	Transthyretin	Systemic	Acquired Hereditary	Senile heart, vessels Prototypical FAP

Table 27-2 Classification of amyloidoses. *Entries in boldface indicate amyloid types with kidney involvement. The following proteins may also cause amyloidosis: calcitonin, islet-amyloid polypeptides, atrial natriuretic factor, prolactin, insulin, lactadherin, keratoepithelin, and Danish amyloid protein (which comes from the same gene as ABri and has an identical N-terminal sequence). *CJD,* Creutzfeldt-Jakob disease; *FAP,* familial amyloidotic polyneuropathy; *FCU,* familial cold urticaria; *FFI,* fatal familial insomnia; *FMF,* familial Mediterranean fever; *GSSD,* Gerstmann-Sträussler-Scheinker disease; *HIDS,* hyper-IgD syndrome; *MWS,* Muckle-Wells syndrome; *TRAPS,* tumor necrosis factor receptor–associated periodic syndrome. *(Modified from reference 2.)*

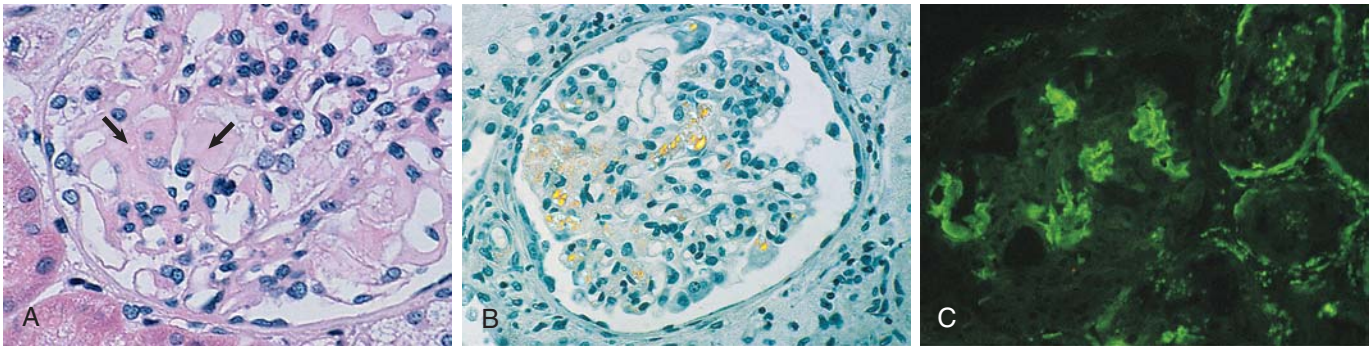

Figure 27-1 Amyloidosis. A, Amyloid deposits *(arrows)* in a glomerulus. (Hematoxylin-eosin [HE] stain; magnification ×312.) **B,** Congo red staining. Apple-green birefringence under polarized light. (×312.) **C,** Immunofluorescence with anti-κ antibody. Note glomerular and tubular deposits. (×312.) *(Courtesy Dr. Béatrice Mougenot, Paris.)*

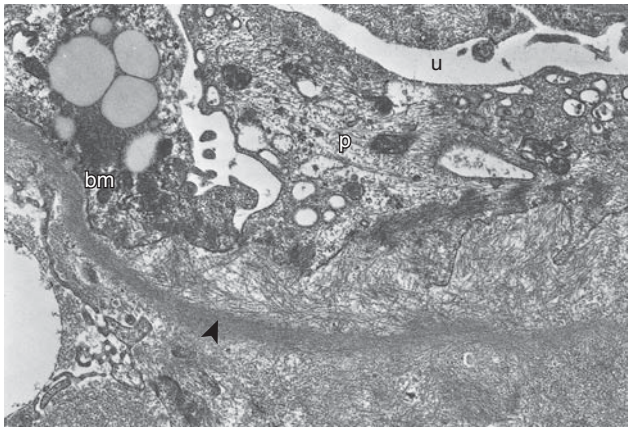

Figure 27-2 Electron micrograph of amyloid deposits invading glomerular basement membrane. Randomly oriented fibrils are located on both sides of the basement membrane *(bm),* and the lamina densa is attenuated *(arrowhead); p,* podocyte; *u,* urinary space. (×10,000.) *(Courtesy Dr. Béatrice Mougenot, Paris.)*

is greatly enhanced by the use of laser microdissection and mass spectrometry.[10]

Pathogenesis

Determinant factors are borne by the precursor light chain. In AL amyloidosis, or primary amyloidosis, there is a striking overrepresentation of the lambda (λ) isotype, which is twofold to fourfold more common than the kappa (κ) isotype. A rarely expressed homology family of light-chain variable regions, the $V_{\lambda VI}$ variability subgroup, is found only in amyloid-associated monoclonal immunoglobulins.

Amyloidogenicity is associated with physicochemical features that include low-molecular-mass light-chain fragments in the urine, abnormal disulfide bonding of light chains, and low isoelectric point (pI). An analysis of almost 200 light-chain sequences identified 12 positions in κ chains and 12 in λ chains where certain residues were associated with amyloidosis. Four structural risk factors were shown to define most fibril-forming κ light chains.[11] Because of their high dimerization constants, light chains from patients with AL amyloidosis may behave as antibodies with affinity for extracellular structures that could favor a nucleation process.

The tropism of organ involvement may be influenced both by the germ-line gene used for the light-chain variable region (V_L) and by somatic mutations occurring in the secreting clone.[12] Patients expressing a monoclonal light chain of the $V_{\lambda VI}$ subgroup are more likely to present with dominant renal involvement and less frequent cardiac and multisystem disease.[13] Patients with κ light chains are more likely to have dominant hepatic involvement. In addition, organ-specific environmental factors are also involved. For example, high intrarenal concentrations of urea enhance fibril formation by reducing the nucleation lag time.

Amyloid light chains may contribute directly to the pathogenesis, independent of extracellular fibril deposition. In the heart and the kidney at least, the infiltration alone does not correlate well with clinical manifestations. Light chains from amyloid patients incubated with mesangial cells induce a macrophage-like phenotype, whereas those from light-chain deposition disease patients induce a myofibroblast-like phenotype.[14]

Epidemiology

The incidence of AL amyloidosis is nine per 1 million population per year. Fewer than one in four patients with AL amyloidosis is considered to have an overt immunoproliferative disease, which usually is multiple myeloma, although other forms are seen, such as Waldenström macroglobulinemia. Amyloid deposits are found in approximately 10% of all patients with myeloma and in 20% of those with pure light-chain myeloma. The apparent prevalence of myeloma depends on the diagnostic criteria used. Epidemiologic characteristics of *primary* amyloidosis, that is, amyloidosis without overt immunoproliferative disease, and myeloma are not significantly different. The median age at diagnosis is 64 years in patients with primary amyloidosis, with a slight predominance of male patients, and about 10% of patients are less than 50 years old.[15]

Clinical Manifestations

The main clinical symptoms at presentation are weakness and weight loss (Table 27-3). Except for bone pain, the initial symptoms in patients with and without myeloma are similar. However, nephrotic syndrome, orthostatic hypotension, and peripheral neuropathy are more frequent in patients with AL amyloidosis without myeloma.[16] Amyloidosis is also different from many types of kidney disease in that the kidneys are often enlarged and hypertension is absent even when renal function is impaired. Proteinuria, mainly albuminuria, occurs in the absence of microhematuria. Indeed, the presence of hematuria should prompt examination for a bleeding lesion in the urinary tract. Renal manifestations may also include renal tubular acidosis (mostly as a part of Fanconi syndrome; see Chapter 50) and polyuria-polydipsia (resulting from urinary concentration defect), when amyloid deposits occur around proximal tubules and Henle loops (or collecting ducts), respectively.

AL amyloidosis may infiltrate almost any organ other than the brain and therefore can be responsible for a wide variety of clinical manifestations. Restrictive cardiomyopathy is found at presentation

Clinical Presentation in 474 Patients with Proven AL Amyloidosis	
Features	**Percentage**
Initial Symptoms	
Fatigue	62
Weight loss	52
Pain	5
Purpura	15
Gross bleeding	3
Physical Findings	
Hepatomegaly	24
Palpable spleen	5
Lymphadenopathy	3
Macroglossia	9
Laboratory Findings	
Increased plasma cells (bone marrow >6%)	56*
Anemia (hemoglobin <10 g/dl)	11
Elevated serum creatinine (1.3 mg/dl) (>113 μmol/l)	45
Elevated alkaline phosphatase	26
Hypercalcemia (>11 mg/dl) (>2.75 mmol/l)	2
Proteinuria (>1.0 g/24 h)	55
Urine light chain κ chain λ chain	73† 23 50

Table 27-3 Clinical and laboratory features at presentation in 474 patients with proven light-chain (AL) amyloidosis. *15% of patients having a myeloma. †Of 429 patients. *(From reference 15.)*

Figure 27-3 Macroglossia in patient with AL amyloidosis. *(Courtesy Dr. S. Aractingi, Paris.)*

Figure 27-4 Skin involvement in AL amyloidosis. Noninfiltrated purpuric macule of the superior eyebrow, typical of AL amyloidosis. *(Courtesy Dr. S. Aractinji, Paris.)*

in up to one third of patients and causes death in about one half. Infiltration of the ventricular walls and the septum may be recognized by echocardiography. Amyloid may also induce arrhythmias and the sick sinus syndrome. Amyloid deposits in the coronary arteries may result in angina and myocardial infarction. Cardiac troponins and N-terminal pro–brain natriuretic peptide (NT-proBNP) are sensitive markers of myocardial dysfunction and powerful predictors of overall survival in patients with AL amyloidosis.

Involvement of the gastrointestinal (GI) tract is common and can cause motility disturbances, malabsorption, hemorrhage, or obstruction. Macroglossia may interfere with eating and obstruct airways (Fig. 27-3). Abnormalities of hepatic function are usually mild. Hyposplenism, diagnosed by abnormal peripheral smear and liver spleen scan and often associated with splenomegaly, predisposes to fatal bacterial infections. Peripheral nerve involvement may result in a painful sensory polyneuropathy, followed later by motor deficits. Autonomic neuropathy causing orthostatic hypotension, lack of sweating, GI disturbances, bladder dysfunction, and impotence may occur alone or together with peripheral neuropathy. Orthostatic hypotension is one of the major hampering complications of AL amyloidosis, with some patients being bedridden. Skin involvement may take the form of purpura, characteristically around the eyes (Fig. 27-4), and ecchymoses, papules, nodules, and plaques, occurring usually on the face and upper trunk. AL amyloidosis may also infiltrate articular structures and mimic rheumatoid or an asymmetric seronegative synovitis. Infiltration of the shoulders may produce severe pain and swelling (shoulder pad sign).

A rare but potentially serious manifestation of AL amyloidosis is an acquired bleeding diathesis that may be associated with deficiency of factor X or factor IX or with increased fibrinolysis. It should be systematically sought before any biopsy of a deep organ. Widespread vascular deposits may also be responsible for bleeding. Prothrombin time and activated partial thromboplastin time measurements as well as determination of bleeding times are required to assess bleeding diathesis.

Monoclonal light chains can be detected by immunoelectrophoresis in 73% of the urine samples of patients with AL amyloidosis. The λ isotype is twice as frequent as the κ, contrasting with the 1:2 ratio of λ to κ observed in myeloma alone. With the use of more sensitive immunochemical techniques, a monoclonal immunoglobulin is found in the serum or the urine in almost 90% of patients. Immunochemical techniques combined with serum free light-chain (FLC) assays detect an abnormal result in 99% of patients.[17]

AL amyloidosis associated with IgM paraproteinemia characterizes a distinctive subset of patients who have a wider variety of underlying, often lymphoid clonal disorders (including 75% Waldenström macroglobulinemia), usually low-level FLC with a predominance of κ isotype, and higher prevalence of lymph node (31% vs. 3%) and lung (17% vs. 2%) involvement compared with patients with non-IgM monoclonal component.[18,19]

Diagnosis

AL amyloidosis should be considered in any patient who presents with nephrotic-range proteinuria with or without renal impairment,

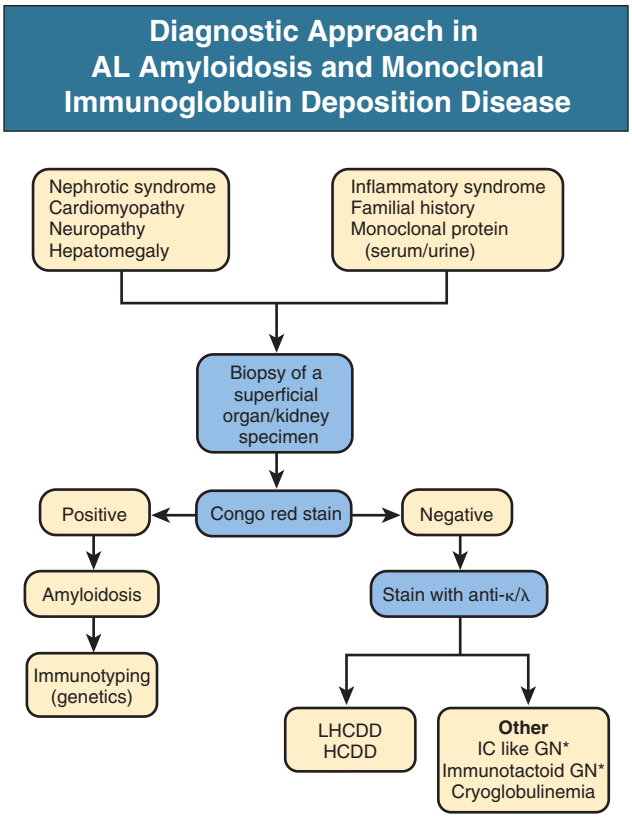

Figure 27-5 Algorithm of diagnostic procedures in light-chain (AL) amyloidosis and monoclonal immunoglobulin deposition disease (MIDD). *No extrarenal manifestation. *GN,* Glomerulonephritis; *IC,* immune complex; *HCDD,* heavy-chain deposition disease; *LHCDD,* light- and heavy-chain deposition disease.

nondilated cardiomyopathy, peripheral neuropathy, hepatomegaly, or autonomic neuropathy, whether or not a paraprotein can be detected in the serum or urine (Fig. 27-5). Particular vigilance should be maintained in patients with multiple myeloma or monoclonal gammopathy of undetermined significance (MGUS), especially of the λ isotype. Initial investigation should confirm the diagnosis of amyloidosis on tissue biopsy, followed by investigations to establish the type of amyloid present and the extent of organ involvement.

All patients require immunofixation of serum and urine (including serum-free light chains) in an attempt to demonstrate the presence of a monoclonal light chain and quantitation of serum FLC. A bone marrow specimen is necessary because 10% of patients will not have a demonstrable monoclonal light chain by immunofixation, and a clone of plasma cells detected in the bone marrow by immunohistochemistry is strong evidence of AL amyloidosis.

Biopsy of an affected organ is usually diagnostic, but less invasive alternatives should be preferred first. Biopsies of salivary glands or of subcutaneous abdominal fat yield positive results in 80% to 90% of cases. Rectal biopsy is diagnostic in more than 80%, provided the biopsy specimen contains submucosal vessels in which early deposits are located. Bone marrow biopsy specimens should be stained with Congo red for the presence of amyloid, and involvement of the bone marrow (observed in about 50% of patients) is strongly suggestive of the AL type. Evaluation of adequate specimens in experienced laboratories is necessary to maintain high diagnostic sensitivity and specificity.

It is not always easy to be certain that amyloidosis is of the AL type because immunohistochemical staining for immunoglobulin light chains may not be diagnostic, and the presence of a monoclonal component is strong but not conclusive evidence of the AL type. Caution is required when patients have an intact monoclonal immunoglobulin in the serum without evidence of FLC in the serum and urine. In those cases, hereditary forms of amyloidosis should be considered because they may produce clinical syndromes indistinguishable from AL and may coexist with MGUS.[9] In cases of doubt, DNA analysis and amyloid fibril sequencing by mass spectrometry are necessary.

Treatment and Outcome

AL amyloidosis is among the most severe complications of plasma cell proliferative disorders. Cardiac involvement responsible for congestive heart failure (CHF) and arrhythmias accounts for at least 40% of deaths. Therapy is aimed at annihilation of the plasma cell clone: "partial response" is now defined by a 50% or greater reduction in the difference between involved FLC (secreted by the plasma cell clone) and uninvolved FLC (the other isotype; dFLC), "very good partial response" by dFLC less than 40 mg/L, and "complete response" by the absence of detectable monoclonal immunoglobulin with normal serum FLC and κ/λ ratio.[20] In the responders, gradual regression of AL amyloid deposits is possible. Clinical improvement does not parallel regression of amyloid load.[21] Scintigraphy after injection of [^{123}I]-SAP component may be helpful for monitoring the extent of systemic amyloidosis, but this technique is available in a few centers only.

Only 15 years ago, overall survival in patients with AL amyloidosis was poor under a combination of melphalan plus prednisone (MP), compared with no treatment or colchicine therapy alone.[22,23] The prognosis of the disease has been transformed with the development of new strategies derived from myeloma treatment. High-dose melphalan followed by autologous stem cell transplantation (HDM/SCT) was introduced,[24] but treatment-related mortality (TRM) was consistently higher than in similarly treated patients with multiple myeloma: TRM was 11% for all patients over 15 years, and 5% in the last 5 years, but with improved patient selection and experienced management.[25] Despite its efficacy, HDM/SCT in AL amyloidosis generally remains restricted to those less than 65 years old, with up to two organs involved and without cardiac amyloidosis. Its place as first-line therapy in systemic AL amyloidosis is questionable.

High-dose dexamethasone-based regimens offer efficacy close to that of HDM/SCT but with much lower TRM.[26,27] M-Dex consists of oral melphalan (10 mg/m^2/day) and dexamethasone (40 mg/day) in 4-day cycles each month. The M-Dex combination is more rapidly effective than MP and may be used even in patients with advanced disease.[26] In a randomized prospective trial, M-Dex achieved similar hematologic and organ responses as HDM/SCT, but the 100-day mortality rate was higher in the HDM/SCT group.[27] In an intention-to-treat analysis, median survival was 57 months in the M-Dex group compared with 22 months in the HDM/SCT group after a median follow-up of 3 years. Problems of the trial included that (1) only 37 of the patients who were randomly assigned to HDM/SCT actually underwent the treatment and (2) TRM in the HDM group (24%) was higher than that reported in single-center studies from amyloidosis referral centers (4% to 14%). The high mortality was likely the result of enrollment of patients who had severe organ dysfunction and would not be eligible for HDM/SCT at many referral centers. A subset analysis of patients with low risk for an adverse outcome of intensive treatment also showed similar survival at 3 years of 80% in the M-Dex group versus 58% in the HDM/SCT group. Furthermore, patients who survived for at least 6 months after randomization and who received their assigned treatment had similar (20% to 30%) mortality.

On the basis of these findings, the following recommendations are proposed: (1) patients with severe organ dysfunction should receive M-Dex as first-line treatment, and (2) patients with less severe disease are eligible for M-Dex or HDM/SCT (still considered the reference treatment in U.S. centers). Patients should be carefully monitored by assessment of FLC, as well as of high-sensitivity cardiac troponin T and serum NT-proBNP levels in case of cardiac involvement. In those who do not show hematologic and NT-proBNP response after 3 to 6 months, treatment should be changed to alternatives, such as regimens based on thalidomide, lenalidomide, or the proteasome inhibitor bortezomib. These novel agents combined with dexamethasone induce rapid hematologic responses in most patients, even in those with refractory or relapsing disease. Bortezomib results in clonal response rates of 70% to 90% of patients, including about 40% complete remission (combined M-Dex plus bortezomib is currently being compared with M-Dex in an international randomized trial). Bortezomib may also be combined with cyclophosphamide and dexamethasone, with good tolerance and impressive response rates. Bortezomib should be used with caution in patients with advanced amyloid heart disease.

Dialysis and Transplantation

Most studies of the clinical course and outcome of dialysis patients include both AL and AA amyloidosis. Patient survival is about 70% at 1 year and decreases to 30% to 44% at 5 to 6 years. Median survival is shorter in patients with AL amyloidosis (26 to 39 months) than with AA amyloidosis; sepsis and cardiac deaths are the main causes of mortality.[28,29]

Cardiac amyloid is the most important predictor of mortality in dialysis patients with AL amyloidosis.[29,30] The management of patients with AL amyloid on hemodialysis (HD) is often complicated by persistent hypotension, GI hemorrhage, chronic diarrhea, and difficulties in the creation and maintenance of vascular access. Peritoneal dialysis (PD) could have several advantages over HD in the management of end-stage renal amyloidosis, including avoidance of vascular access and deleterious effects on blood pressure, although PD may induce protein loss in the dialysate and thus aggravate malnutrition. However, survival of AL and AA amyloidosis patients treated with PD is similar to that of patients receiving HD.

Kidney transplantation is limited by the severity of heart involvement and the recurrence of deposits in the transplanted kidney. It may be offered to select patients who have achieved persistent hematologic remission, at least for 1 year.[31] When solid-organ transplantation is considered (heart, liver, kidney), it should be preceded or followed by chemotherapy to avoid systemic progression and amyloid recurrence on the transplanted organ.[32,33] Patient survival was 9 years in those who had achieved at least a partial clonal response after kidney transplantation, versus 5 years in those who had no response.[34]

Secondary-Associated Amyloidosis (AA Amyloidosis)

Epidemiology

AA amyloidosis, or secondary amyloidosis, develops in 5% of patients with sustained elevation of serum amyloid A protein (SAA). Patients at risk are those with a long duration of chronic inflammatory disease (median 17 years),[35] high magnitude of acute-phase SAA response, homozygosity for SAA1 genotype, familial Mediterranean fever trait (heterozygosity for variant pyrin), and family history of AA amyloidosis.

An important epidemiologic aspect of AA amyloidosis is the changing spectrum of underlying disease. Pyogenic and granulomatous infections, especially tuberculosis, account for far fewer cases at present (15%) than previously.[35] In these patients, antibiotic treatment efficiently prevents AA amyloidosis by suppressing its cause. In contrast, the prevalence of chronic inflammatory arthritis has increased dramatically (60%).[35] However, it may be expected that effective disease-modifying treatments, including anti–tumor necrosis factor α (TNF-α) and rituximab, will induce a decline in the incidence of AA amyloidosis complicating rheumatoid arthritis, similar to AA amyloidosis in patients with Hodgkin disease, which has virtually disappeared with more efficient treatment of the hematologic disease. AA amyloidosis can be observed in a variety of other conditions, such as inflammatory bowel disease, non-ANCA systemic vasculitis, neoplasia, and immunodeficiency states. Hereditary AA amyloidoses associated with familial recurrent fever syndromes account for an increasing proportion of cases, about 10% in recent series.

Clinical Manifestations

Table 27-4 provides clinical features of AA amyloidosis.[35] The main target organ is the kidney, which is affected in almost all patients with AA amyloidosis. Presentation may be acute with nephrotic syndrome or very insidious. Proteinuria is absent in about 5% of cases. GI disturbances (e.g., diarrhea, constipation, malabsorption) and hepatosplenomegaly are the next most common manifestations. In contrast to AL amyloidosis, CHF, peripheral neuropathy, macroglossia, and carpal tunnel syndrome occur infrequently.

Diagnosis

Because half of patients in whom amyloid was found on renal tissue at autopsy had been reported to have proteinuria before death, some

Characteristics at Presentation of 374 Patients with Systemic AA Amyloidosis

Age, yr (range)	50 (9-87)
Male gender, no. (%)	210 (56)
Race or Ethnic Group, no. (%)	
White	307 (82)
South Asian	27 (7)
Other	40 (11)
Duration of Inflammatory Disease at Diagnosis (yr)	
Median	17
Range	0-68
Renal Dysfunction	
Proteinuria >500 mg/day or serum creatinine >133 µmol/l, no. (%)	363 (97%)
End-stage renal disease, no. (%)	41 (11%)
Proteinuria, g/day median (range)	3.9 (0-26.0)
Liver Involvement	
Hepatomegaly, no. (%)	35 (9%)
Deposits on SAP scintigraphy, no. (%)	85 (23%)
Splenic Involvement	
Deposits on SAP scintigraphy, no. (%)	370 (99%)
Cardiac Involvement	
Cardiac failure, no.	1
Cardiac infiltration, no.	2

Table 27-4 Characteristics at presentation of 374 patients with systemic secondary (AA) amyloidosis. *SAP,* Serum amyloid P component. *(From reference 35.)*

recommend a systematic search for amyloidosis in patients with active, long-lasting inflammatory arthritis, even in the absence of proteinuria and chronic kidney disease (CKD). The identification of even asymptomatic amyloid deposits should prompt more effective control of inflammation. Although findings on kidney biopsy are positive in almost 100% of symptomatic patients, less invasive biopsy procedures should be attempted first. Biopsies of accessory salivary glands and abdominal fat yield positive results in more than 80% of patients. Immunohistochemical staining using antibodies to SAA is required to confirm that Congo red–positive amyloid deposits are of the AA type. SAP scintigraphy shows that bones are not affected (unlike AL amyloidosis).

Natural History and Treatment

Survival time of patients with AA amyloidosis is 133 months, much longer than with AL amyloidosis.[35] Main causes of death are infections and dialysis-related complications but not cardiac complications. Amyloid load and clinical outcome relate to circulating concentrations of SAA. The relative risk of death among patients with an SAA concentration below 4 mg/l is almost 18 times lower than among patients with an SAA concentration of 155 mg/l or greater. Even a very modest elevation in the SAA concentration of 4 to 9 mg/l is associated with a risk of death increased by a factor of 4. These data emphasize the importance of vigorous treatment of the underlying inflammatory disease. SAA (preferable to C-reactive protein) levels should be monitored monthly and maintained at a target value of less than 4 mg/l.[35]

Amyloid deposits regress in 60% of patients who have a median SAA concentration below 10 mg/l, and survival in these patients is superior to survival when amyloid deposits do not regress. Other factors associated with increased mortality are older age and end-stage renal disease (ESRD).

Eprodisate, a member of a newer class of compounds interfering with interactions between amyloidogenic proteins and GAGs, thus inhibiting polymerization of amyloid fibrils, slowed decline of renal function in patients with AA amyloidosis.[36] However, eprodisate had no beneficial effect on proteinuria, ESRD, amyloid content of abdominal fat, or mortality risk. The combination of CPHPC and SAP antibody is currently under evaluation (see previous discussion). Emphasis should remain on treatment of the underlying inflammatory disorder.

Most described patients receiving renal transplantation in AA amyloidosis are those with rheumatic diseases. Amyloid deposits recur in about 10% of the grafts. Infections and cardiovascular events are the main cause of early death and require careful management.[37]

Familial Mediterranean Fever and Other Hereditary Recurrent Fever Syndromes

Familial Mediterranean fever (FMF) represents a particular type of AA amyloidosis and is the most frequent cause of familial amyloidosis. Colchicine has proved to be efficient in its prevention and treatment. FMF is usually transmitted as an autosomal recessive disorder and occurs most often in Sephardic Jews and Armenians. It is caused by mutations of the gene *(MEFV)* encoding a protein called pyrin, or marenostrin.[38] Clinically, there are two independent phenotypes. In the first, brief, episodic, febrile attacks of peritonitis, pleuritis, or synovitis occur in childhood or adolescence and precede the renal manifestations. In the second phenotype, renal symptoms precede and may long be the only manifestation of the disease. The attacks are accompanied by dramatic elevations of acute-phase reactants, including SAA. Amyloid deposits are responsible for severe renal lesions with prominent glomerular involvement, leading to ESRD at a young age, and for early death. Colchicine can prevent the development of proteinuria, may occasionally reverse the nephrotic syndrome, and may prevent the glomerular filtration rate (GFR) decline in patients with non-nephrotic proteinuria. It is less effective in preventing progression in patients with nephrotic syndrome or renal impairment. The minimum daily dose of colchicine for prevention of amyloidosis is 1 mg, and patients with clinical evidence of amyloidotic kidney disease should receive daily doses of 1.5 to 2 mg. However, about 10% of patients are unresponsive to colchicine. Interleukin-1 receptor (IL-1R) antagonists are second-line agents. In patients with intolerance of colchicine, the drug should be stopped, then reintroduced at lower doses.

The recent identification of genes responsible for syndromes of periodic fever with amyloidosis has led to a molecular diagnosis of hereditary AA amyloidosis. These syndromes include the TNF receptor–associated periodic syndrome, the Muckle-Wells syndrome, and the familial cold autoinflammatory syndrome. Only a few cases of systemic AA amyloidosis have been reported in the hyperimmunoglobulinemia D with periodic fever syndrome. Most of these conditions can be controlled by means of anti–IL-1 or anti-TNF agents.[39]

MONOCLONAL IMMUNOGLOBULIN DEPOSITION DISEASE

History and Definition

It was known from the late 1950s that nonamyloidotic forms of glomerular disease "resembling the lesion of diabetic glomerulosclerosis" could occur in multiple myeloma. Subsequently, monoclonal light chains were detected in these lesions.[40]

In clinical and pathologic terms, light-chain, light- and heavy-chain, and heavy-chain deposition disease (LCDD, LHCDD, and HCDD, respectively) are similar and may therefore be referred to as monoclonal immunoglobulin deposition disease (MIDD). These forms differ from amyloidosis in that the deposits lack affinity for Congo red and do not have a fibrillar organization. The distinction also relates to different pathophysiology of amyloid, which implicates one-dimensional elongation of a pseudocrystalline structure, and MIDD, which rather involves a one-step precipitation of immunoglobulin chains.

Epidemiology

Light-chain deposition disease is found in 5% of myeloma patients at autopsy, whereas the prevalence of AL amyloidosis is about 11%. LCDD and HCDD may occur in a wide range of ages (28 to 94), with a male preponderance (Table 27-5). More than 20 patients with HCDD have been described so far, but the disease is most likely underdiagnosed.

Pathogenesis

Light-chain deposition may require light chains with distinct properties that favor deposition in tissues. Various properties of light-chain variable domains may contribute to MIDD pathogenesis[41]:

- Restricted use of three κ germ-line genes, with an apparent overrepresentation of the rare $V_{\kappa IV}$ variability subgroup.
- Size abnormalities of light chains, present in one third of patients.
- Unusual amino acid substitutions in LCDD light chains may modify the light-chain conformation or be responsible for hydrophobic interactions between V domains or between V domains and extracellular matrix proteins.

Clinical Features in Patients with MIDD		
Characteristics	**LCDD/LHCDD**	**HCDD**
Male-to-female ratio	1.5	0.7
Age, yr (range)	57 (28-94)	56 (26-79)
Hypertension (%)	53	90
Renal failure (serum creatinine ≥130 µmol/l) (1.47 mg/dl) (%)	93	85
Nephrotic syndrome* (%)	35	50
Hematuria (%)	45	88
Nodular glomerulosclerosis (%)	31-100	96
Multiple myeloma (%)	52	22
Monoclonal protein (blood or urine) (%)	84	56†

Table 27-5 Clinical, histologic, and laboratory features in patients with monoclonal immunoglobulin deposition disease (MIDD). *Proteinuria ≥3 g/day. †Including two cases with only free κ chain. *LCDD,* Light-chain deposition disease; *LHCDD,* light- and heavy-chain deposition disease; *HCDD,* heavy-chain deposition disease. *(From reference 66.)*

- When pathogenic light chains were undetected in serum and urine, they were found to be *N*-glycosylated, suggesting that glycosylation increases their propensity to precipitate in tissues. However, as in AL amyloidosis, extrinsic conditions may also contribute to aggregation of the light chain. The same light chain can form granular aggregates or amyloid fibrils, depending on the environment, and different, partially folded intermediates of the light chain may be responsible for amorphous or fibrillar aggregation pathways.[42]

Heavy-chain deposition disease may also be associated with unique heavy chains. A deletion of the first constant domain C_H1 was found in deposited or circulating heavy chains in patients with γ-HCDD.[41,43] In the blood, the deleted heavy chain either was associated with light chains or circulated in small amounts as a free unassembled subunit.[44] It is likely that the C_H1 deletion facilitates the secretion of free heavy chains that are rapidly cleared from the circulation by organ deposition. The variable V_H domain also is probably required for tissue precipitation.

A striking feature of LCDD and HCDD is extracellular matrix accumulation. Nodules are made of normal matrix constituents. In cultured mesangial cells, LCDD light chains enhance the production of tenascin-C and of profibrotic cytokines, such as transforming growth factor β and platelet-derived growth factor.[45]

Clinical Manifestations

A systemic disease with immunoglobulin chain deposition in a variety of organs, MIDD leads to various clinical manifestations, but visceral immunoglobulin chain deposits may be totally asymptomatic and found only at autopsy.[41]

Renal Manifestations

Renal involvement is a constant feature of MIDD, and renal symptoms, mostly proteinuria and CKD, often dominate the clinical presentation[41,46,47] (Table 27-5). In 18% to 53% of LCDD patients, albuminuria is associated with the nephrotic syndrome. In about one fourth, however, albuminuria is less than 1 g/day, and these patients exhibit mainly a tubulointerstitial syndrome. Albuminuria is not correlated with the presence of nodular glomerulosclerosis, at least initially, and may occur in the absence of significant glomerular lesions on light microscopy. Hematuria is more common, especially in HCDD, than would be expected for a nephropathy in which cell proliferation is usually modest.

The high prevalence, early appearance, and severity of CKD are other salient features of LCDD. In most cases, GFR declines rapidly, which is a main reason for referral. CKD occurs with comparable frequency in patients with either low or high protein excretion and may present in the form of subacute tubulointerstitial nephritis or rapidly progressive glomerulonephritis (RPGN), respectively. The prevalence of hypertension is variable, but it must be interpreted according to associated medical history. Renal features of patients with HCDD are basically similar to those seen in LCDD and LHCDD, with a higher prevalence of hypertension and hematuria; extrarenal manifestations occur less often (Table 27-5).

Extrarenal Manifestations

Liver and cardiac involvement occurs in about 25% of patients with LCDD and LHCDD. Liver deposits are constant. They are either discrete and confined to the sinusoids and basement membranes of biliary ductules without associated parenchymal lesions or massive with marked dilation and multiple ruptures of sinusoids, resembling peliosis. Hepatomegaly with mild alterations of liver function test results is the most common symptom, but patients may also develop life-threatening hepatic insufficiency and portal hypertension.

Cardiac involvement is also frequent in LCDD and may be responsible for cardiomegaly and severe heart failure. Arrhythmias, conduction disturbances, and CHF are seen. Echocardiography and catheterization may reveal diastolic dysfunction and reduction in myocardial compliance similar to that found in cardiac amyloidosis.

Deposits may also occur along the nerve fibers and in the choroid plexus as well as in the lymph nodes, bone marrow, spleen, pancreas, thyroid gland, submandibular glands, adrenal glands, GI tract, abdominal vessels, lungs, and skin. They may be responsible for peripheral neuropathy (20% of the reported cases), GI disturbances, pulmonary nodules, amyloid-like arthropathy, and sicca syndrome. Extrarenal deposits are less common in patients with HCDD.

Hematologic Findings

Myeloma is diagnosed in about 50% of the patients with LCDD or LHCDD and in about 25% of those with HCDD. MIDD, as with AL amyloidosis, is often the presenting disease that leads to the discovery of myeloma at an early stage. MIDD may occasionally complicate Waldenström macroglobulinemia, chronic lymphocytic leukemia (CLL), and nodal marginal zone lymphoma. MIDD often occurs in the absence of a detectable malignant process, even after prolonged (>10 years) follow-up. A monoclonal bone marrow plasma cell population is then easily detectable on immunohistology.

Pathology

Light Microscopy

Because MIDD is not only a glomerular disease, tubular lesions may be more conspicuous than the glomerular damage. Tubular lesions are characterized by the deposition of a refractile, eosinophilic, periodic acid–Schiff (PAS)–positive, ribbon-like material along the outer part of the tubular basement membranes. The deposits predominate around the distal tubules, the loops of Henle, and, in some instances, the collecting ducts, whose epithelium is flattened and atrophied. Typical myeloma casts are only occasionally seen in pure forms of MIDD. In advanced stages, a marked interstitial fibrosis including refractile deposits is frequently associated with tubular lesions.

Glomerular lesions are heterogeneous. Nodular glomerulosclerosis is the most characteristic and is found in 30% to 100% of patients

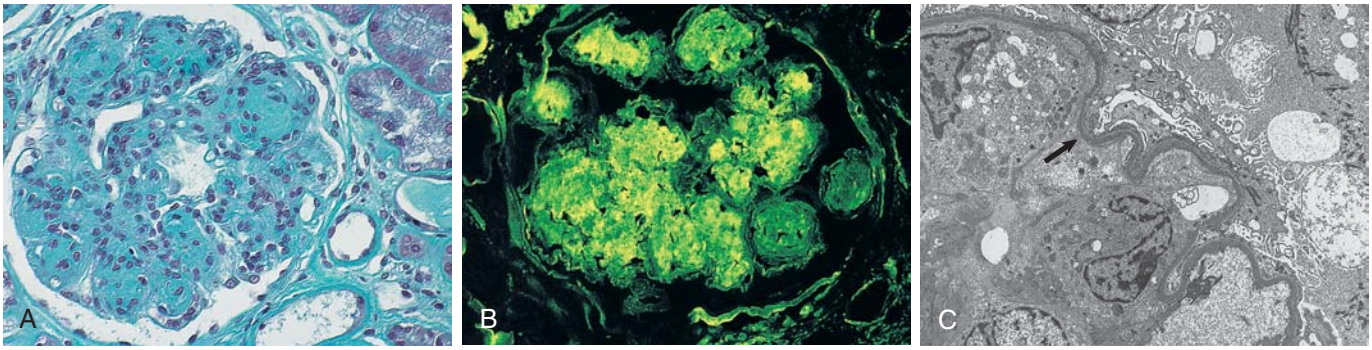

Figure 27-6 Light-chain deposition disease. A, Nodular glomerulosclerosis with mesangial matrix accumulation. (Masson trichrome stain; ×312.) **B,** Staining of mesangial nodules and tubular basement membranes with anti-κ antibody. (Immunofluorescence; ×312.) **C,** Electron micrograph showing a layer of dense granular deposits *(arrow)* under the endothelium along the glomerular basement membrane. (×2500.) *(Courtesy Dr. Béatrice Mougenot, Paris.)*

with LCDD (Fig. 27-6, *A*). Expansion of the mesangial matrix with nodular glomerulosclerosis characterizes HCDD. Mesangial nodules are composed of PAS-positive, membrane-like material and are often accompanied by mild mesangial hypercellularity. Lesions resemble diabetic nodular glomerulosclerosis, with distinctive characteristics: the distribution of the nodules is fairly regular in a given glomerulus; the nodules are often poorly argyrophilic; and exudative lesions (e.g., fibrin caps and extensive hyalinosis of efferent arterioles) are not observed. In occasional cases with prominent endocapillary cellularity and mesangial interposition, the glomerular features mimic membranoproliferative glomerulonephritis (MPGN). Crescents are very uncommon except in α-HCDD.[48] Milder forms of LCDD show increased mesangial matrix or cells and a modest GBM thickening, with abnormal brightness and rigidity. Glomerular lesions may be detectable only by immunostaining or ultrastructural examination in early stages, or if they are induced by light chains with weak pathogenic potential.

Arteries, arterioles, and peritubular capillaries all may contain PAS-positive deposits in close contact with their GBM. Deposits do not show the staining characteristics of amyloid, but Congo red–positive amyloid deposits co-occur in approximately 10% of patients.[47]

Immunohistology

Immunohistology is central in the diagnosis of the various forms of MIDD. A criterion required for the diagnosis of MIDD is monotypic light-chain (mainly κ; Fig. 27-6, *B*) or heavy-chain fixation along tubular basement membranes. The tubular deposits stain strongly and predominate along the loops of Henle and the distal tubules, but also often are detected along the proximal tubules. In contrast, glomerular immunohistology patterns display marked heterogeneity. In patients with nodular glomerulosclerosis, deposits of monotypic immunoglobulin chains are usually found along the peripheral GBM and to a lesser extent in the nodules themselves (Fig. 27-6, *B*). Glomerular staining is typically weaker than that observed along the tubular basement membranes. This may not relate to the actual amount of deposited material because glomerular immunohistology may be negative despite prominent granular glomerular deposits observed by EM. Local modifications of deposited light chains thus might change their antigenicity. In patients without nodular lesions, glomerular staining occurs along the GBM and less frequently in the mesangium. A linear staining usually decorates Bowman capsule. Deposits are common in vascular walls and interstitium.

In patients with HCDD, immunohistology with anti–light-chain antibodies is negative despite typical nodular glomerulosclerosis. Monotypic deposits of γ, α, or μ heavy chains may be identified. Any γ subclass may be observed. Analysis of the kidney biopsy specimen with monoclonal antibodies specific for the constant domains of the γ heavy chain allowed identification of a deletion of the C_H1 domain in all tested cases. In most cases of HCDD, especially when a γ1 or γ3 chain is involved, complement components including C1 could be demonstrated in a granular or pseudolinear pattern. Complement deposits were often associated with signs of complement activation in serum.[49]

Recently, eculizumab treatment in dense deposit disease was shown to induce an HCDD-like pathology.[50]

Electron Microscopy

The most characteristic ultrastructural features on EM are finely to coarsely granular electron-dense deposits along the outer (interstitial) aspect of the tubular basement membranes. In the glomerulus, the deposits predominate in a subendothelial position along the GBM and are located mainly along and in the lamina rara interna (Fig. 27-6, *C*). Deposits can also be found in mesangial nodules, Bowman capsule, and the wall of small arteries between the myocytes. Nonamyloid fibrils have been reported in a few patients with LCDD or HCDD.

Diagnosis

The diagnosis of MIDD must be suspected in any patient with the nephrotic syndrome or rapidly progressive tubulointerstitial nephritis or with echocardiographic findings indicating diastolic dysfunction and the presence of a monoclonal immunoglobulin component in the serum or the urine (see Fig 27-5). The same combination is also seen in AL amyloidosis, but AL amyloidosis is more often associated with the λ light-chain isotype. Sensitive techniques such as urine immunofixation fail to identify a monoclonal immunoglobulin component in 10% to 20% of patients with LCDD or LHCDD and about 40% of those with HCDD (see Table 27-5), although the serum FLC ratio is consistently abnormal.[46] The kidney biopsy thus plays an essential role in the diagnosis of MIDD and of the associated dysproteinemia.

The definitive diagnosis is made by the immunohistologic analysis of tissue from an affected organ, in most cases the kidney, with use of a panel of immunoglobulin chain–specific antibodies, including anti-κ and anti-λ light-chain antibodies to stain the noncongophilic deposits. When the biopsy specimen stains for a single heavy-chain isotype and does not stain for light-chain isotypes, the diagnosis of HCDD should be suspected.

The diagnosis of the plasma cell dyscrasia relies on bone marrow aspiration and bone marrow biopsy with cell morphologic evaluation and, if necessary, immunophenotyping with anti-κ and anti-λ antisera to demonstrate monoclonality.

Outcome and Treatment

The outcome of MIDD remains uncertain, mainly because extrarenal deposits of light chains can be totally asymptomatic or cause severe organ damage leading to death. As in AL amyloidosis, treatment of patients with MIDD should be aimed at reducing immunoglobulin production. Nodular mesangial lesions and light-chain deposits may be reversible after effective chemotherapy. In the most recent series, 57% had stable or improved renal function, whereas 39% progressed to ESRD. The mean renal and patient survival rates were 64 and 90 months, respectively.[46] The only variable independently associated with renal survival was serum creatinine at biopsy, and the only predictor of death was the presence of lytic bone lesions.

Most patients treated with HDM/SCT achieve a hematologic and organ response with very low TRM.[51-53] The combination of bortezomib and dexamethasone may be used alone or as an induction in anticipation of HDM/SCT. To reduce the risk of disease recurrence on the graft, only patients who achieve a complete hematologic response should be candidates for renal transplantation.[54]

Monitoring of light-chain production should rely on serum FLC assay, particularly when a blood or urine monoclonal component cannot be detected by conventional methods.

Renal Diseases Associated with Monoclonal Immunoglobulin Deposition Disease

Myeloma Cast Nephropathy

The association of monoclonal light-chain deposits, mostly along renal tubular basement membranes, with typical myeloma cast nephropathy, occurs more frequently than reported initially. It was found in 11 of 34 patients with MIDD.[47] Nodular glomerulosclerosis, however, occurs infrequently (<10%), and some ribbon-like tubular basement membranes are seen in less than half the patients. In addition, one third of patients do not have granular dense deposits on EM.

AL Amyloidosis

Amyloid deposits are found in one or more organs in about 7% of LCDD patients. Because amyloid deposits are focal, their true incidence may be greatly underestimated. Although this association may result from peculiar light chains endowed with intrinsic properties that make them prone to form both fibrillar and nonfibrillar deposits, depending on the environment,[42] one cannot exclude the possibility that the coexisting diseases are induced by different variant clones.

NONAMYLOID FIBRILLARY AND IMMUNOTACTOID GLOMERULOPATHIES

Definition

Fibrillary and immunotactoid glomerulopathies are characterized, respectively, by fibrillar and microtubular deposits in the mesangium and the glomerular capillary loops (Table 27-6). These deposits do not have an amyloid-like cross-β structure and are readily distinguishable from amyloid by the larger thickness of fibrils and lack of Congo red staining. For other glomerulopathies, the distinction between nonamyloid fibrillary and immunotactoid glomerulopathy is of great clinical and pathophysiologic interest in patients with plasma cell dyscrasias. About 30% of immunotactoid glomerulopathies are associated with hematologic malignancies, mainly CLL, while this association is uncommon in fibrillary glomerulopathies.[55-57]

Epidemiology

The incidence of glomerulopathy with nonamyloid deposition of fibrillar or microtubular material in a nontransplant adult biopsy population is estimated at around 1%. It is most likely underestimated because of the insufficient attention given to atypical reactions with histochemical amyloid stains and the frequent lack of immunoultrastructural studies.

Immunologic and Clinical Characteristics of Fibrillary and Immunotactoid Glomerulopathies

Characteristics	Amyloidosis (AL Type)	Fibrillary Glomerulopathy	Immunotactoid Glomerulopathy
Congo red staining	Yes	No	No
Composition	Fibrils	Fibrils	Microtubules
Fibril or microtubule size	8-15 nm	12-22 nm	>30 nm*
Organization in tissues	Random (β-pleated sheet)	Random	Parallel arrays
Immunoglobulin deposition	Monoclonal LC (mostly λ)	Usually polyclonal (mostly IgG4), occasionally monoclonal (IgG1, IgG4)	Usually monoclonal (IgGκ or IgGλ)
Glomerular lesions	Deposits spreading from mesangium	MPGN, CGN, MP	Atypical MN, MPGN
Renal presentation	Severe NS, absence of hypertension and hematuria	NS with hematuria, hypertension; RPGN	NS with microhematuria and hypertension
Extrarenal manifestations (fibrillar deposits)	Systemic deposition disease	Pulmonary hemorrhage	Microtubular inclusions in leukemic lymphocytes
Association with LPD	Yes (myeloma)	Uncommon	Common (CLL, NHL, MGUS)
Treatment	Melphalan + dexamethasone; intensive therapy with blood stem cell autograft	Corticosteroids ± cyclophosphamide (crescentic GN)	Treatment of the associated LPD

Table 27-6 Immunologic and clinical characteristics of fibrillary and immunotactoid glomerulopathies. *Mean diameter of the substructures did not differ between fibrillary glomerulonephritis (15.8 ± 3.5 nm) and immunotactoid glomerulopathy (15.2 ± 7.3 nm) in the series of Bridoux and colleagues.[54] *CGN,* Crescentic glomerulonephritis; *CLL,* chronic lymphocytic leukemia; *GN,* glomerulonephritis; *LC,* light chain; *LPD,* lymphoproliferative disorder; *MGUS,* monoclonal gammopathy of undetermined significance; *MN,* membranous nephropathy; *MP,* mesangial proliferation; *MPGN,* membranoproliferative glomerulonephritis; *NHL,* non-Hodgkin lymphoma; *NS,* nephrotic syndrome; *RPGN,* rapidly progressive glomerulonephritis.

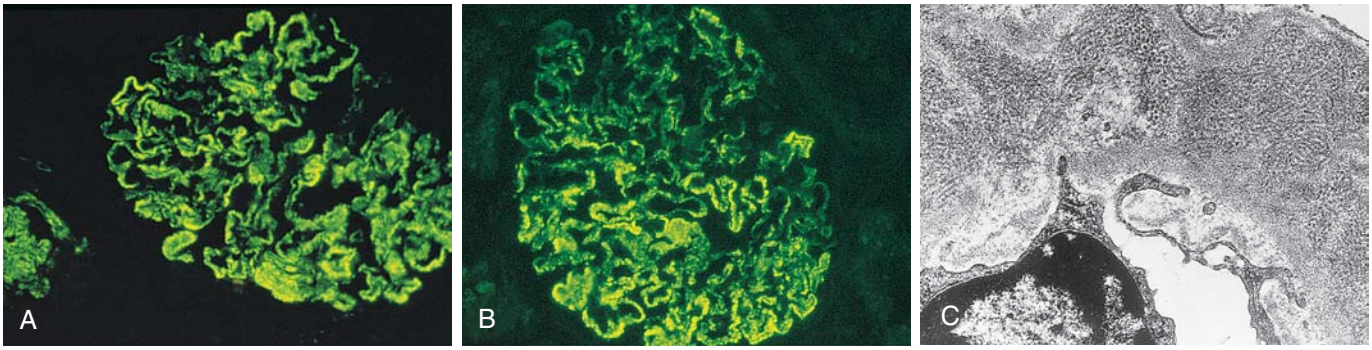

Figure 27-7 Immunotactoid glomerulopathy. Atypical membranous nephropathy showing exclusive staining of the deposits with **A,** anti-γ antibodies, and **B,** anti-κ antibodies. (Immunofluorescence; ×312.) **C,** Electron micrograph of glomerular basement membrane shows microtubular structure of the subepithelial deposits. (Uranyl acetate and lead citrate; ×20,000.) *(Courtesy Dr. Béatrice Mougenot, Paris.)*

Clinical Manifestations

The characteristics of fibrillary and immunotactoid glomerulopathies are described in Table 27-6 in comparison to AL amyloidosis. Patients with immunotactoid and fibrillary glomerulopathies have a mean age of 55 to 60 years (extreme: 19 to 86 years). They usually present with the nephrotic syndrome, microscopic hematuria, and mild to severe CKD. Recent series show no significant difference between immunotactoid and fibrillary glomerulopathy patients in serum creatinine level, incidence of nephrotic syndrome, microscopic hematuria, hypertension, or CKD.[55,56] Extrarenal manifestations are uncommon and may involve the lung, skin, and peripheral nervous system.

Pathology

Immunotactoid Glomerulopathy

Renal biopsy shows membranous nephropathy (often associated with segmental mesangial proliferation; Fig. 27-7) or lobular MPGN. Granular deposits of IgG and C3 with activation of the classical and terminal pathway of complement are observed along capillary basement membranes and in mesangial areas.[57] In a series of 23 patients in whom diagnosis was based on ultrastructural appearance of the deposits, IgG deposits were monotypic in 13 of 14 patients with immunotactoid glomerulopathy (κ, seven cases; λ, six cases) and in only one of nine patients with fibrillary glomerulopathy.[55] A circulating monoclonal immunoglobulin was detected in only 6 of 14 patients with immunotactoid glomerulopathy. On EM, the distinguishing morphologic features of immunotactoid glomerulopathy are organized deposits of large, thick-walled microtubules (typically >30 nm in diameter), at times arranged in parallel arrays (Fig. 27-7, *C*).

Patients with immunotactoid glomerulopathy exhibit a high prevalence of CLL, lymphoplasmacytic lymphoma, and MGUS.[55,57] Intracytoplasmic crystal-like immunoglobulin inclusions were found in four patients with CLL and in the lymphoma patient.[55]

Fibrillary Glomerulopathy

Mesangial proliferation and aspects of MPGN are predominantly reported in series of fibrillary glomerulopathy. Glomerular crescents are present in about 30% of the biopsy specimens. Immunofluorescence studies mainly show IgG deposits of the IgG subclass with a predominant mesangial localization. Monotypic deposits containing mostly IgGκ are detected in no more than 15% of patients. On EM, fibrils are randomly arranged, and their diameter varies between 12 and 22 nm. The fibril size alone is not sufficient to distinguish nonamyloidotic fibrillary glomerulonephritis (GN) from amyloid.[55]

Diagnosis

Diagnosis of immunotactoid and fibrillary glomerulopathies relies on EM, which must be performed in patients with atypical membranous nephropathy or MPGN as well as in those with monotypic deposits in glomeruli. Renal biopsy specimens from such patients with glomerular disease should be routinely examined with anti-κ and anti-λ light-chain antibodies. In patients with immunotactoid glomerulopathy, lymphoproliferative disease should be sought. Association of immunotactoid and fibrillary glomerulopathy with hepatitis C virus or human immunodeficiency virus infection has also been reported.

Outcome and Treatment

Patients with fibrillary glomerulopathy usually respond poorly to corticosteroids and cytotoxic drugs, with an incidence of ESRD of about 50%.[55,57] Preliminary reports suggest that they may respond to rituximab.[58] The prognosis of immunotactoid glomerulopathy appears to be better than that of fibrillary glomerulonephritis. Therapy directed against the underlying hematologic malignancy usually leads to remission of the nephrotic syndrome.[55,59] Renal transplantation has been performed in a few patients. Disease recurred in several, especially in those with a persistent monoclonal gammopathy.[58]

GLOMERULAR LESIONS ASSOCIATED WITH WALDENSTRÖM MACROGLOBULINEMIA

Symptomatic renal disease is much less common in patients with Waldenström macroglobulinemia than in those with multiple myeloma. Glomerulonephritis with intracapillary thrombi of aggregated IgM (intracapillary monoclonal deposit disease) is the most characteristic renal morphologic finding, but it has become rare, probably because of increased efficacy of chemotherapy. This entity may also occur with other IgM-secreting monoclonal proliferations.[61] Waldenström macroglobulinemia is associated with variable degrees of proteinuria and altered renal function. It is characterized by PAS-positive, Congo red–negative intracapillary deposits, sometimes voluminous enough to occlude capillary lumina. On immunohistology, thrombi and deposits stain with anti-μ and with anti-κ. The deposits are electron dense and granular without microtubular organization. Some of these patients have strong activation of the classical complement pathway with or without cryoglobulinemia. Other patients have MPGN with a bright μ and κ staining along the glomerular capillaries, without cryoglobulinemia. Renal manifestations usually improve with chemotherapy. Renal amyloidosis (mostly

AL) is uncommon but should be suspected in patients presenting with massive proteinuria. Because renal biopsy may be hazardous in patients with Waldenström macroglobulinemia, who frequently have increased bleeding time, it is wise to search for amyloid deposits first by a less invasive tissue biopsy. Hematopoietic stem cell transplantation and purine analogues may represent the most effective therapies.[19]

OTHER TYPES OF GLOMERULONEPHRITIS

In some patients, glomerular deposition of monoclonal IgG can produce a proliferative GN that mimics immune complex GN on light and electron microscopy.[62] Proper recognition of this entity requires confirmation of monoclonality by immunostaining for the γ heavy-chain subclasses. Tissue fixation of complement was observed in 90% of cases, and 40% of patients had hypocomplementemia. Clinical presentation included CKD in 80%, proteinuria in 100%, nephrotic syndrome in 44%, and microhematuria in 60%. Minute amounts of a monoclonal serum protein with the same heavy- and light-chain isotype as that of the glomerular deposits was identified in 50% of cases. No patient had overt myeloma or lymphoma at presentation or during follow-up. Proliferative GN with monoclonal IgG deposits recurs in the allograft.[63]

Few cases of nonorganized MIDD with a membranous pattern have been reported. The majority of these patients have IgG1 deposits, and those with proliferative lesions have mainly IgG3 deposits.[64] A circulating monoclonal IgG could be detected in only one fourth of these patients.

Several cases of GN with isolated C3 deposits and monoclonal gammopathy have been reported. These may be related to complement activation through an autoantibody activity of the monoclonal IgG against a complement alternative pathway regulatory protein.[65]

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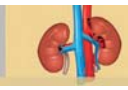
CHAPTER 28



Other Glomerular Disorders and the Antiphospholipid Syndrome

Richard J. Glassock

This chapter provides a description of several glomerular and vascular diseases, not necessarily related to each other. Each disorder must be recognized and differentiated from other, more common glomerular disorders to estimate the prognosis, to determine whether a familial disorder is present, to plan appropriate therapy, or to determine the risk of a recurrence in the transplanted kidney.

MESANGIAL PROLIFERATIVE GLOMERULONEPHRITIS WITHOUT IgA DEPOSITS

Mesangial proliferative glomerulonephritis (MesPGN) encompasses a heterogeneous collection of disorders having a diverse and largely unknown etiology and pathogenesis. The common feature that binds these various disorders is a histologic pattern on light microscopy of glomerular injury characterized by diffuse mesangial proliferation[1-3] (Fig. 28-1). Thus, MesPGN is noted for a diffuse and global increase in mesangial cells, often accompanied by an increase in mesangial matrix. Other cells (e.g., monocytes) may also contribute to the hypercellularity. As such, MesPGN is a glomerular lesion, not a specific disease entity.

For the purpose of this discussion, other forms of cellular proliferation that occur within the mesangial zones but are more focally and segmentally distributed are not included. These focal and segmental forms of proliferative glomerulonephritis (GN), often accompanied by areas of segmental necrosis of the glomerular tufts and very localized crescents, may be a part of the evolutionary stages of an initially pure MesPGN, but they often signify the presence of systemic disease processes, including systemic lupus, Henoch-Schönlein purpura and IgA nephropathy, infective endocarditis, microscopic polyangiitis, granulomatous polyangiitis (Wegener granulomatosis), Goodpasture disease, rheumatoid vasculitis, and mixed connective tissue disease. On occasion, a lesion of focal and segmental proliferative GN is discovered in the absence of any recognizable multisystem disease process and in the absence of IgA deposits (i.e., idiopathic focal and segmental proliferative GN). Such patients have a clinical presentation, course, and response to treatment that are similar to those described for pure MesPGN, but they are not discussed further in this section.

In "pure" MesPGN, the peripheral capillary walls are thin and delicate without obvious deposits, reduplication, focal disruptions, or cellular necrosis. The visceral and parietal epithelial cells, although occasionally enlarged, have not undergone proliferation. Crescents and segmental sclerosis should be absent in the "pure" form of the disorder. In addition, large deposits staining with periodic acid–Schiff or fuchsin in the mesangium should be absent, because these deposits suggest IgA nephropathy (see Chapter 23) or lupus nephritis (see Chapter 26). The tubulointerstitium and vasculature are usually normal, unless reduced renal function or hypertension is present or the patient is of advanced age.

On immunofluorescence (IF) microscopy, a wide variety of patterns of immunoglobulin and complement deposition are observed (Table 28-1). Most often, diffuse and global IgM and C3 deposits are found scattered throughout the mesangium in a granular pattern (so-called IgM nephropathy), but isolated C3, C1q, or even IgG deposits may also be seen.[4] If IgA is the predominant immunoglobulin deposited, the diagnosis is IgA nephropathy. In some cases, no immunoglobulin deposits are found at all. Prominent C3 deposition in the absence of immunoglobulin deposition should suggest a C3 glomerulopathy (see Chapter 22).[5] Extensive C1q deposits, with or without immunoglobulin deposits should suggest C1q nephropathy.[6]

On electron microscopy (EM), the number of mesangial cells is increased, with an occasional infiltrating monocyte or polymorphonuclear leukocyte. The amount of mesangial matrix is frequently but not invariably diffusely increased. Electron-dense deposits within the mesangium can be seen in many cases, particularly those with immunoglobulin (IgG or IgM) deposits on IF microscopy. Very large mesangial or paramesangial electron-dense deposits suggest IgA nephropathy even if IF microscopy is not available. Subendothelial, intramembranous, or subepithelial deposits are not seen. If present, these suggest a postinfectious etiology such as underlying lupus nephritis or a C3 glomerulopathy. Deposits of multiple immunoglobulin classes identified by immunohistology and large numbers of tubuloreticular inclusions on EM suggest underlying lupus nephritis.

The clinical presentation of MesPGN is quite varied, although persistent or recurring microscopic or macroscopic hematuria with mild proteinuria is most common. Nephrotic syndrome with heavy proteinuria is a less frequent initial presentation but is seen more often in association with diffuse mesangial IgM deposits (IgM nephropathy)[2] or C1q deposits (C1q nephropathy).[4,6] Pure MesPGN is a rather uncommon lesion (<5%) in patients diagnosed with idiopathic nephrotic syndrome.[2,3] Lesions of MesPGN have been observed in acute parvovirus B19 disease and in association with Castleman disease.[7,8]

Renal function and blood pressure are usually normal, at least initially. Serologic studies are generally unrewarding. Serum C3 and C4 complement components and hemolytic complement activity (CH50) are normal. A low C3 level suggests a C3 glomerulopathy. Assay results for antinuclear antibody (ANA), antineutrophil cytoplasmic autoantibody (ANCA), anti–glomerular basement membrane (anti-GBM) autoantibody, and cryoimmunoglobulins are negative. Nevertheless, these studies should be performed in most patients to exclude known causes. MesPGN can also be a finding in

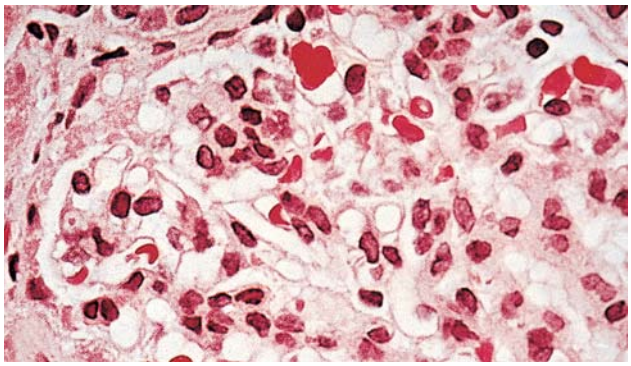


Figure 28-1 Pure mesangial proliferative glomerulonephritis (MesPGN). Note the increase in mesangial cellularity, the delicate peripheral capillary walls, and the absence of sclerosis or parietal epithelial cell proliferation. (Hematoxylin-eosin stain; magnification ×410.) *(Modified from reference 1.)*

Immunofluorescence Microscopy Patterns in MesPGN

Pattern	Associated Disorders
Predominantly mesangial IgA deposits	IgA nephropathy (± IgM, C3)
Predominantly mesangial IgG deposits	Often associated with systemic lupus (± IgM, C3)
Predominantly mesangial IgM deposits	IgM nephropathy (± C3)
Mesangial C1q deposits	C1q nephropathy (± IgG, IgM, C3)
Isolated mesangial C3 deposits	Often associated with resolving poststreptococcal GN
Negative for immunoglobulin or complement deposits	Idiopathic MesPGN

Table 28-1 Immunofluorescence microscopy patterns in mesangial proliferative glomerulonephritis (MesPGN).

resolving postinfectious (poststreptococcal) GN. Isolated C3 deposits with scanty, subendothelial or subepithelial (hump-like) deposits on EM may be seen in this situation. Urinary protein biomarkers may help to determine prognosis.[9]

IgM Nephropathy

IgM nephropathy[2] is characterized by diffuse and generalized glomerular deposits of IgM often accompanied by C3. Mesangial electron-dense deposits are also observed. On light microscopy, a picture of "pure" MesPGN is usually observed, sometimes with superimposed focal segmental glomerulosclerosis (FSGS).[10] It is an uncommon finding accounting for <5% of all renal biopsies.[10] Patients may present with recurring macroscopic hematuria and proteinuria, the latter in the nephrotic range in as many as 50% of patients. Persisting abnormalities and a poor response to corticosteroids or immunosuppressive therapy are often seen. As many as 50% of patients will eventually progress to typical FSGS and, if unresponsive to corticosteroids, will slowly develop chronic kidney disease (CKD) and end-stage renal disease (ESRD). Treatment of IgM nephropathy is highly uncertain, although steroid therapy may be associated with a complete or partial remission in as many as 50% of patients. The etiology and pathogenesis are unknown.

C1q Nephropathy

C1q nephropathy is characterized by diffuse deposits of C1q, often accompanied by IgG, IgM, or both.[4,6] C3 deposits are observed less frequently. These immunopathologic features resemble those seen in lupus nephritis; however, these patients have none of the clinical features of systemic lupus erythematosus (SLE) and do not develop SLE even after prolonged follow-up.[11] In addition to MesPGN, other morphologic lesions, including FSGS, are typically observed by light microscopy. Nephrotic-range proteinuria occurs, often with hematuria. Males predominate, and African Americans are often affected. Serum C3 components, ANA, and anti–double-stranded DNA (anti-dsDNA) antibodies are consistently normal or negative. The response to treatment is poor, and progression to ESRD may occur.

Mesangial Proliferative Glomerulonephritis Associated with Minimal Change Disease

MesPGN may also be a part of the spectrum of minimal change disease (MCD)–FSGS lesions (see also Chapters 17 to 19). Distinct mesangial hypercellularity superimposed on a lesion of MCD (diffuse foot process effacement seen on EM) may point to a greater likelihood for corticosteroid unresponsiveness and an eventual evolution to the FSGS lesion.

Natural History of Mesangial Proliferative Glomerulonephritis

The natural history of MesPGN varies, undoubtedly the result of etiologic and pathogenetic heterogeneity. In many patients, a benign course ensues, especially if hematuria and scant proteinuria (<1 g/day) are the principal features. Persisting nephrotic syndrome has a less favorable prognosis, and such patients may evolve into FSGS (see Chapters 18 and 19) and accompanying progressive CKD.[3,10]

Treatment of Mesangial Proliferative Glomerulonephritis

The treatment of "pure" MesPGN, unaccompanied by other underlying diseases or lesions such as SLE, C1q nephropathy, IgM nephropathy, MCD lesion, or IgA nephropathy, has not been well defined.[2,3] No prospective, randomized controlled trials (RCTs) have been performed because of the uncommon nature of the disorder. The prognosis for patients with isolated hematuria or hematuria combined with mild proteinuria (<500 mg/day) is generally benign, and thus no treatment other than management of hypertension is needed. For those patients with nephrotic syndrome, with or without impaired renal function, a more aggressive approach is often recommended, especially in the presence of diffuse IgM deposits, as discussed earlier, because many such patients will eventually progress to FSGS. Even in the absence of RCTs, an initial course of corticosteroid therapy may be justified in most patients with nephrotic-range proteinuria, such as prednisone, 60 mg/day or 120 mg every other day for 2 to 3 months, followed by lowered doses on alternate-day regimen for 2 to 3 additional months. About 50% of these patients experience a decrease in proteinuria to subnephrotic levels. Complete remissions occasionally occur. However, relapses of proteinuria are common when steroids are tapered or discontinued. Such relapsing, partially corticosteroid-responsive patients might benefit from the addition of cyclophosphamide, chlorambucil, or even cyclosporine or mycophenolate mofetil (MMF) to the regimen, although information on the therapeutic efficacy and safety of these agents in pure MesPGN is very limited.

Collagen Vascular (Rheumatic) Diseases Associated with Glomerular Lesions
Systemic lupus erythematosus (SLE; see Chapter 26)
Rheumatoid arthritis
Mixed connective tissue disease
Rheumatic fever
Ankylosing spondylitis
Reiter syndrome
Dermatomyositis/polymyositis
Scleroderma
Relapsing polychondritis
Systemic or renal-limited polyangiitis (see Chapter 25)

Box 28-1 Collagen vascular (rheumatic) diseases associated with glomerular lesions.

Patients with persistent treatment-unresponsive nephrotic syndrome will almost invariably progress to ESRD over several years. Whereas transplantation is not contraindicated, patients who do progress to ESRD rapidly and who develop superimposed FSGS may have a high risk of recurrence of proteinuria and FSGS in the transplanted kidney.

GLOMERULONEPHRITIS WITH RHEUMATIC DISEASE

Several so-called collagen vascular diseases other than SLE may be complicated by GN (Box 28-1). This section covers the glomerulonephritides that accompany rheumatoid arthritis,[11] mixed connective tissue disease,[12] polymyositis and dermatomyositis, acute rheumatic fever, scleroderma, and relapsing polychondritis. IgA nephropathy may also be seen in association with the seronegative spondyloarthropathies.

Rheumatoid Arthritis

A wide variety of glomerular, tubulointerstitial, and vascular lesions of the kidney may complicate rheumatoid arthritis (RA) (Box 28-2). Clinical abnormalities, including abnormal urinalyses (hematuria, leukocyturia, proteinuria), and reduced renal function are common in patients with RA, particularly those with severe or longstanding disease. Membranous nephropathy (MN) (see Chapter 20) is the most common glomerular lesion encountered, possibly because of the underlying disease itself or its therapy (parenteral or oral gold or penicillamine). The presence of HLA-DR3 increases the risk for development of MN in a patient with RA. The lesion is not associated with anti–phospholipase A_2 receptor (anti-PLA_2R) autoantibodies.

The course of MN in association with RA, in the absence of drugs, is similar to that of the idiopathic disease, although spontaneous remissions appear less likely to occur. By comparison, MN associated with drugs used to treat RA is most likely to remit after discontinuance of the drug therapy.[11] Such remissions may take many months to occur. Nevertheless, 60% to 80% of RA patients with drug-induced MN will remit within 1 year of stopping treatment.

Secondary (AA) amyloidosis (see Chapter 27) is found in 5% to 20% of patients with RA undergoing renal biopsy. Nephrotic syndrome and progressive renal failure are common.

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) may also produce tubulointerstitial nephritis or MCD (see also Chapters 60 and 17).[13] A severe, necrotizing polyangiitis may complicate the course of longstanding RA (rheumatoid vasculitis).[14] These patients may have profound reduction in C3 levels, striking elevation of rheumatoid factors, and marked polyclonal hypergammaglobulinemia. Renal involvement in rheumatoid vasculitis is now relatively uncommon for poorly understood reasons. The use of TNF-α inhibitors for treatment of rheumatoid arthritis can evoke a picture resembling lupus nephritis (see Chapter 26).

Renal Disease in Rheumatoid Arthritis
Glomerular Lesions that May Be Direct Complications of the Disease
Membranous nephropathy (MN)
MesPGN (± IgA or IgM deposits)
Diffuse proliferative GN
Necrotizing and crescentic GN (rheumatoid vasculitis)
Amyloidosis (AA type)
Glomerular Lesions Associated with Agents Used in Treatment of Rheumatoid Arthritis
Gold: MN, MCD, acute tubular necrosis
Penicillamine: MN, crescentic GN, MCD
NSAIDs: acute tubulointerstitial nephritis (TIN) with MCD, acute tubular necrosis, MCD without TIN
Cyclosporine: chronic vasculopathy and TIN, focal and segmental glomerulosclerosis (?)
Azathioprine/6-mercaptopurine: TIN
Pamidronate: focal segmental glomerulosclerosis

Box 28-2 Renal disease in rheumatoid arthritis. *MCD,* Minimal change disease; *MesPGN,* mesangial proliferative glomerulonephritis; *NSAIDs,* nonsteroidal anti-inflammatory agents.

Mixed Connective Tissue Disease

Mixed connective tissue disease is characterized by features that overlap with those of SLE, scleroderma, and polymyositis.[12] Typically, the serum of such patients contains high-titer autoantibodies to extractable nuclear antigens (ribonucleoprotein-extractable nuclear antigen, U1 ribonucleoprotein antigen). Low titers of anti-dsDNA antibody may also be found. Renal disease, originally thought to be quite rare, is found in 10% to 50% of patients, most frequently MN and MesPGN.[14] Treatment with steroids is generally effective, but some patients exhibit progressive CKD. Patients with severe GN may respond to treatment regimens similar to those used in the treatment of lupus nephritis (see Chapter 26).

Polymyositis and Dermatomyositis

The related collagen vascular diseases polymyositis and dermatomyositis are characterized by inflammatory lesions in muscle and variable skin lesions and often include Raynaud phenomenon.[15] On occasion, patients have proteinuria and hematuria secondary to MesPGN with IgM deposits. Acute kidney injury (AKI) may rarely supervene when severe muscle injury and myoglobinuria are present. Treatment with steroids may, at least in part, ameliorate the renal manifestations in concert with improvement in the muscle and skin manifestations.

Acute Rheumatic Fever

Acute rheumatic fever secondary to a pharyngeal (but not cutaneous) infection with a rheumatogenic strain of group A β-hemolytic

streptococci is seldom accompanied by renal disease[16] (see Chapter 57). Poststreptococcal GN and acute rheumatic fever almost never coexist because of the distinct difference between nephritogenic and rheumatogenic strains of streptococci. In addition, cutaneous streptococcal infections are never associated with acute rheumatic fever sequelae. Nevertheless, on rare occasions, MesPGN has been associated with acute rheumatic fever.[16] MesPGN usually manifests with hematuria with scant proteinuria and often resolves with appropriate treatment and control of acute rheumatic fever.

Ankylosing Spondylitis and Reiter Syndrome (Seronegative Spondyloarthropathies)

The seronegative spondyloarthropathies and oligoarticular arthropathies may be associated with mesangial IgA deposition or MesPGN in some patients. Clinical manifestations are usually mild and nonprogressive. AA amyloidosis may complicate longstanding ankylosing spondylitis.

Scleroderma (Systemic Sclerosis)

Scleroderma is a heterogeneous disorder of unknown etiology and pathogenesis characterized by uncontrolled expansion of connective tissue in the skin and other visceral organs. There is also a marked tendency to produce vascular thickening and narrowing. Clinical manifestations vary from increased connective tissue in localized patches of skin (morphea) to diffuse and generalized disease (systemic sclerosis). The latter pattern leads to thickening of the skin of the face and hands, telangiectasia, Raynaud phenomenon, tendon friction rubs, and sclerodactyly. A characteristic pattern of blood vessel abnormalities is seen in the nail beds. Visceral involvement in the systemic form causes interstitial pulmonary fibrosis, loss of esophageal and other gastrointestinal motility, restrictive cardiomyopathy, and renal disease. Limited forms of the disease (CREST syndrome: calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) also occur but are seldom associated with renal disease. The disorder is seen more frequently in females, with an onset usually in young adults. Approximately 90% of patients will have a speckled pattern of fluorescent ANA; 20% will have detectable antibody to topoisomerase I (Scl-70). Anticentromere antibody is strongly associated with the CREST syndrome. Anti-DNA polymerase is associated with a poor prognosis and a high prevalence of renal involvement. Rarely, the visceral abnormalities may occur in the absence of cutaneous lesions (scleroderma sine scleroderma).

Renal involvement in scleroderma can be quite varied, from a low-grade proteinuria and slight impairment of glomerular filtration rate (GFR), to a more marked reduction in renal blood flow leading to a greatly elevated filtration fraction due to a mild MesPGN, to severe AKI. The last is referred to as *scleroderma renal crisis* and consists of severe (hyperreninemic) hypertension, encephalopathy, systolic and diastolic congestive heart failure, and AKI. There is often an accompanying microangiopathic hemolytic anemia with schistocytes in the peripheral blood film and greatly elevated serum lactate dehydrogenase levels. On occasion, AKI may develop in the absence of hypertension. AKI results from primary involvement of the arcuate and interlobular arteries (Fig. 28-2). It may be superimposed on lesions of hypertensive emergencies (malignant hypertension, such as fibrinoid necrosis of the afferent arterioles) and ischemic glomerular changes, such as wrinkling of the capillary wall and thickening of the basal lamina.

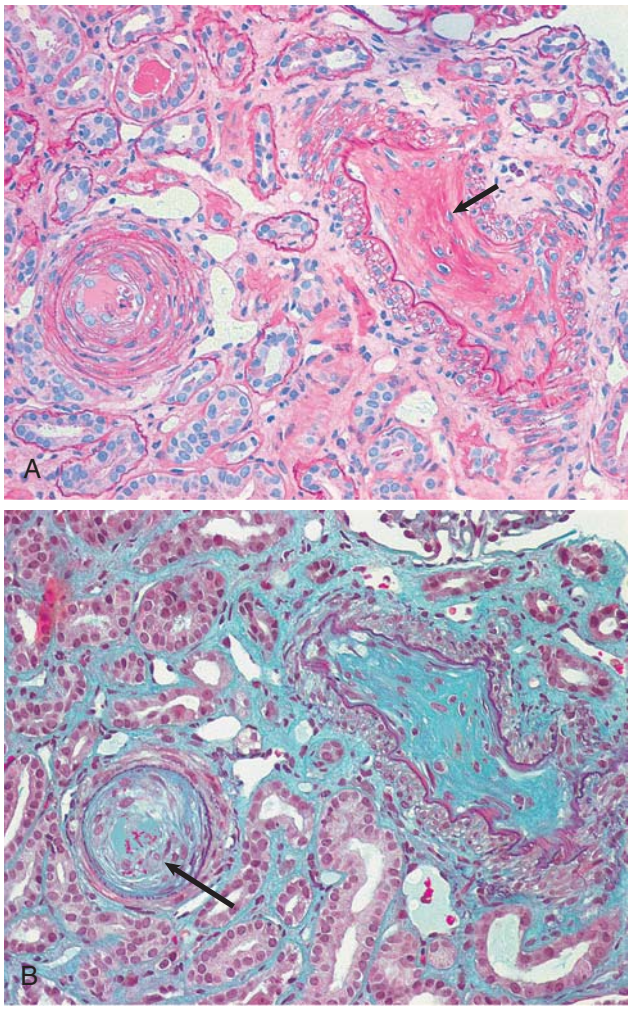


Figure 28-2 Scleroderma. A, Two interlobular arteries, one transversely and one tangentially cut, show a pronounced subendothelial thickening with weakly periodic acid–Schiff–positive mucinous material and myofibroblasts *(arrow)*. **B,** Fragmented erythrocytes (schistocytes) can be seen in the Goldner elastica stain in *red (arrow)*. The process is limited to the intima as the lamina elastica interna is preserved. Surrounding tubules are collapsed and have atrophic epithelia due to postarteriolar ischemia. *(Courtesy H. J. Groene, Heidelberg, Germany.)*

The prognosis of patients with scleroderma crisis has remarkably improved with the use of angiotensin-converting enzyme (ACE) inhibitors. In one study, ACE inhibitor treatment was associated with better patient survival at 1 year (75% vs. 15%) and with significant preservation or recovery of renal function.[17] Transplantation may be a reasonable treatment option, but progression of disease in other visceral organs may limit life expectancy.

Relapsing Polychondritis

Polychondritis is a chronic relapsing disorder characterized by destructive inflammation of cartilage (ear, nose, trachea, costal cartilage) and may be associated with crescentic GN, MesPGN, or MN. Lesions of cartilage may lead to deformities (saddle nose, floppy ears, tracheal collapse or stenosis), and the renal disease may be severe and progressive, leading to renal failure. Aggressive management of progressive disease with corticosteroids and cytotoxic agents (cyclophosphamide) is indicated to control both the systemic and renal manifestations.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

The antiphospholipid antibody syndrome (aPLA syndrome, APS) is a prothrombotic disorder characterized by venous and arterial thrombosis and by the presence of circulating autoantibodies to phospholipid-protein complexes, including those of the coagulation cascade.[18-20] The syndrome was first recognized by Graham Hughes in 1983 and in the succeeding three decades has been described to have protean manifestations ranging from migraine headaches to multiple thrombosis and multiorgan failure ("catastrophic" aPLA syndrome).[19] The clinical features are quite varied, and a high degree of clinical suspicion is required for early diagnosis. Neurologic symptoms and signs are common, including transient cerebral ischemic attacks (TIAs), strokes, migraine, seizures, myelitis, and balance and sensory disturbances (often resembling multiple sclerosis). Cardiovascular problems, such as pulmonary hypertension, premature atheromatous disease, renal artery stenosis, and myocardial infarction, are common. Livedo reticularis is an important diagnostic clue (Fig. 28-3). Adrenal infarction or hepatic venous thrombosis may lead to acute adrenal insufficiency or Budd-Chiari syndrome, respectively. Visual loss, field defects, anosmia, aseptic bone necrosis, fracture, spinal claudication, and autonomic dystrophy are other, less well-described complications. Pulmonary hemorrhage or fibrosing alveolitis can be a presenting feature.[21] Repeated pregnancy loss (two or more) is observed often. The kidneys are frequently involved with a form of thrombotic microangiopathy (see Chapter 29).

The aPLA syndrome may occur as a "primary" form without any known systemic disease or may accompany SLE (see also Chapter 26). The aPLA syndrome (primary or SLE related) should always be suspected whenever a history of migraine, headache, TIA or stroke, multiple pregnancy loss, or arterial or venous thrombosis or a family history of autoimmune disease is elicited. In 2006, the criteria for the definite diagnosis of APS were revised and updated.[22] These include the presence of at least both one clinical criteria plus one laboratory criteria: Clinical- i) thrombosis (arterial or venous); ii) Pregnancy morbidity (spontaneous abortions, still births). Laboratory (two or more occasions at least 12 weeks apart):- i) Lupus anticoagulant; ii) anticardiolipin antibody; iii) anti-β_2 glycoprotein-I antibody.

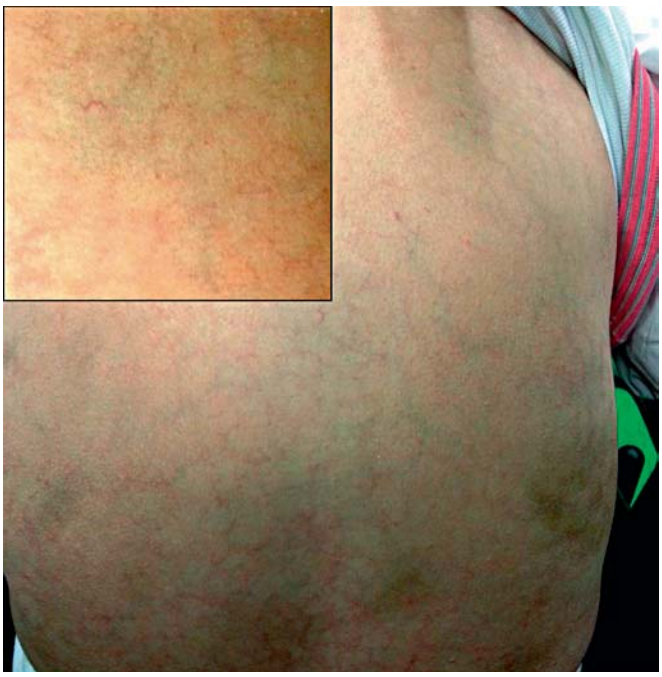


Figure 28-3 Livedo racemosa (livedo reticularis) in patient with antiphospholipid antibody syndrome. Note reticulated skin changes (*insert,* higher magnification) on the patient's back in addition to some hematomas related to her warfarin therapy. *(Courtesy J. Floege, Aachen, Germany.)*

The pathogenesis of APS is quite complex and probably multifactorial. The thrombotic state seems to involve generation of reactive oxygen species leading to alterations in β_2-glycoprotein-1 function, impaired function of endothelial nitric oxide synthase, activation of prothombotic receptors by autoantibodies, increased expression/activation of tissue factor, increased modified forms of prothrombotic factor XI, disruption of annexin A5 shield, and antibody-mediated activation of C3 and/or C5.[23]

Laboratory testing will usually reveal an autoantibody to phospholipids (anticardiolipin, anti–β_2-glycoprotein 1, or prothrombin), but "antibody-negative" aPLA syndrome has been described.[24,25] False-positive test results for syphilis and a "lupus anticoagulant" are common.[24,25] A prolonged prothrombin or partial thromboplastin time that does not correct when plasma is diluted 1:1 with normal plasma is found in such circumstances. Antiphospholipid antibodies may also cross-react with platelet factor 4–heparin complex and thus may be associated with a "false positive" for antibody in heparin-induced thrombocytopenia, giving rise to significant clinical confusion. Mild thrombocytopenia is common (platelet counts about 100,000/mm^3, but usually not less than 80,000/mm^3). Thrombocytopenia may be an *in vitro* phenomenon related to the effect of the aPLA antibody on platelet membrane biology. A mild hemolytic anemia (Coombs negative or positive) may coexist, giving rise to confusion with thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and Evans syndrome. A frank microangiopathic hemolytic anemia is relatively uncommon.

In the primary aPLA syndrome, overt renal manifestations are generally mild (proteinuria, hematuria, hypertension, reduced renal function) and are frequently absent. Nephrotic syndrome is relatively rare. In APS associated with SLE, the renal manifestations are determined largely by the severity of the underlying glomerular lesions, but the coexistence of APS adds a dimension of vascular disease (microangiopathy) that contributes to a worsened prognosis and to a multiplicity of extrarenal manifestations (neurologic, cardiovascular, osseous, ophthalmologic, pulmonary, hepatic, visceral, and obstetric) (see also Chapter 26). A strong association of aPLA with alveolar hemorrhage exists in SLE.[21]

The therapy for primary aPLA syndrome and that accompanying SLE is difficult and controversial. Immunosuppressive agents, such as steroids or cytotoxic agents, even when they are used to control SLE, have yielded disappointing results. Symptomatic patients are best treated with anticoagulation. Aspirin (or clopidogrel) can be used routinely in mild cases. Combinations of aspirin and low-dose warfarin might be effective, but the risk of bleeding may be increased. Warfarin is the mainstay of treatment in severe cases, with the international normalized ratio (INR) adjusted to a level depending on symptoms; INR between 2.0 and 3.5 may be required. Low-molecular-weight heparin (subcutaneous or intravenous) is the treatment of choice for pregnancy complicated by aPLA syndrome and is also useful in alleviating migraine headache. Aspirin therapy in pregnancy with an aPLA-like syndrome does not appear to be effective.[26] High-dose intravenous IgG can have dramatic beneficial effects, especially in acutely evolving disease associated with SLE. The benefits of newer immunomodulating agents such as rituximab have not been adequately evaluated in APS, but preliminary reports are encouraging when used with intensive plasma exchange.[27] Intensive plasma exchange (plus immunosuppression) may rarely be effective in pregnancy, but this therapy has been used in other

circumstances, such as in APS associated with SLE, with variable degrees of success.[28] Recently, a monoclonal antibody to C5 (eculizumab) has been used to treat catastrophic aPLA syndrome with success, but further evaluation is required before this becomes acceptable treatment.[29]

The previously posited pathogenetic mechanisms lend credence to some suggested novel therapeutic approaches to the aPLA syndrome, such as hydroxychloroquine, coenzyme Q10, statins, *N*-acetylcysteine, phosphodiesterase inhibitors, factor XI inhibitors, and eculizumab (anti-C5 monoclonal antibody). None of these has yet been thoroughly tested for safety and efficacy in RCTs.

GLOMERULONEPHRITIS ASSOCIATED WITH MALIGNANT DISEASE

Many malignant disorders and their treatment may be complicated by the development of glomerular lesions.[30] Furthermore, the treatment of glomerular disease with certain agents may give rise to neoplasia. Malignant neoplasms may also be associated with a wide variety of fluid, electrolyte, acid-base, divalent ion, tubulointerstitial, and vascular disorders, including direct invasion of the renal parenchyma by neoplastic cells.

Table 28-2 lists the glomerular lesions frequently observed in association with neoplastic processes. Membranous nephropathy is the most common lesion (see also Chapter 20). Approximately 7% to 20% of patients with MN will be found to have an underlying malignant neoplasm. Most patients are adults older than 50 years; however, despite the increasing frequency of malignant disease with age in the general population, epidemiologic studies support that the prevalence of malignant disease is higher in patients with MN than in age-matched controls.[31] In addition, remissions (although temporary) can be achieved by surgical removal or chemotherapy of the neoplastic disease, and relapses may develop with recurrence of tumor. Furthermore, tumor neoantigens or antibodies have been detected within the glomerular deposits, suggesting an immune complex pathogenesis. In about one third of patients, the neoplastic disorder is already evident before the development of glomerular lesions; in about one third it is discovered concomitantly with the onset of glomerular disease; and in about one third the neoplastic process is detected after the diagnosis of glomerular disease. MN occurring with an underlying malignant neoplasm can closely resemble the idiopathic disease both clinically and morphologically, so it is prudent to undertake an exploration for possible malignant disease in any patient older than 50 years who presents with an apparent "idiopathic" MN. This can consist of a careful physical examination, several stool specimens for occult blood, colonoscopy, computed tomographic (CT) scan of the chest (especially in smokers), mammography in women, and prostate-specific antigen determination in men. Some studies have also suggested that prominent IgG1 and IgG2 instead of IgG4 deposits in the glomeruli are suggestive of a malignant cause or underlying lupus nephritis. In MN, positive anti-PLA_2R autoantibodies in the circulation or PLA_2R antigens in the glomerular deposits strongly indicate an idiopathic form of MN.[32]

Major Cancers That Can Be Associated with Specific Glomerular Lesions

Glomerular Disease	Most Commonly Associated Malignancy
MN	Colon, breast, stomach, and lung cancer
MCD	Hodgkin lymphoma, pancreatic cancer, mesothelioma, prostate cancer
FSGS	Leukemia, lymphoma
MPGN	Chronic lymphocytic leukemia, lymphoma (some associated with HCV)
IgA nephropathy	Lung carcinoma
Crescentic GN, systemic vasculitis	Lung carcinoma
Systemic amyloidosis AL type	Multiple myeloma, Waldenström macroglobulinemia
Systemic amyloidosis AA type	Carcinoma (especially renal)
Cryoglobulinemic GN	Chronic lymphocytic leukemia (often hepatitis C associated)
Light-chain nephropathy	Lymphoma, myeloma
Fibrillary (immunotactoid) GN	Lymphoma
Hemolytic-uremic syndrome	Gastric cancer, mucin-producing cancer

Table 28-2 Major glomerular lesions associated with neoplastic disease. *MN,* Membranous nephropathy; *MCD,* minimal change disease; *FSGS,* focal segmental glomerulosclerosis; *MPGN,* membranoproliferative glomerulonephritis; *HCV,* hepatitis C virus; *GN,* glomerulonephritis.

Less frequent lesions observed in patients with neoplasia include MCD, FSGS, proliferative GN (including crescentic GN), thrombotic microangiopathy, monoclonal immunoglobulin deposition diseases (MIDD), and amyloidosis. MCD may be associated with lymphoma (particularly Hodgkin) and certain other cancers (pancreas, mesothelioma, prostate). Membranoproliferative GN (MPGN) may be associated with chronic lymphocytic leukemia (CLL) and lymphoma. FSGS may also occasionally be encountered in patients with underlying malignant disease, including CLL and lymphoma. IgA nephropathy and crescentic GN may be associated with lung cancer. Vasculitis accompanied by crescentic GN, often resembling Henoch-Schönlein purpura, has been reported with several malignant neoplasms, most notably lung cancer.

Systemic amyloidosis (AL type) may affect the kidney and produce nephrotic syndrome and renal failure in 10% to 15% of patients with multiple myeloma and rarely in association with Waldenström macroglobulinemia (see Chapter 27). Carcinomas, including renal cell carcinoma, are also rarely complicated by amyloidosis, which is usually of the AA variety. MIDD may accompany lymphomas and leukemias (Chapter 27). Light-chain nephropathy, in which deposits of either κ or γ light chain are found in the glomerular capillaries and tubular basement membranes, may occur in association with a variety of neoplastic lymphoproliferative states (Chapter 27).

Thrombotic microangiopathy, producing renal cortical necrosis or glomerular lesions resembling MPGN, may be seen in association with disseminated cancer (carcinoma of stomach) and other mucin-producing carcinomas. It may also appear secondary to treatment with certain antineoplastic agents, especially mitomycin C.

Interferon (IFN) treatment, used in the management of certain malignant neoplasms, may cause MCD, often in association with interstitial nephritis, and IFN therapy may also be associated with development of FSGS (see Chapters 17 to 19).

OTHER UNCOMMON DISORDERS

Lipoprotein Glomerulopathy

Lipoprotein glomerulopathy is believed to be caused by an abnormality in lipoprotein metabolism[33,34] (see also Chapter 19), It is

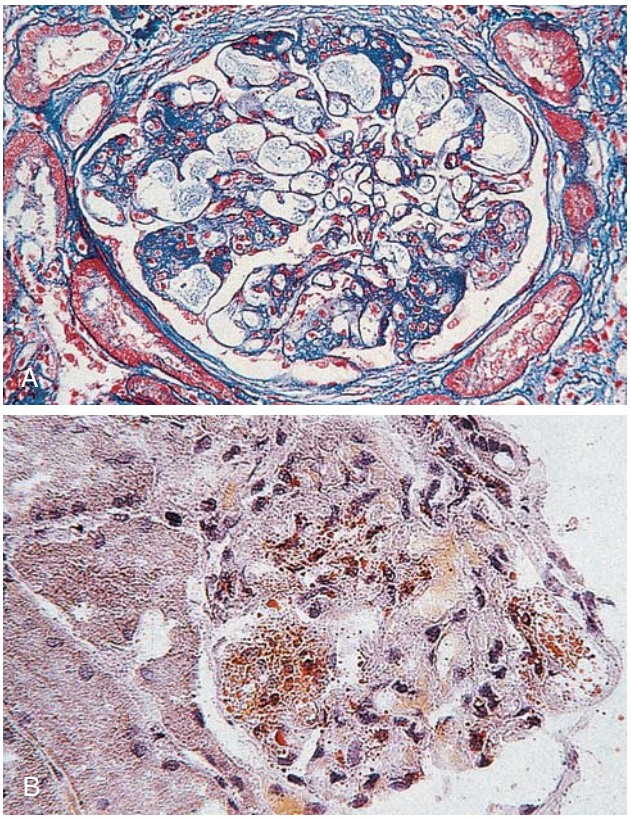


Figure 28-4 Lipoprotein glomerulopathy. A, Dilated capillary lumina containing a pale, trichrome-stained, mesh-like or granular substance. (×260.) **B,** The granules stain positively with oil red O and antilipoprotein E antisera. (×260.) *(Modified from reference 1.)*

characterized by extensive deposits of apolipoproteins A, B, and E in the glomeruli (mostly apoE), leading to greatly expanded capillaries filled with a pale-staining, mesh-like substance having the appearance of lipid "thrombi" (Fig 28-4). Clinically, there may be heavy proteinuria with nephrotic syndrome. Apolipoprotein B and E levels are increased in plasma in association with a type III hyperlipoproteinemia. The apoE usually shows a heterozygous E2/E3 or E2/E4 phenotype, but homozygosity for apolipoprotein E2 or E3 has also been observed. Homozygous apolipoprotein E2 is also seen in familial type III hyperlipoproteinemia. Decreased low-density lipoprotein (LDL) receptor binding and increased heparin affinity may explain some of the pathogenetic processes in lipoprotein glomerulopathy. The disease may be associated with psoriasis.[35] Otherwise, there are no distinctive clinical features. Familial cases have strongly suggested a hereditary abnormality. Lipoprotein glomerulopathy may recur in the renal transplant. Treatment with bezafibrate or fenofibrate may be effective.[36,37] Treatment with Heparin-induced Extracorporeal Lipoprotein Precipitation–apheresis systems (HELP-apheresis) can achieve a complete remission in some patients.[38]

Lecithin–Cholesterol Acyltransferase Deficiency

Lecithin–cholesterol acyltransferase (LCAT) deficiency is an autosomal recessive disorder associated with a very low high-density lipoprotein HDL cholesterol but a remarkably variable and often low frequency of cardiovascular disease in carriers[39-41] (see also Chapter 19). The clinical characteristics include corneal opacities (misty deposits, also known as "fish eye"), normocytic normochromic anemia

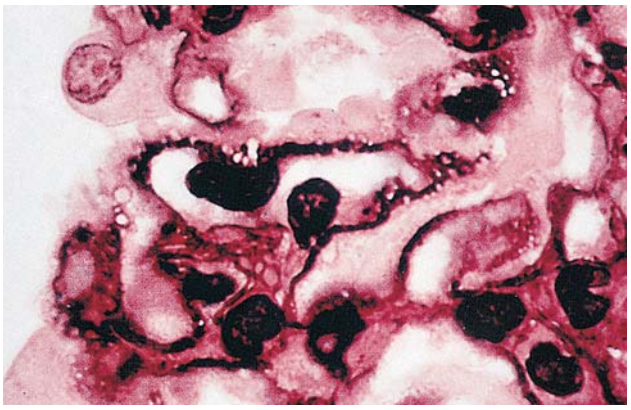


Figure 28-5 Lecithin–cholesterol acyltransferase deficiency. Note the irregular, thickened glomerular capillary walls containing clear vacuoles, which are characteristic of the LCAT lesion. (Periodic acid–Schiff reaction; ×1000.) *(Modified from reference 1.)*

(with target cells), low HDL and α-lipoprotein levels, and elevated LDL level. Proteinuria, including the nephrotic syndrome, as well as hypertension and progressive renal failure are the main renal manifestations. On light microscopy, the glomeruli reveal foam cells, intimal hyperplasia, and thickening of the glomerular basement membrane (GBM) with effacement of the foot processes (Fig. 28-5). Progressive renal failure is the rule; however, it is of slow and insidious onset and is usually first detected in the fourth decade of life. Treatment is generally ineffective, but theoretically, an inhibitor of hepatic acyl coenzyme A–cholesterol acyltransferase activity might be of benefit.[42] A case report of beneficial effects of steroid therapy recently appeared, but this approach is of unconfirmed value.[43] The disease can recur in the renal allograft.[44]

Collagen III Glomerulopathy

Collagen III glomerulopathy, also known as *collagenofibrotic glomerulopathy,* is an autosomal recessive systemic disorder with prominent renal manifestations that may be a *forme fruste* of nail-patella syndrome (see Chapter 48) because the glomerular abnormalities are similar.[45-47] Nevertheless, patients with collagen III glomerulopathy lack the typical skeletal abnormalities observed in the nail-patella syndrome. Clinically, patients present with proteinuria and slowly progressive renal failure. Patients may be of any age, and males predominate. On light microscopy, the glomeruli are enlarged with a marked expansion of the mesangial matrix by material weakly positive for periodic acid–Schiff (PAS) reaction (Fig. 28-6). Conventional IF microscopy is usually negative, but rarely will show "full-house" immunoglobulin and complement deposition.[48] However, antisera to collagen type III will strongly react with the glomerular deposits. EM shows bundles spirally arranged and frayed fibrillar deposits (Congo red negative) with periodicity characteristic of collagen. Similar deposits may be found in the spleen, liver, myocardium, and thyroid in fatal cases. No treatment is known to be effective, and there are no data yet on recurrent disease after renal transplantation, but because of the systemic nature of collagen III (collagenofibrotic) glomerulopathy, such recurrences would be likely.

Fibronectin Glomerulopathy

Fibronectin glomerulopathy is a rare, autosomal dominant, nonamyloid, fibrillary glomerular disease with onset usually in early adolescence with proteinuria, microhematuria, hypertension, distal (type

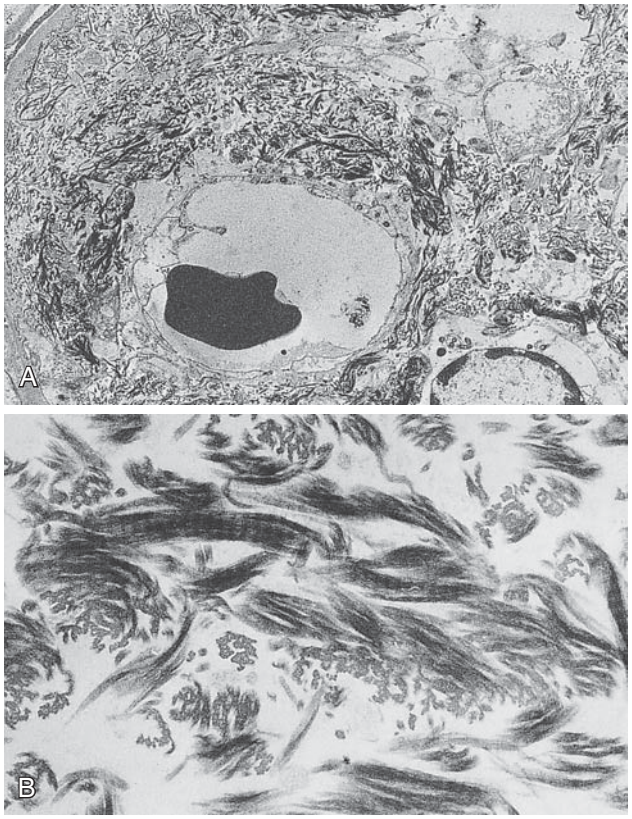


Figure 28-6 Electron microscopy of collagen III (collagenofibrotic) glomerulopathy. A, Fine fibrils occur in the mesangial and subendothelial areas. (×3000.) **B,** These fibrils are randomly oriented with typical periodicity and average 30 nm in diameter. The fibrils are strongly positive for periodic acid–Schiff reaction with anti–collagen type III antibodies. (×15,000.) *(Modified from reference 1.)*

4) renal tubular acidosis, and slowly progressive renal failure.[49,50] The gene *(FN1)* responsible for the disorder maps to chromosome 2q32.[51] Most patients reach ESRD between the second and sixth decade of life. The renal pathology usually reveals enlarged, hyperlobular, and normocellular glomeruli with a homogeneous or fibrillar material (on PAS staining) in the mesangium and subendothelium. These fibrils are Congo red negative. EM shows randomly oriented fibrils (12 to 16 nm wide and 120 to 170 nm long). IF is negative for antibody and complement components but will stain brightly with use of an antifibronectin antibody. The pathogenesis of the disease is unknown, although mice "knocked out" for uteroglobin develop a similar lesion. However, studies in humans have not documented any linkage to genes for uteroglobin or fibronectin. The differential diagnosis includes other disorders associated with fibril deposition (see Chapter 27). There is no known effective treatment of fibronectin glomerulopathy. The disease can recur in renal allografts.[52]

Nephropathic Cystinosis

Late-onset adult cystinosis is a variant of typical pediatric cystinosis in which the mutations in the *CTNS* gene result in a milder phenotype. These patients may present with glomerular disease during the teenage years. Nephrotic syndrome may occur, and the glomerular lesions resemble FSGS except that crystals of cystine are found in glomerular and tubular epithelial cells.[53] Patients with cystinosis may also have blond hair, photophobia, hypothyroidism, corneal deposits, rickets, and Fanconi syndrome with tubular proteinuria (see Chapter 50).

Miscellaneous Storage Diseases and Other Unusual Glomerular Lesions

A variety of diseases associated with storage of abdominal lipids or carbohydrates in tissue may provoke glomerular lesions. These include Hurler syndrome (type I mucopolysaccharidoses), von Gierke disease (glycogen storage disease), Gaucher disease, Refsum disease, nephrosialidosis, and I cell disease (mucolipidosis type II). Juvenile malabsorption of vitamin B_{12} with megaloblastic anemia (Imerslund syndrome; cubulin deficiency) can be associated with prolonged glomerular proteinuria (albuminuria), but progressive renal disease does not develop. Asphyxiating thoracic dystrophy (Jeune syndrome) is associated with glomerular, tubular, and interstitial abnormalities. Hereditary osteolysis causing arthralgias and deformities of wrists and ankles can be accompanied by chronic GN. The nail-patella syndrome and Fabry disease are discussed in Chapter 48.

"Idiopathic" Nodular Glomerulosclerosis

An intercapillary nodular expansion of the mesangium encroaching on the glomerular capillary lumina is characteristically called the *Kimmelstiel-Wilson* lesion and is most commonly associated with diabetes mellitus and proliferative diabetic retinopathy (see Chapter 30). However, in recent years, a small group of patients have been described in whom a similar or identical lesion is seen in the absence of any overt features of diabetes mellitus or disordered glucose metabolism or other known causes of a similar lesion, such as κ light-chain nephropathy (see Chapter 27), chronic thrombotic microangiopathy, MIDD, fibrillary GN, and fibronectin glomerulopathy. Thus, idiopathic nodular glomerulosclerosis is a diagnosis of exclusion.

The first examples of this new disorder were recognized in 1989,[54] and approximately 65 additional cases have subsequently been reported.[55-58] Whereas some of these patients may have had intermittent manifestation of diabetes or only mild abnormalities of glucose homeostasis, such as an abnormal glucose tolerance test result, most have not had features conventionally used to define the presence of diabetes mellitus (i.e., normal fasting blood glucose concentration and hemoglobin A_{1c} measurements). Thus, the intercapillary nodular lesion does not appear to require prolonged abnormal glucose homeostasis for its generation.

The clinical features are nonspecific and nondiagnostic. Patients with idiopathic nodular glomerulosclerosis are usually older (average age of about 70 years), and female gender and nephrotic syndrome are a common presentation. A heavy smoking history, obesity, and longstanding hypertension are frequently present, but the role of these abnormalities in the pathogenesis of the lesion is unknown.

The pathology includes typical intercapillary nodular glomerulosclerosis with thickening of the GBM and varying degrees of arteriolonephrosclerosis and hyalinosis identical to the diabetes-associated Kimmelstiel-Wilson lesions. No electron-dense or organized deposits are seen on EM. The GBM and tubular basement membrane may "stain" with IgG and albumin on IF. Neovascularization can be seen within the nodules.

The prognosis is poor and relates to the persistence of nephrotic-range proteinuria. Most patients with idiopathic nodular glomerulosclerosis will progress to ESRD, sometimes quite rapidly. The 50% renal survival point in those who continue to smoke heavily is about 1 year after diagnosis. There is no known effective therapy, other than angiotensin inhibition to reduce the proteinuria. Stopping smoking may be beneficial and should be urged for all patients with this diagnosis.

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CHAPTER 29

Thrombotic Microangiopathies, Including Hemolytic Uremic Syndrome

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DEFINITIONS

Thrombotic microangiopathy (TMA) is a lesion of arteriolar and capillary vessel wall thickening with intraluminal platelet thrombosis and a partial or complete obstruction of the vessel lumina. Laboratory features of thrombocytopenia and microangiopathic hemolytic anemia are almost invariably present in patients with TMA lesions and reflect the consumption and disruption of platelets and erythrocytes in the microvasculature. Depending on whether renal or brain lesions prevail, two pathologically indistinguishable but somehow clinically different entities have been described: the hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). Because HUS can involve extrarenal manifestations and TTP may be associated with severe renal disease, the two can be difficult to distinguish on clinical grounds only.[1] Newly identified pathophysiologic mechanisms, however, have allowed for the differentiation of the two syndromes on a molecular basis (Table 29-1). These new data also show, that, for example, pregnancy-associated HUS is genetically determined (Table 29-1) with pregnancy or transplantation acting as a trigger of TMA in a genetically predisposed individual.

The term *hemolytic uremic syndrome* was introduced in 1955 by Gasser and coworkers[2] in their description of an acute fatal syndrome in children characterized by hemolytic anemia, thrombocytopenia, and severe renal failure. HUS occurs most frequently in children younger than 5 years, in whom the incidence is 5 to 6 children per 100,000 children population per year, compared with an overall incidence of 0.5 to 1/100,000/yr. Most cases (>90% of pediatric cases) are associated with infection by Shiga-like toxin (Stx)–producing *Escherichia coli* (STEC). STEC-HUS occurs primarily in children, except in epidemics, when it may occur in patients with a wider age range. For example, from May to July 2011, several European countries, particularly northern Germany, experienced one of the largest STEC-HUS outbreaks ever reported, with 3816 patients who had *E. coli* O104:H4 infection, with 845 cases. Almost 90% of affected patients were adults and, compared to previous STEC epidemics, there was a higher prevalence of affected young and middle-aged women.[3] *Streptococcus pneumoniae* causes a distinctive form of HUS, accounting for 40% of cases not associated with Stx-producing bacteria.[4]

Approximately 10% of HUS cases are classified as "atypical," caused neither by Stx-producing bacteria (STEC or *Shigella dysenteriae*) nor by *Streptococcus*.[5] Atypical HUS is significantly less common than STEC-HUS, with an incidence of 0.5 to 2 per 1 million population per year.[4] It occurs at any age. Patients with atypical HUS have a poor outcome; 50% progress to end-stage renal disease (ESRD), and 25% may die in the acute phase.[4,6] Neurologic symptoms and fever can occur in 30% of patients. Pulmonary, cardiac, and gastrointestinal manifestations can also occur.[4,6]

Thrombotic thrombocytopenic purpura was first described in 1925 by Moschcowitz[7] in a 16-year-old female patient with a fulminant febrile attack, hemolytic anemia, bleeding, renal failure, and neurologic involvement. Pathologic changes were characterized by widespread hyaline thrombosis of small vessels. TTP is a rare disease, with an incidence of approximately 2 to 4 cases per 1 million persons per year. TTP can affect any age group. TTP classically presents with the pentad of thrombocytopenia, microangiopathic hemolytic anemia, fever, and neurologic and renal dysfunction.[7] Neurologic symptoms can be seen in more than 90% of patients over the course of the disease. Central nervous system (CNS) involvement mainly represents thrombo-occlusive disease of the gray matter, but can also include headache, cranial nerve palsies, confusion, stupor, and coma. Up to half of patients who present with neurologic involvement may be left with sequelae. Chronic kidney disease (CKD) may occur. One group has reported 25% of patients with creatinine clearance less than 40 ml/min receiving long-term follow-up. Cardiac involvement may be common in TTP patients.[8]

LABORATORY SIGNS

Laboratory features of thrombocytopenia and microangiopathic hemolytic anemia are almost invariably present in patients with TMA lesions and reflect consumption and disruption of platelets and erythrocytes in the microvasculature.[5] Hemoglobin levels are low, less than 10 g/dl in more than 90% of patients. Reticulocyte counts are uniformly elevated. The peripheral smear reveals increased schistocyte numbers, with polychromasia and often nucleated red blood cells (RBCs) (Fig. 29-1). Detection of fragmented erythrocytes is crucial to confirm the microangiopathic nature of the hemolytic anemia, provided that heart valvular disease and other anatomic arterial abnormalities that may cause erythrocyte fragmentation are excluded. Other indicators of intravascular hemolysis include elevated lactate dehydrogenase (LDH), increased indirect bilirubin, and low haptoglobin level.[5] The Coombs test is negative. Moderate leukocytosis may accompany the hemolytic anemia. Thrombocytopenia is uniformly present in HUS and TTP. It may be severe but is usually less so in patients with predominant renal involvement.[9] The presence of giant platelets in the peripheral smear or reduced platelet survival time (or both) is consistent with peripheral consumption. In children with STEC-HUS, the duration of thrombocytopenia is variable and does not correlate with the course of renal disease. Bone marrow biopsy specimens usually show erythroid hyperplasia and an increased number of megakaryocytes.

Classification of Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura

Clinical Presentation	Etiology
Hemolytic Uremic Syndrome	
Stx associated	Infections by Shiga toxin (Stx)–producing bacteria
Neuraminidase associated	Infections by *Streptococcus pneumoniae*
Atypical Hemolytic Uremic Syndrome	
Familial	Mutations: *CFH*, 40%-45%; *CFI*, 5%-10%; *C3*, 8%-10%; *MCP*, 7%-15%; *THBD*, 9%; *CFB*, 1%-2%
Sporadic	
Idiopathic	Mutations: *CFH*, 15%-20%; *CFI*, 3%-6%; *C3*, 4%-6%; *MCP*, 6%-10%; *THBD*, 2%; *CFB*, <1% Anti-CFH antibodies: 6%-10%
Pregnancy associated	Mutations: *CFH*, 40%-50%; *CFI*, 10%-20%; *MCP*, 10%; *C3*, 14%
HELLP syndrome	Mutations: *CFH*, 10%; *CFI*, 20%; *MCP*, 10%
Transplantation (*de novo* atypical HUS)	Mutations: *CFH*, 15%; *CFI*, 16%
Thrombotic Thrombocytopenic Purpura	
Congenital	Homozygous or compound heterozygous mutations in *ADAMTS13* gene
Idiopathic	Anti-ADAMTS13 autoantibodies
Secondary	
Ticlopidine, clopidogrel	Anti-ADAMTS13 autoantibodies (ticlopidine, 80%-90%, clopidogrel, 30%)
HSC transplantation	Unknown; rarely, low ADAMTS13 levels
Malignancies	Unknown; rarely, low ADAMTS13 levels
HIV	HIV; rarely, low ADAMTS13 levels
SLE, APS, and other autoimmune disease	Depends on the specific primary disease

Table 29-1 Classification of hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) according to clinical presentation and underlying etiology. *HELLP,* Hemolytic anemia, elevated liver enzymes, and low platelet count; *HSC,* hematopoietic stem cell; *SLE,* systemic lupus erythematosus; *APS,* antiphospholipid syndrome. For all other abbreviations, refer to Table 29-3.

Prothrombin time, partial thromboplastin time, fibrinogen level, and coagulation factors are normal, thus differentiating HUS and TTP from disseminated intravascular coagulation (DIC). Mild fibrinolysis with minimal elevation in fibrin degradation products, however, may be observed. Evidence of renal involvement is present in all patients with HUS (by definition) and in about 25% of patients with TTP.[1,10] Microscopic hematuria and subnephrotic proteinuria are the most consistent findings. STEC-HUS in 90% of patients is preceded by diarrhea, often bloody.

PATHOLOGY

The diagnostic histologic lesions of TMA consist of widening of the subendothelial space and microvascular thrombosis. Electron microscopy best identifies the characteristic lesions of swelling and detachment of the endothelial cells from the glomerular basement membrane and the accumulation of fluffy material in the subendothelium, intraluminal platelet thrombi, and partial or complete obstruction of vessel lumina[11] (Figs. 29-2 and 29-3). These lesions

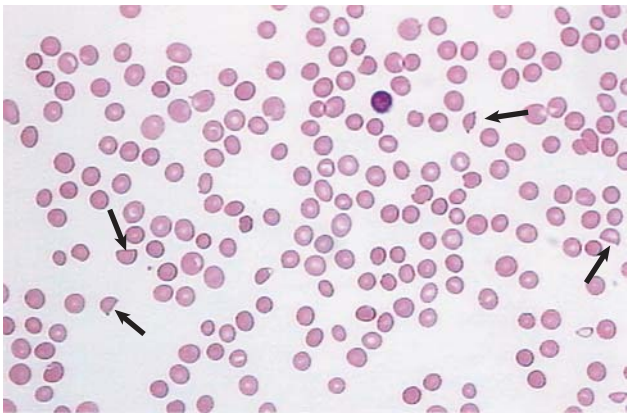

Figure 29-1 Peripheral blood smear from patient with hemolytic uremic syndrome. The presence of fragmented red blood cells with the appearance of a helmet *(arrows)* is pathognomonic for microangiopathic hemolysis in patients with no evidence of heart valvular disease.

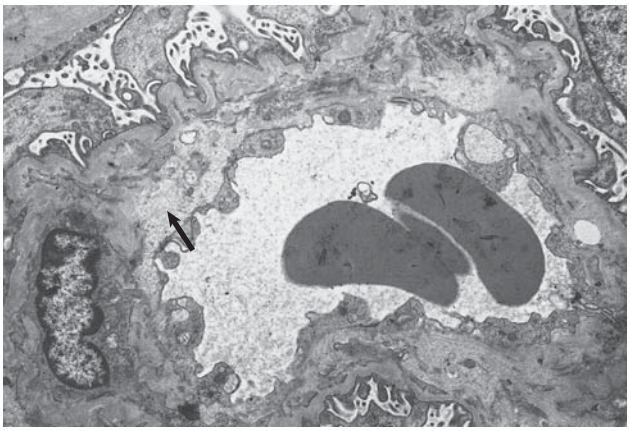

Figure 29-2 Electron micrograph of glomerular capillary in hemolytic uremic syndrome. The endothelium is detached from the glomerular basement membrane (GBM); the subendothelial space is widened and occupied by electron-lucent fluffy material and cell debris *(arrow).* Beneath the endothelium is a thin layer of newly formed GBM.

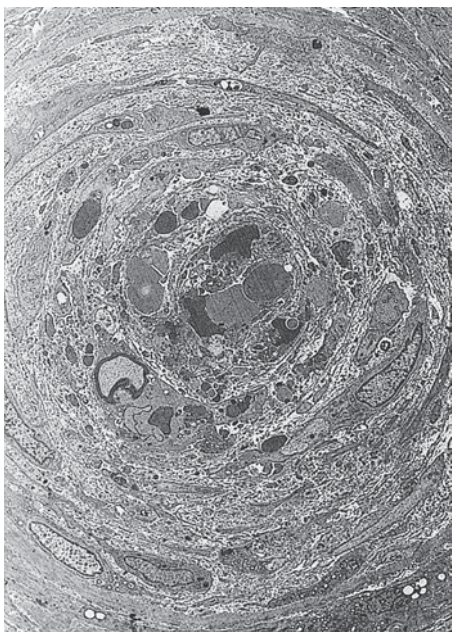

Figure 29-3 Electron micrograph of renal arteriole in hemolytic uremic syndrome. The vascular lumen is completely occluded by thrombi. There is marked intimal edema with consequent separation of myointimal cells.

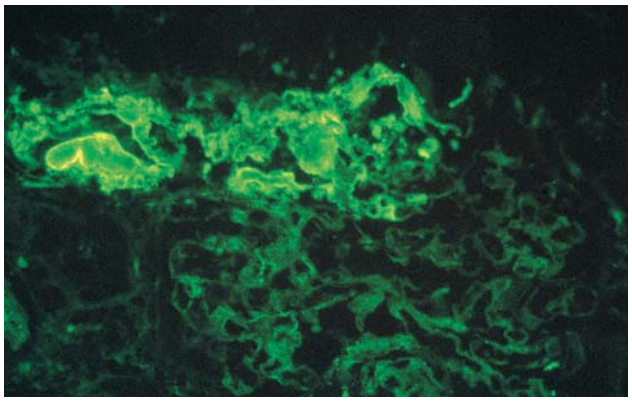

Figure 29-4 Glomerulus with its vascular pole from patient with STEC-associated hemolytic uremic syndrome. Strong staining with immunofluorescence-labeled antifibrinogen antibody occurs in the glomerulus and in the arteriolar wall. *STEC,* Shiga toxin-producing *E. coli*.

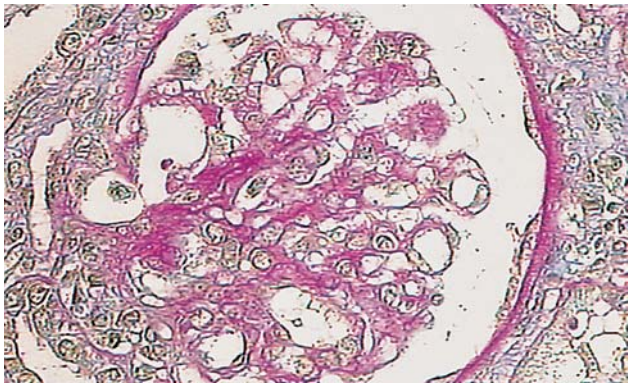

Figure 29-5 Glomerulus from patient with STEC-associated hemolytic uremic syndrome. Marked thickening of the glomerular capillary wall occurs, with many double contours. *STEC,* Shiga toxin-producing *E. coli*.

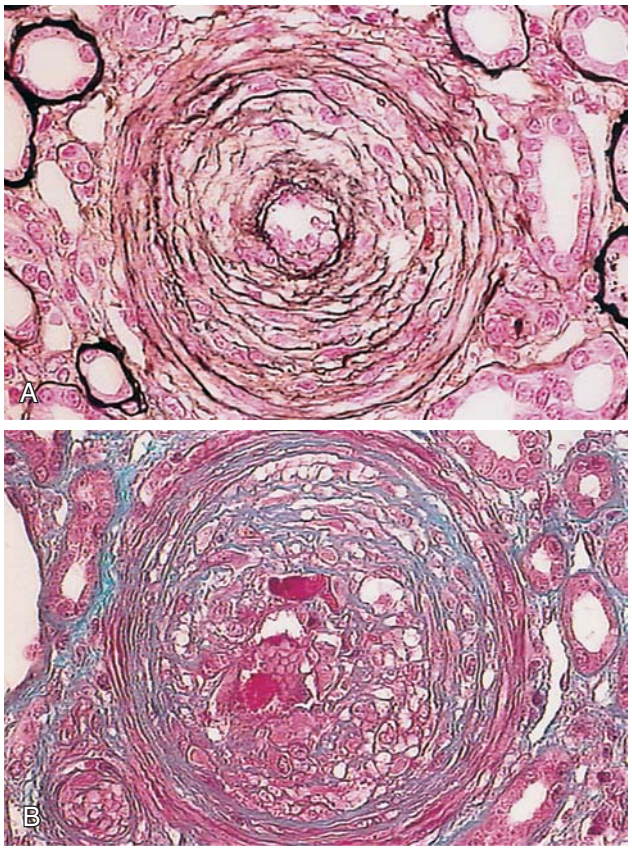

Figure 29-6 Interlobular artery in hemolytic uremic syndrome with severe vascular involvement. A, The vascular lumen is almost completely occluded. Changes include myointimal proliferation and reduplication of the lamina elastica. **B,** Thrombotic material and erythrocytes can be seen in the lumen and within the vascular wall.

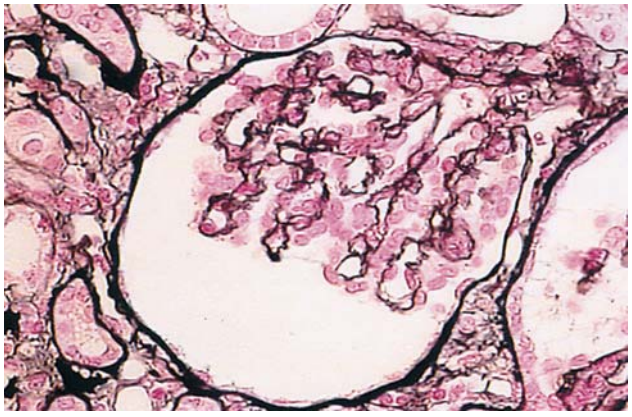

Figure 29-7 Glomerulus from patient with atypical hemolytic uremic syndrome with predominant vascular involvement. Severe ischemic changes have occurred. Note the shrinkage of the glomerular tuft and marked thickening and wrinkling of the capillary wall.

are similar to those seen in other renal diseases, such as scleroderma, malignant nephrosclerosis, chronic transplant rejection, and calcineurin inhibitor nephrotoxicity. In HUS, microthrombi are present primarily in the kidneys; in TTP, they mainly involve the brain. In pediatric patients, particularly those younger than 2, and in those with STEC-HUS, the glomerular injury is predominant[11] (Figs. 29-4 and 29-5). Thrombi and infiltration by leukocytes are common in the early phases of HUS and usually resolve after 2 to 3 weeks. Patchy cortical necrosis may be present in severe cases; crescent formation is uncommon. In idiopathic and familial forms and in adults, the injury mostly involves arteries and arterioles, with thrombosis and intimal thickening (Fig. 29-6; see also Fig. 29-3), and secondary glomerular ischemia and retraction of the glomerular tuft (Fig. 29-7). Focal segmental glomerulosclerosis may be a long-term sequela of acute cases of HUS and is usually seen in children with long-lasting hypertension and progressive deterioration in renal function.

The typical pathologic changes of TTP are the thrombi that occlude capillaries and arterioles in many organs and tissues. These thrombi consist of fibrin and platelets, and their distribution is widespread. Thrombi are most frequently detected in kidneys, pancreas, heart, adrenals, and brain. Compared with HUS, pathologic changes of TTP are more extensively distributed, probably reflecting the more systemic nature of the disease.

MECHANISMS, CLINICAL FEATURES, AND MANAGEMENT OF SPECIFIC FORMS OF THROMBOTIC MICROANGIOPATHY

Shiga Toxin–Producing *Escherichia coli*–Associated Hemolytic Uremic Syndrome

Mechanisms

Shiga toxin–producing *E. coli*–associated HUS may follow gastrointestinal (GI) infection by certain strains of *E. coli or S. dysenteriae*

that produce powerful exotoxins (Shiga toxins, Stx).[12] Most patients present with bloody diarrhea that may still be active or that may resolve at presentation of HUS. Several strains of *E. coli* were found to produce Stx (STEC), mostly the serotype O157:H7, but also other serotypes, such as O111:H8, O103:H2, O123, O26, O145, and the O104:H4 strain of the recent German outbreak,[3] isolated from patients with diarrhea. After food (beef, vegetables, fruit) or water contaminated by STEC or *S. dysenteriae* is ingested, the toxin is released into the gut and may cause watery or most often bloody diarrhea because of a direct effect on the intestinal mucosa. Stx-producing *E. coli* closely adhere to the epithelial cells of the GI mucosa, causing destruction of brush border villi. Shiga toxins are transported to the intracellular space of polarized GI cells via transcellular pathways and then translocated into the circulation. Circulating human blood cells (e.g., erythrocytes, platelets, monocytes) express Stx receptors on their surface and could serve as Stx carriers from the intestine to the kidney and other target organs.

In the kidney, Shiga toxins bind mainly to glomerular endothelial cells, but also to podocytes, mesangial cells, and proximal tubules. After binding to cell receptors, the toxin is internalized in the cytosol within 2 hours and inhibits protein synthesis. Treatment of endothelial cells with sublethal doses of Stx, exerting minimal influence on protein synthesis, leads to increased messenger RNA levels and protein expression of chemokines and cell adhesion molecules. By altering endothelial cell adhesion properties and metabolism, Shiga toxins favor leukocyte-dependent inflammation and induce loss of thromboresistance in endothelial cells, leading to microvascular thrombosis.[13]

Evidence is also emerging that complement activation at the renal endothelial level may contribute to microangiopathic lesions in STEC-HUS. High plasma levels of complement activation products Bb and C5b-9 were measured in children with STEC-HUS, indicating complement activation by the alternative pathway. Stx induced the expression of P-selectin on cultured human microvascular endothelial cell, and P-selectin bound and activated C3 via the alternative pathway, leading to thrombus formation under flow conditions.[14] In a murine model of HUS induced by Stx/lipopolysaccharide (LPS), factor B–deficient mice, which cannot activate the alternative pathway of complement, exhibited less thrombocytopenia and were protected against glomerular abnormalities and renal function impairment.[14]

In vitro, tubular epithelial and mesangial cells are as susceptible to the cytotoxic effects of Shiga toxins as endothelial cells. The tubular damage caused by Stx can lead to a reduction in the renal water-handling capacity. The toxins inhibit water absorption across human renal tubular epithelial cell monolayers, which may contribute to the early events in the pathogenesis of renal dysfunction in STEC-HUS.

Diagnosis

Diagnosis depends on the detection of *E. coli* O157:H7 and other STEC and their products in stool cultures. When infection with STEC is suspected, physicians should ensure that stool specimens are collected promptly and specifically cultured for STEC.[12] Unlike most other *E. coli*, serotype O157:H7 does not ferment sorbitol rapidly and thus forms colorless colonies on sorbitol-containing MacConkey agar (SMAC). The use of SMAC provides a simple, inexpensive, and generally reliable method of screening stools for *E. coli* O157. Suspect colonies can be assayed for the O157 antigen with commercially available antiserum or latex agglutination kits. The use of tests that identify Shiga toxins or the genes encoding them (by polymerase chain reaction) is helpful for diagnosis. Convalescent-phase serum samples can be assayed for antibodies to O157 or other specific strain-derived LPS. However, results may be biased by false-positives caused by antibodies preformed during antecedent STEC exposure.[12]

E. coli O157:H7 and other STEC have been responsible for multiple outbreaks throughout the world, becoming a public health problem in both developed and developing countries.[12] Contaminated undercooked ground beef, meat patties, raw vegetables, fruit, milk, and recreational or drinking water have all been implicated in the transmission of STEC; healthy cattle are a major reservoir for human infection. The large 2011 outbreak of HUS in Germany was caused by ingestion of sprouts contaminated by an unusual STEC strain O104:H4. The chain of transmission appeared to have started in Egypt with fecal contamination of fenugreek seeds by either humans or farm animals. The higher prevalence of women in this outbreak may reflect a gender-specific dietary preference.[3]

Clinical Course

After exposure to STEC, 38% to 61% of individuals develop hemorrhagic colitis, and 3% to 9% (in sporadic infections) to 20% (in epidemic forms) progress to overt HUS[12] (Fig. 29-8). STEC-induced hemorrhagic colitis not complicated by HUS is self-limiting and is not associated with an increased long-term risk of high blood pressure or renal dysfunction. STEC-HUS is characterized by prodromal diarrhea followed by acute kidney injury (AKI). The average interval between *E. coli* exposure and illness is 3 days. Illness typically begins with abdominal cramps and nonbloody diarrhea; diarrhea may become hemorrhagic in 70% of patients, usually within 1 or 2 days.[12] Vomiting occurs in 30% to 60% and fever in 30%. Leukocyte count is usually elevated. HUS is usually diagnosed 6 to 10 days after onset of diarrhea. In patients who develop HUS, 70% require RBC transfusions, and 40% to 50% need dialysis for an average 10 days, whereas the remainder have milder renal involvement without the need for dialysis.[12,15] About 25% of STEC-HUS patients have neurologic involvement, including lethargy, apnea, cortical blindness, hemiparesis, stroke, seizures, and coma. Rare complications include pancreatitis, diabetes mellitus, and pleural or pericardial effusions. From 1% to 2% of patients die during the acute phase of STEC-HUS. More than 90% of children with STEC-HUS fully recover from the acute disease. However, a meta-analysis of 49 published studies (3476

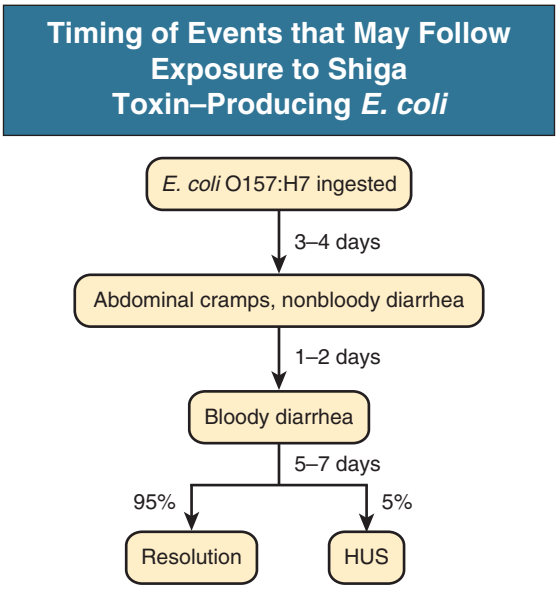

Figure 29-8 Timing of events that may follow exposure to Shiga toxin–producing *E. coli*. *HUS,* Hemolytic uremic syndrome.

patients, including children and adults, mean follow-up of 4.4 years) describing the long-term prognosis of patients who survived an episode of STEC-HUS reported death or permanent ESRD in 12% and glomerular filtration rate (GFR) less than 80 ml/min/1.73 m^2 in 25% of patients.[15]

Disease presentation and outcome were particularly severe during the STEC O104:H4 German outbreak, in which 53 of the 855 patients with HUS died.[3] Compared with previous STEC epidemics, there was a higher incidence of dialysis-dependent AKI patients (20% vs. 6%) and mortality (6% vs. 1%).[3] Almost half the patients presented with neurologic symptoms, and 20% had seizures. The severe clinical phenotype was explained by the lack of previous immunity to this novel STEC strain and its exceptional virulence. *E. coli* O104:H4 not only produces the same Stx as STEC enterohemorrhagic strains, but also has 93% of the genomic sequence of enteroaggregative *E. coli* strains that form fimbriae, which facilitate adhesion to the intestinal wall. The evolution of *E. coli* O104:H4 is likely the result of the acquisition by an enteroaggregative strain of *E. coli* of a Stx-encoding phage from a Stx-producing enterohemorrhagic strain of *E. coli*. The combination of these two virulence factors would lead to increased gut colonization and thus the release of increased quantities of toxin into the circulation. Moreover, whereas enterohemorrhagic *E. coli* bacteria are found in the GI tract of ruminants, enteroaggregative *E. coli* appear to have their reservoir in humans. This might explain why *E. coli* O104:H4 strain has acquired new resistances to the most common antibiotics used in human disease.

Therapy

Typical pediatric STEC-HUS treatment relies on supportive management of anemia, renal failure, hypertension, and electrolyte and water imbalance. Initiating intravenous isotonic volume expansion as soon as an *E. coli* O157:H7 infection is suspected, that is, within the first 4 days of illness, even before culture results are available, may limit the severity of AKI and the need for renal replacement therapy.[16] Up to 80% of patients receive packed RBCs for symptomatic anemia. Patients with severe STEC-HUS require careful monitoring, including urine output, weight, volume status, cardiovascular/respiratory function, and early signs of CNS or other organ involvement. Bowel rest is important for the enterohemorrhagic colitis associated with STEC-HUS. Antimotility agents should be avoided because these may prolong the persistence of *E. coli* in the intestinal lumen, increasing patient exposure to its toxin. The use of antibiotics should be restricted to the very limited number of patients presenting with bacteremia. In children with gastroenteritis, antibiotics may increase the risk of HUS 17-fold;[17] possibly because antibiotic-induced injury to the bacterial membrane might favor the acute release of large amounts of preformed toxin. Alternatively, antibiotic therapy might give *E. coli* O157:H7 a selective advantage if these organisms are not as readily eliminated from the bowel as are the normal intestinal flora. Moreover, several antimicrobial drugs, particularly the quinolones, trimethoprim, and furazolidone, are potent inducers of Stx gene expression and may increase the level of toxin in the intestine. An interesting exception may be azithromycin; its use appeared to have some benefit on the duration of bacterial shedding in adult patients from the German O104:H4 epidemic.[18] In contrast to *E. coli*–associated HUS, hemorrhagic colitis and HUS caused by *Shigella* dysentery type 1 should be treated with antibiotics. Treatment shortens the duration of diarrhea, decreases the incidence of complications, and reduces the risk of transmission by shortening the duration of bacterial shedding.

Careful blood pressure control and renin-angiotensin system (RAS) blockade may be particularly beneficial in the long term for those patients who have CKD after an episode of STEC-HUS. Thus, 8 to 15 years of treatment with angiotensin-converting enzyme (ACE) inhibitors after severe STEC-HUS normalized blood pressure, reduced proteinuria, and improved GFR.[19]

Among newer treatments for Stx-HUS, Stx-neutralizing monoclonal antibodies are the most advanced, including dual antibodies against Stx 1 and 2 (SHIGATEC) given at the time of GI infection; results of a completed Phase 2 clinical trial are forthcoming. Peptides impairing the ability of enterohemorrhagic *E. coli* to survive under the acidic conditions of the gastric system could halt the disease process at even earlier stages by preventing bacterial intrusion into the gut. Heparin and antithrombotic agents may increase the risk of bleeding and should be avoided.

The efficacy of specific treatments in adult patients is difficult to evaluate because most information is derived from uncontrolled series that also may include atypical HUS cases. In particular, no prospective, randomized controlled trials (RCTs) are available to establish definitely whether plasma infusion or exchange offers specific benefit compared with supportive treatment alone (Table 29-2). However, comparative analyses of two large series of patients treated[20] or not treated[21] with plasma suggest that plasma therapy may dramatically decrease overall mortality of STEC O157:H7–associated HUS. Plasma infusion or exchange should therefore be considered in adult patients with severe AKI and CNS involvement.

Kidney transplantation is effective and safe for children who progress to ESRD. Recurrence rates range from 0% to 10% (due to potential coincident genetic complement abnormalities), and graft survival at 10 years is even better than in control children with other diseases.

Evidence that uncontrolled complement activation may contribute to microangiopathic lesions of STEC-HUS[14] led to complement inhibitor therapy in three children with severe STEC-HUS who fully recovered with the humanized anti-C5 monoclonal antibody eculizumab.[22] Eculizumab therapy in HUS patients of the STEC O104:H4 outbreak in Germany showed no significant difference in outcome between patients who received eculizumab together with plasma exchange and those who received plasma exchange alone[23] (Table 29-2). However, these data are retrospectively collected. Moreover, patients given eculizumab also had the most severe disease. Whether eculizumab is a useful adjunct to treating the most severe forms of STEC-HUS needs to be clarified by prospective RCTs.

Neuraminidase-Associated Hemolytic Uremic Syndrome

Mechanisms

Neuraminidase-associated HUS is a rare but potentially fatal disease that may complicate pneumonia, or less frequently, meningitis caused by *S. pneumoniae*[24] (see Table 29-1). Neuraminidase produced by *S. pneumoniae* cleaves *N*-acetylneuraminic acid from the glycoproteins on the cell membrane of erythrocytes, platelets, and glomerular cells. This exposes the normally hidden Thomsen-Friedenreich antigen (T antigen), which can then react with anti-T IgM antibody naturally present in human plasma. This antigen-antibody reaction occurs more frequently in infants and children and causes polyagglutination of RBCs *in vitro*. Therefore, unlike in other forms of HUS, in neuraminidase-associated HUS there is a positive Coombs test.

Clinical Course and Therapy

Patients with neuraminidase HUS are usually less than 2 years old and present with severe microangiopathic hemolytic anemia. The clinical picture is severe, with respiratory distress, neurologic involvement, and coma. The acute mortality is about 25%. The outcome

Specific Therapies Used in HUS and TTP: Dosing and Efficacy		
Therapy	**Dosing**	**Efficacy**
Immunosuppressive Agents		
Prednisone	200 mg tapered to 60 mg/day, then 5 mg reduction per week	Probably effective in addition to plasma exchange in patients with TTP and anti-ADAMST13 autoantibodies or in aHUS with anti–factor H autoantibodies and in forms associated with autoimmune diseases Lack of evidence from controlled trials in immune-mediated HUS or TTP
Prednisolone	200 mg tapered to 60 mg/day, then 5 mg reduction per week	
Immunoglobulins	400 mg/kg/day	
CD20 Cell-Depleting Agent		
Rituximab	375 mg/m^2/week, up to CD20 depletion	Effective in treatment or prevention of TTP associated with immune-mediated ADAMTS13 deficiency resistant to or relapsing after immunosuppressive therapy
Fresh-Frozen Plasma		
Exchange	1-2 plasma volumes/day	First-line therapy for aHUS and TTP Unproven efficacy in childhood STEC-HUS
Infusion	20-30 ml/kg, followed by 10-20 ml/kg/day	To be considered if plasma exchange not available
Cryosupernatant	See Exchange, Infusion	To replace whole plasma in the event of plasma resistance or sensitization
Solvent-detergent–treated plasma	See Exchange, Infusion	To limit risk of infections
Liver-Kidney Transplant		
		To prevent CFH-associated HUS recurrence post-transplant; about 30% mortality risk
Complement Inhibition		
Eculizumab	900 mg weekly for first 4 weeks 1200 mg every 14 days, thereafter	Reported efficacy in aHUS

Table 29-2 Dosing and effectiveness of specific therapies for patients with hemolytic uremic syndrome or thrombotic thrombocytopenic purpura. *aHUS,* Atypical hemolytic uremic syndrome; *STEC,* Shiga toxin–producing *E. coli.*

strongly depends on the effectiveness of antibiotic therapy. In theory, plasma infused or exchanged is contraindicated because adult plasma contains antibodies against the Thomsen-Friedenreich antigen, which may accelerate polyagglutination and hemolysis. Thus, patients should be treated only with antibiotics and washed RBCs. In some cases, however, plasma therapy, occasionally in combination with steroids, has been associated with recovery.

Atypical Hemolytic Uremic Syndrome

Atypical HUS (aHUS) includes a number of associations and presentations.[5] Atypical HUS is usually sporadic, and fewer than 20% of cases are familial. Although some are in siblings, suggesting autosomal recessive transmission, others occur across two to three generations, indicating an autosomal dominant mode. Incomplete penetrance of the disease in mutation carriers is a common feature, which confounds the interpretation of inheritance. Indeed, many individuals with sporadic cases of aHUS were found to have inherited the disease-associated genetic defect from an unaffected parent.

Various precipitants of aHUS have been described in complement gene mutation carriers, including nonenteric bacterial and viral infections,[5] immunotherapeutic agents (e.g., cyclosporine, tacrolimus), malignant hypertension, transplantation, and pregnancy.[5] *De novo* post-transplant HUS has been reported in patients receiving renal transplants or other organs, caused by calcineurin inhibitors (CNIs) or humoral rejection. HUS occurs in 5% to 10% of renal transplant patients who receive cyclosporine and approximately 1% of those given tacrolimus. In 20% of female patients, aHUS manifests during pregnancy, tending to occur at term or postpartum, within 3 months of delivery in most cases.[6] Pregnancy-associated increased concentrations of procoagulant factors, decreased fibrinolytic activity, and reduced expression of endothelial thrombomodulin may be predisposing factors. A severe form of pregnancy-associated TMA is the HELLP syndrome, in which microangiopathic hemolysis and liver injury accompany hypertension and renal dysfunction (see Chapter 44). About 50% of patients with sporadic aHUS show no clear trigger (idiopathic HUS) (see Table 29-1).

Mechanisms

Atypical HUS is linked to uncontrolled activation of the complement system[5] (Fig. 29-9). Reduced serum levels of C3 with normal C4 in aHUS patients were known since 1974. In cases of familial aHUS, serum C3 was low even during remission, suggesting genetic defects.[25] Low C3 reflected complement activation and consumption with high levels of activated products, C3b, C3c, and C3d (see Table 29-1).

The complement system is part of innate immunity and consists of several plasma and membrane-bound proteins protecting against invading organisms. Three activation pathways (classical, lectin, alternative) produce protease complexes, the C3 and C5 convertases, that cleave C3 and C5, respectively, eventually leading to the membrane attack complex (MAC, C5b-9) that causes cell lysis (Fig. 29-9). The alternative pathway is initiated spontaneously in plasma by C3 hydrolysis responsible for covalent deposition of a low amount of C3b onto practically all plasma-exposed surfaces (Fig. 29-10). On bacterial surfaces, C3b leads to opsonization for phagocytosis by neutrophils and macrophages. Without regulation, a small initiating stimulus is quickly amplified to a self-harming response until complement components are consumed. On host cells, such a dangerous cascade is controlled by membrane-anchored and fluid-phase regulators. Both favor the cleavage of C3b to inactive iC3b by the plasma serine-protease factor I (CFI, cofactor activity) and dissociate the

multicomponent C3 and C5 convertases (decay acceleration activity). Foreign targets and injured cells that either lack membrane-bound regulators or cannot bind soluble regulators are attacked by complement.

The C3 convertases of classic and lectin pathways are formed by C2 and C4 fragments, whereas the alternative pathway convertase requires cleavage of C3 only (Fig. 29-10). Thus, low serum C3 levels in aHUS with normal C4 indicate selective alternative pathway activation.[25]

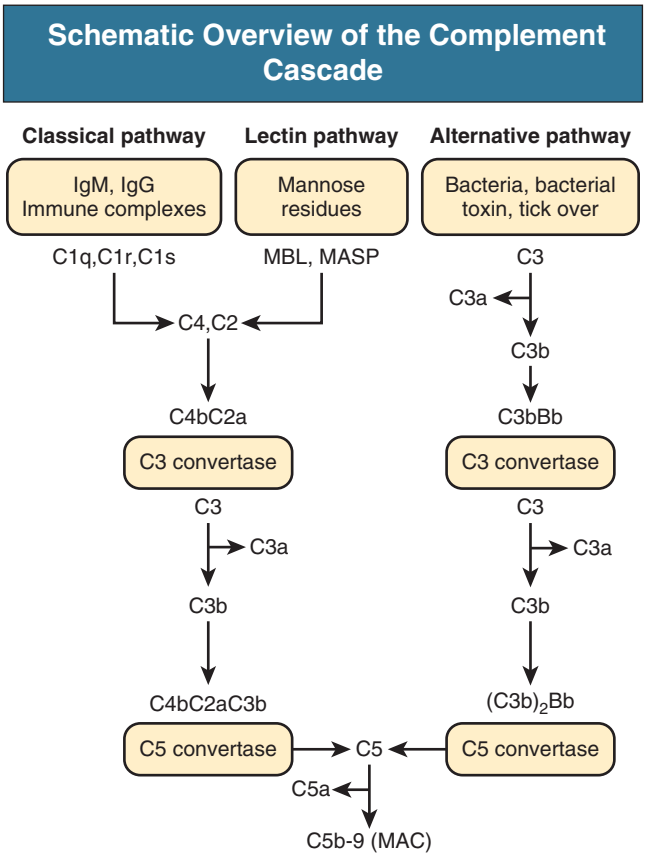

Figure 29-9 Schematic overview of complement cascade. The three activation pathways (classical, lectin, and alternative) and the membrane attack complex *(MAC)* are shown. *MBL,* Mannose-binding lectin; *MASP,* mannose-associated serine protease.

A variety of genetic abnormalities in members of the alternative pathway of complement have been described in aHUS, which account for about 60% of cases (see Table 29-1). Of note, different genetic abnormalities account for different patterns of dysfunction of the complement system with different outcome, response to therapy, and risk of recurrence after kidney transplantation (Table 29-3).

Complement Factor H Complement factor H (CFH) regulates the alternative pathway by competing with complement factor B (CFB) for C3b recognition, by acting as a cofactor for CFI, and by enhancing dissociation of C3 convertase (see Fig. 29-10). More than 100 *CFH* mutations have been identified in aHUS patients (mutation frequency ~30%)[26,27] (see http://www.FH-HUS.org). These mutations most often do not result in a quantitative deficiency in CFH, but instead result in normal levels of a protein that is unable to bind to and regulate complement on endothelial cells and platelets.[28] A high degree of sequence identity between *CFH* and the genes *CFHR1* to *CFHR5* for five factor H–related proteins (CFHR) located in tandem to *CFH* may predispose to nonallelic recombinations.[29] In 3% to 5% of patients with aHUS, a heterozygous hybrid gene deriving from an uneven crossover between *CFH* and *CFHR1* contained the first 21 *CFH* exons and the last two *CFHR1* exons,[29] resulting in a gene product with decreased complement regulatory activity on endothelial surfaces. Additional forms of CFH/CFHR hybrid genes have been recently described.

Acquired defects of CFH function are also seen in the form of inhibitory antibodies, reported in 5% to 10% of aHUS patients.[30] Analogous to the genetic defect seen in CFH, these autoantibodies also predominantly target the C-terminal end of the protein, thereby impairing complement regulation on host cell surfaces. The development of CFH autoantibodies in aHUS has a genetic predisposition, being strongly associated with a deletion of the *CFHR1* and *CFHR3* genes.

Membrane Cofactor Protein Membrane cofactor protein (MCP) is a transmembrane complement regulator widely expressed on the surface of all cells except erythrocytes. MCP serves as a cofactor for CFI to cleave C3b and C4b on cell surfaces (see Fig. 29-10). *MCP* mutations account for 10% to 15% of aHUS cases.[27,31,32] Most are heterozygous (see http://www.FH-HUS.org). The majority cluster in critical extracellular modules for regulation. Expression on blood

Outcome of Atypical Hemolytic Uremic Syndrome According to Associated Genetic Abnormality

Affected Gene	Affected Protein (Main Effect)	Frequency in aHUS (%)	Rate of Remission with Plasma Exchange* (%)	Mortality (5-10 yr) or ESRD (%)	Rate of Recurrence After Kidney Transplant (%)
CFH	Factor H (no binding to endothelium)	30	60 (dose and timing dependent)	70-80	60-70
CFHL1, CFHL3	Factor HR1, R3 (anti–factor H antibodies)	5-10	70-80 (combined with immunosuppression)	30-40	40
MCP	Membrane cofactor protein (no surface expression)	10-15	No indication to plasma exchange	<20	15-20
CFI	Factor I (low levels/low cofactor action)	4-10	30-40	60-70	70-80
CFB	Factor B (C3 convertase stabilization)	1-2	30	70	One case reported
C3	Complement C3 (resistance to C3b inactivation)	8-10	40-50	60	40-50
THBD	Thrombomodulin (reduced C3b inactivation)	4-5	60	60	One case reported

Table 29-3 Outcome of atypical hemolytic uremic syndrome (aHUS) according to the associated genetic abnormality. *Complete remission or hematologic remission with renal sequelae.

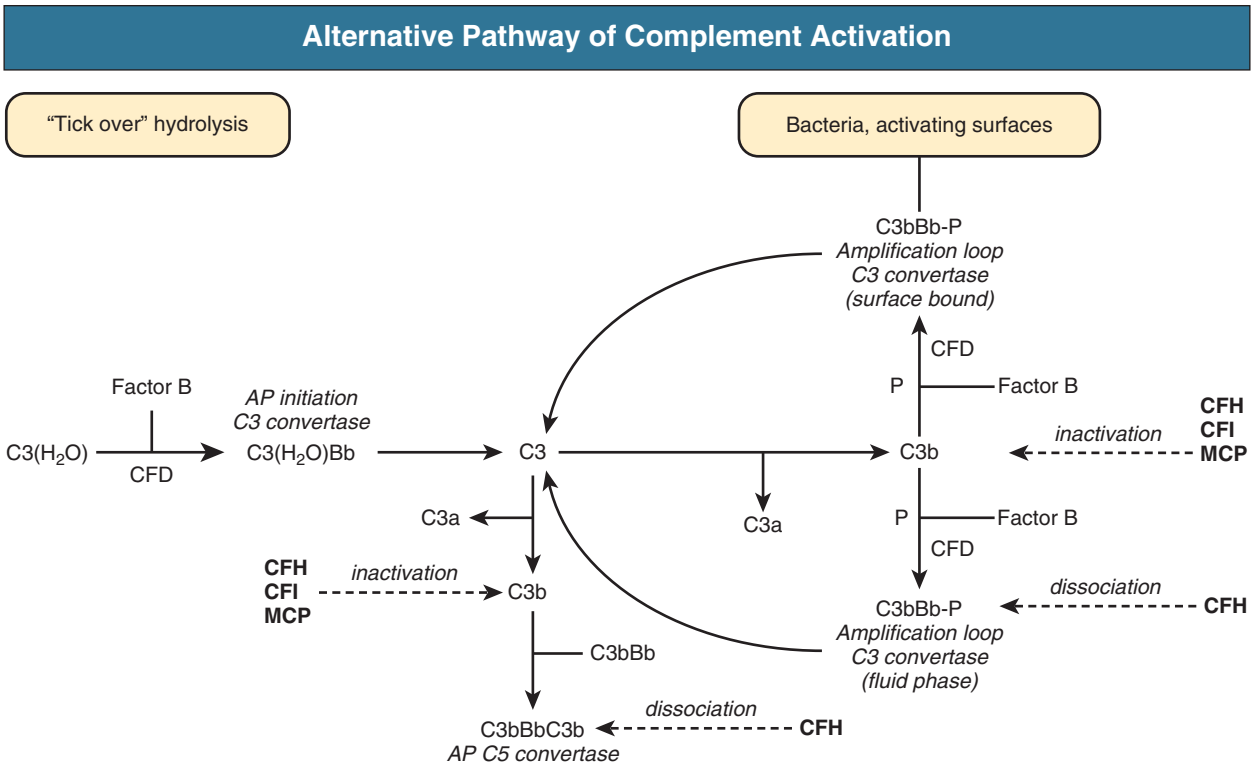

Figure 29-10 Alternative pathway of complement activation. The alternative pathway *(AP)* is continuously activated in plasma by low-grade hydrolysis of C3 (a process called tick over), which binds factor B to form a $C3(H_2O)B$ complex. Factor D *(CFD)* cleaves factor B to form the AP-initiating C3 convertase that cleaves C3 to C3b. The activation is then amplified by the covalent binding of a small amount of C3b to hydroxyl groups on cell surface carbohydrates and proteins of target cells (e.g., bacterial cells). This C3b binds factor B to form the amplification loop C3 convertase C3bBb. The binding of properdin *(P)* stabilizes this enzyme. C3 convertase enzymes cleave many molecules of C3, resulting in a positive-feedback amplification loop. C3b also binds to the C3 convertase, forming the C5 convertase enzyme $C3b_2Bb$. The AP is highly regulated to prevent nonspecific damage to host cells and limit the deposition of complement to the surface of pathogens. This fine regulation occurs through a number of membrane-anchored and fluid-phase regulators. *CFI,* Complement factor I (degrades C3b and C4b); *CFH,* complement factor H (acts as cofactor for factor I for C3b cleavage and favors decay of C3 convertase of AP); *MCP,* membrane cofactor protein (binds C3b and C4b and has cofactor activity for both classical and alternative pathways).

leukocytes was reduced for about 75% of mutants, causing quantitative defect. Others instead have low C3b-binding capability and decreased cofactor activity.[27]

Complement Factor I The plasma serine-protease CFI regulates the three complement pathways by cleaving C3b and C4b in the presence of cofactor proteins (see Figs. 29-9 and 29-10). *CFI* mutations affect 4% to 10% of aHUS patients.[27,33] All mutations are heterozygous, and 80% cluster in the serine-protease domain. Approximately 50% of mutations result in low CFI levels. Some mutants are secreted but have impaired proteolytic activity.[27,33]

Complement Factor B and C3 Gain-of-function mutations can affect genes encoding the alternative pathway C3 convertase components, CFB and C3.[34,35] *CFB* mutations are rare in aHUS (1% to 2%).[35] CFB mutants have excess C3b affinity and form a hyperactive C3 convertase resistant to dissociation.[35] About 10% of aHUS patients have heterozygous mutations in *C3,* usually with low C3 levels.[34] Most mutations reduce C3b binding to complement regulators, severely impairing degradation of mutant C3b.[34]

Thrombomodulin Heterozygous mutations in the gene *THBD* encoding thrombomodulin, a membrane-bound glycoprotein with anticoagulant properties that modulates complement activation on cell surfaces, have been found in 3% to 4% of patients with aHUS.[36] Cells expressing these variants inactivate C3b less efficiently than cells expressing wild-type thrombomodulin. These data document a functional link between complement and coagulation.

Diacylglycerol Kinase Epsilon Homozygous or compound heterozygous mutations in the diacylglycerol kinase ε *(DGKE)* gene cosegregated with aHUS in nine unrelated kindreds with autosomal recessive inheritance.[37] Mutation carriers presented with aHUS before age 1 year; had persistent hypertension, hematuria, and proteinuria; and developed CKD with age. *DGKE* is expressed in endothelium, platelets, and podocytes. *DGKE* is apparently unrelated to the complement cascade, and the mechanism by which *DGKE* mutations cause aHUS remains to be elucidated.

Determinants of Disease Penetrance Two other factors are thought to determine the development of aHUS. First, in most patients there is a *trigger;* infection and pregnancy are most often described.[38] Second, a further genetic variant *(modifier)* can increase the risk of developing the disease. This trigger can be in the form of either an additional mutation in one of the aforementioned genes or the presence of a common at-risk genetic variant. It is now recognized that about 10% of aHUS patients will have mutations in more than one gene.[39] Common at-risk genetic variants (single-nucleotide polymorphisms and haplotype blocks) in *CFH*, MCP and *CFHR1* have been shown to act as susceptibility factors for the development of HUS.[39]

Diagnosis and Screening

Differential diagnosis of aHUS is made on exclusion of infections by STEC or neuraminidase-producing *S. pneumoniae,* of ADAMTS13 deficiency, and systemic-associated diseases. Full analysis of disease-associated genes and screening for anti-CFH antibodies is recommended, in particular in the perspective of kidney transplantation for patients who progress to ESRD. Reference laboratories in several

countries are equipped for genetic and antibody screening. Although new sequencing techniques are reducing cost and timing, a complete screening still requires several days of work. Treatment of acute episodes (plasma exchange or eculizumab, if available and affordable; see later) should be started quickly after clinical diagnosis, without waiting for results of genetic and anti-CFH antibody tests.

Clinical Course

Regardless of mutation type, 60% of aHUS patients are affected during childhood,[27] and almost all patients with anti-CFH antibodies developed the disease before 16 years of age.[30] Acute episodes manifest with severe hemolytic anemia, thrombocytopenia, and AKI. Extrarenal involvement (CNS or multivisceral) occurs in 20% of patients.[5,27,38] Short-term and long-term outcomes vary according to the underlying complement abnormality (see Table 29-3). About 60% to 70% of patients with *CFH, CFI,* or *C3* mutations and 40% of children with anti-CFH autoantibodies lose renal function or die during the presenting episode, or they develop ESRD after relapse.[5,27] *CFB* mutations are associated with poor renal outcome (renal function loss in 7 of 8 patients).[35] Chronic complement dysregulation may lead to atheroma-like lesions with cardiovascular complications and excess mortality. In *MCP* mutation carriers, recurrences are common but long-term outcome is good; 80% of patients remain dialysis free.[5,27] However, rare patients with *MCP* mutations had severe disease, immediate ESRD, intractable hypertension, and coma, possibly because of concurrent genetic abnormalities.[39]

Therapy

Fresh-Frozen Plasma Guidelines suggest that plasma therapy (plasma exchange, 1 to 2 plasma volumes/day; plasma infusion, 20 to 30 ml/kg/day) should be started within 24 hours of diagnosis of aHUS.[5] Plasma exchange allows supplying larger amounts of plasma than would be possible with infusion while avoiding fluid overload (see Table 29-2). Trials of plasma therapy in HUS are scanty and not current. CFH is a plasma protein, so plasma infusion or exchange provides normal CFH to patients carrying *CFH* mutations[27,38] (see Table 29-3). Long-term treatment may fail, however, with development of plasma resistance.[40] Heterozygous *CFH* mutation carriers usually have normal levels of CFH, half of which is dysfunctional. The beneficial effect of plasma depends greatly on the amount, frequency, and modality of administration, with plasma exchange being superior to plasma infusion for remission and prevention of recurrences, by removal of mutant *CFH* that could antagonize the normal protein. Plasma exchange is used to remove anti-CFH antibodies,[30] but the effect is usually transient. Immunosuppressants (corticosteroids and azathioprine or mycophenolate mofetil) combined with plasma exchange allowed long-term dialysis-free survival in 60% to 70% of patients.[41] Data on the effect of rituximab, an anti-CD20 antibody, in such patients are scanty and inconsistent; of five patients treated with rituximab alone or with plasma exchange, only two showed disappearance of anti-CFH antibodies.[41] Thus, until better evidence is available, starting with plasma exchange plus steroids remains the treatment of choice for aHUS associated with anti-CFH antibodies.

Patients with *CFI* mutations show a partial response to plasma.[5,27,38] From 30% to 40% of patients with *CFB* mutations and 50% of those with *C3* mutations respond to plasma infusion or exchange.[5,34,35] These patients may need abundant and frequent plasma exchanges to clear the hyperfunctioning mutant *CFB* and *C3*.[5] Because MCP is a cell-associated protein, effects of plasma are unlikely in patients with *MCP* mutations. Indeed, 80% of patients with *MCP* mutation undergo remission independent of plasma treatment[5,27,38] (see Table 29-3).

Transplantation Disease recurs in 50% to 80% of transplanted patients with *CFH, CFI, CFB,* and *C3* mutations, and graft failure occurred in 80% to 90% (see Chapter 108).[34,35,42] Living related donation is contraindicated given the high risk of recurrence, and it may be risky to donors because uninephrectomy may precipitate aHUS in complement gene mutation carriers. For example, a male with a heterozygous *CFH* mutation developed *de novo* HUS after donating a kidney to his child. Most studies have shown that plasma exchange therapy fails to prevent graft loss in patients with recurrent post-transplant HUS.[42] A preemptive plasma infusion or exchange strategy has been successful in preventing recurrent aHUS in eight renal transplant recipients. In some of the patients, however, delayed recurrence occurred when plasma therapy was tapered.[43]

Simultaneous kidney and liver transplant was performed in two children with aHUS and *CFH* mutations, to correct the genetic complement abnormality defect.[44] However, both cases were complicated by premature liver failure. The first child recovered after a second liver transplantation. It was thought that the surgical stress with ischemia and reperfusion induced complement activation in a liver that could not be regulated because of functional CFH deficiency. A modified approach to the combined transplant was applied to eight patients,[45] including extensive plasma exchange before surgery to provide timely normal CFH until the liver graft recovered synthetic functions. This procedure was successful in seven patients. However, another child developed severe hepatic thrombosis and fatal encephalopathy. The risks of kidney and liver transplantation require a careful assessment of benefits for candidate patients.

The risk of post-transplant aHUS recurrence in patients with anti-CFH autoantibodies is not well known; available reports describe only 12 renal transplants in eight patients.[41] A reduction in autoantibody levels with plasma exchange, steroids, and rituximab enabled successful renal transplantation in few patients.[41]

The outcome of kidney transplant is favorable in patients with *MCP* mutations. About 80% did not experience HUS recurrence, with long-term graft survival comparable to patients transplanted for other causes.[5,38,42] MCP is a transmembrane protein highly expressed in kidney. Not surprisingly, a kidney graft corrects the defect of *MCP*-mutated recipients. However, about 20% of patients with *MCP* mutations also carry a mutation in another complement gene. Such patients have a worse graft outcome, with higher incidence of recurrences than patients with an isolated *MCP* mutation.[39]

Screening for mutations on all disease-associated genes should allow patients and clinicians to make informed decisions regarding listing for transplantation based on risk of recurrence.

Complement Inhibitors Identifying complement genetic abnormalities has paved the way for tailored treatments aimed at specifically downregulating complement activation. In particular, eculizumab will radically change short-term and long-term prognosis of aHUS. More than 35 aHUS patients treated with eculizumab have been reported in the literature thus far.[46] Some were treated for aHUS affecting the native kidneys; others received eculizumab to treat or to prevent post-transplant aHUS recurrence. Most patients treated during acute episodes achieved remission with eculizumab, including dramatic cases with severe neurologic involvement or with peripheral gangrene. The efficacy of eculizumab in aHUS has been definitely proved in two open-label controlled trials of adult and adolescent patients with plasma therapy–sensitive or plasma therapy–resistant aHUS[47,48] (see ClinicalTrials.gov Identifier: NCT1410916). Based on these results, in late 2011, eculizumab received approval for the treatment of atypical HUS in the United States and Europe.

Duration of eculizumab therapy and ideal treatment regimen remain to be established. Conceivably, lifetime treatment with

eculizumab at doses that can persistently block the complement cascade might be indicated to prevent disease recurrence in genetic forms. However, whether and to which extent this applies to all patients with aHUS and complement intrinsic abnormalities is unknown. Reasonably, different underlying genetic defects, different clinical courses before eculizumab therapy, and different residual complement activity while receiving eculizumab should be considered when planning strategies for long-term eculizumab therapy. Findings suggest that chronic treatment with regimens able to inhibit persistently the complement system may be required at least in some patients. On the other hand, the risk of sensitization associated with chronic drug exposure or with eculizumab deposition in tissues (see also Chapter 22), as well as the enormous costs in resource-limited settings, suggests that careful treatment, tapering up to withdrawal whenever possible, should be attempted in most aHUS patients under tight control of disease and complement activity.

Thrombotic Thrombocytopenic Purpura

In the microvasculature of patients with TTP, systemic platelet thrombi develop, mainly formed by platelets and von Willebrand factor (vWF). This protein plays a major role in primary hemostasis by forming platelet plugs at sites of vascular injury under high shear stress. The vWF is a large glycoprotein synthesized in vascular endothelial cells and megakaryocytes as a high-molecular-weight polymer.[49] Secretion of vWF occurs primarily through the Weibel-Palade bodies. Exocytosis of vWF from the storage granules may be swiftly increased by exposing endothelial cells to secretagogues such as histamine, thrombin, phorbolmyristate acetate, or calcium ionophores. On stimulation, vWF is secreted by endothelial cells as ultralarge (UL) multimers that form string-like structures attached to the endothelial cells, possibly through interaction with P-selectin. Under fluid shear stress, ULvWF strings are cleaved to generate the range of vWF multimer sizes that normally circulate in the blood.[50] The proteolytic cleavage of vWF multimers appears to be critical to prevent thrombosis in the microvasculature.

ADAMTS13 is the protease responsible for cleaving vWF, creating 140-kd and 176-kd fragments (Fig. 29-11). It derives primarily from the stellate cells of the liver. ADAMTS13 is also expressed, although at lower levels, in other types of cells, such as renal podocytes and tubular cells, vascular endothelial cells, and platelets. The plasma concentration of ADAMTS13 is approximately 1 µg/ml, or 5 nmol/L. The elimination half-life of ADAMTS13 is 1 to 2 days in the circulation.

Mechanisms

In the majority of patients with primary TTP, ADAMTS13 is deficient, leading to accumulation of ULvWF multimers that are highly reactive with platelets.[51,52] Exposure of ULvWF multimers and platelets to shear stress leads to platelet aggregation. The levels of shear stress necessary for inducing platelet aggregation is in the range found in normal arteriolar and capillary circulation. Therefore, vWF and platelets have a propensity to form aggregates in normal arterioles and capillaries that needs to be constantly regulated. By cleaving ULvWF multimers before they are activated by shear stress to cause platelet aggregation, ADAMTS13 prevents spontaneous microvascular thrombosis in the normal circulation (see Fig. 29-11). The platelet aggregation observed in patients with TTP and ADAMTS13 deficiency is thus a direct consequence of the accumulation of ULvWF multimers. Consequently, microvascular thrombi occur in almost all organ vessels, resulting in diffuse organ ischemia and thrombocytopenia secondary to platelet consumption. Microangiopathic

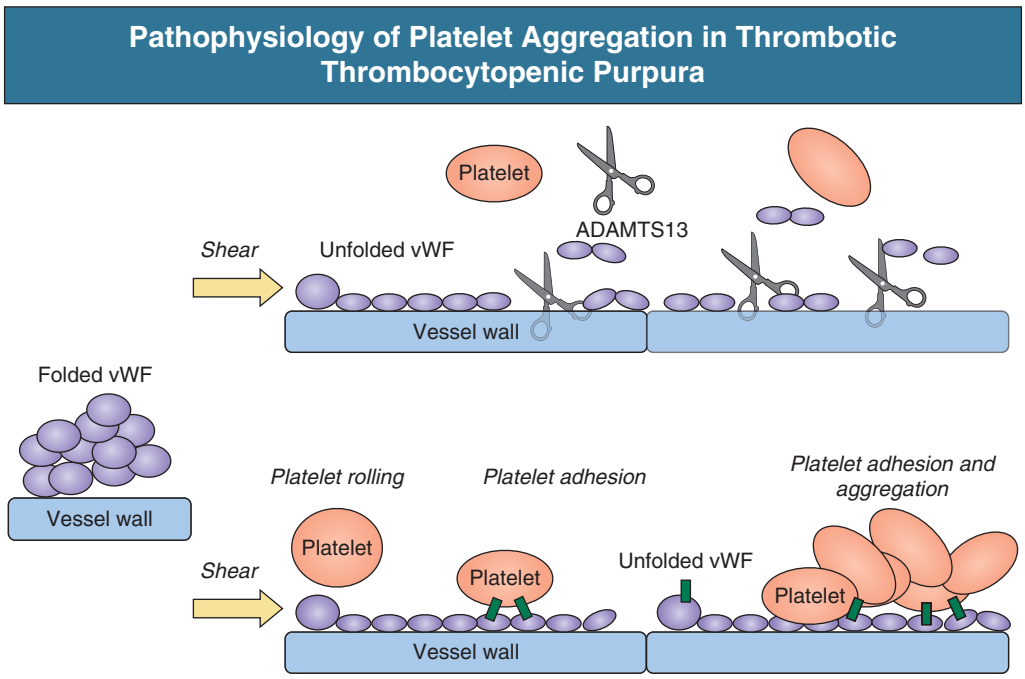

Figure 29-11 Pathophysiology of platelet aggregation in thrombotic thrombocytopenic purpura. Von Willebrand factor *(vWF)* is synthesized and stored as ultralarge (UL) multimers in endothelial cells and megakaryocytes. On stimulation, ULvWF multimers are secreted by endothelial cells into the circulation in a folded structure. On exposure to enhanced shear stress, UL multimers form string-like structures that adhere to endothelial cells. *Upper panel,* Normally, ULvWF strings are cleaved by ADAMTS13 to generate vWF multimers from 500 kDa to 20 million Da and prevent thrombosis in the microvasculature. *Lower panel,* When the ADAMTS13 proteolytic activity is defective because of the inhibitory effect of anti-ADAMTS13 autoantibodies or congenital defective synthesis of the protease, ULvWF multimers accumulate and interact with activated platelets to facilitate platelet adhesion and aggregation, with thrombi formation and occlusion of the vascular lumen.

hemolysis is caused by the passage of blood through the damaged capillaries and arterioles occluded by thrombi.

Two mechanisms for deficiency of the ADAMTS13 activity have been identified in patients with primary TTP: an acquired deficiency, caused by formation of anti-ADAMTS13 autoantibodies (acquired TTP), and a genetic deficiency, caused by homozygous or compound heterozygous mutations in *ADAMTS13* (congenital TTP) (see Table 29-1).

Associated with Immune-Mediated Deficiency of ADAMTS13 This acquired form of TTP accounts for the majority of acute primary cases (60% to 90%). The disease is characterized by severe deficiency of ADAMTS13,[52] the activity of which is inhibited by specific autoantibodies that develop transiently and tend to disappear during remission.[52] Patients with TTP secondary to hematopoietic stem cell transplantation, malignancies, or human immunodeficiency virus (HIV) infection rarely have severe ADAMTS13 deficiency and inhibitory IgG antibodies.[53] Severe ADAMTS13 deficiency and ADAMTS13 inhibitory antibodies were detected in 80% to 90% of patients with ticlopidine-associated TTP and in a few patients with clopidogrel-induced TTP. The deficiency resolved after the drugs were discontinued. ADAMTS13 inhibitors have not been described in other drug-associated TTP. TTP diagnosed during pregnancy accounts for about 7% of all TTP cases. The majority of these women have acquired ADAMTS13 deficiency, but pregnancy has also been reported as a triggering event in patients with genetic ADAMTS13 deficiency, as discussed later.

The pathogenicity of TTP-associated anti-ADAMTS13 autoantibodies is evidenced by their usual disappearance from the circulation when remission is achieved after effective treatment, which occurs in parallel with normalization of ADAMTS13 activity.

Associated with Congenital Deficiency of ADAMTS13 This rare inherited form of TTP is associated with a genetic defect of *ADAMTS13* and accounts for about 5% of all of cases of TTP (see Table 29-1). TTP associated with congenital ADAMTS13 deficiency can present both with and without a family history of the disease.[51,54] In both cases the disease is inherited as a recessive trait. To date, more than 120 *ADAMTS13* mutations have been identified in patients with TTP.[55] Studies on secretion and activity of the mutated forms showed that most led to impaired secretion of the protease from the cells, and when the mutated protein is secreted, the proteolytic activity is greatly reduced.

Most patients are carriers of compound heterozygous mutations; only 20% of mutations have been observed in homozygous form.

Clinical Course

Compared with patients who have nonsevere ADAMTS13 deficiency, severely deficient patients experience higher rates of therapy-induced remissions (82% to 88% vs. 20% to 75%) and lower mortality (8% to 18% vs. 18% to 80%).[53,56] The high mortality in non–severely deficient patients may be caused by the higher proportion of secondary causes and death from underlying diseases, such as patients with hematologic malignancies.

Among patients who have a severe ADAMTS13 deficiency, patients with inhibitory antibodies experience a more severe manifestation of the disease, take substantially longer time to achieve clinical remission, and require a higher plasma volume than patients with congenital ADAMTS13 deficiency. In patients with inhibitory antibodies, risk as high as 50% to develop relapses has been reported, and undetectable ADAMTS13 activity and persistence of anti-ADAMTS13 inhibitors during remission predict recurrences.

Thrombotic thrombocytopenic purpura has been reported in one of every 1600 to 5000 patients treated with ticlopidine, with 11 cases reported during clopidogrel therapy. The overall survival rate is 67% and is improved by early treatment withdrawal and plasma therapy.

Approximately 60% of patients with congenital deficiency of ADAMTS13 experience their first acute episode of disease in the neonatal period or during infancy, but a second group (10% to 20%) manifests the disease after the third decade of life. TTP recurrences occur in 80% of patients,[55] but their frequency varies widely. Whereas some patients with congenital ADAMTS13 deficiency depend on frequent chronic plasma infusions to prevent recurrences, others who achieved clinical remission after plasma treatment remain disease free for long periods after plasma discontinuation. The type and location of *ADAMTS13* mutations may influence the age of onset of TTP and the penetrance of the disease in mutation carriers. Patients carrying mutations associated with some residual ADAMTS13 activity in blood had a longer disease-free survival compared with patients with completely absent protease activity.[57]

Environmental factors may contribute to induce full-blown manifestation of the disease. According to this "two-hit model," deficiency of ADAMTS13 predisposes to microvascular thrombosis, and thrombotic microangiopathy supervenes after a triggering event that activates microvascular endothelial cells and causes the secretion of ULvWF multimers and P-selectin expression. Again, potential triggers of these phenomena are infections and pregnancy.

Therapy

Plasma is the cornerstone of therapy in an acute episode in TTP patients because it replaces defective protease activity. In patients with anti-ADAMTS13 antibodies and compared with infusion, plasma exchange may offer the advantage of also rapidly removing anti-ADAMTS13 antibodies[8] (see Table 29-2).

Because of the potential for sudden clinical deterioration, treatment should be initiated as soon as possible after diagnosis of TTP. The treatment approach consists of a daily 1 to 2 plasma volume exchange with plasma until clinical symptoms have resolved and the platelet count has reached a normal level (≥150,000/μl). Fresh-frozen plasma (FFP) and cryosupernatant plasma are considered equivalent because of comparable levels of ADAMTS13.

Corticosteroids, given in combination with plasma therapy, may be of benefit in autoimmune forms of TTP by inhibiting the synthesis of anti-ADAMTS13 autoantibodies. The rationale of combined treatment is that plasma exchange will have only a temporary effect on the presumed autoimmune basis of the disease, and additional immunosuppressive treatment may cause a more durable response (see Table 29-2).

Prospective studies have successfully and safely used rituximab, an anti-CD20 monoclonal antibody depleting B lymphocytes, in patients who failed to respond to standard daily plasma exchange and methylprednisolone, as well as in patients with relapsed acute TTP who had previously demonstrated antibodies to ADAMTS13. Treatment was associated with clinical remission in all patients, disappearance of anti-ADAMTS13 antibodies, and increased ADAMTS13 activity to levels greater than 10%.[58] Of the about 100 rituximab-treated patients reported, normalization of platelets and LDH has been noted in about 95%, although time to remission has been variable, from 1 to 4 weeks after the first dose. The duration of remission ranged from 9 months to 4 years, with relapses reported in approximately 10%. Rituximab has been also used electively to prevent relapses in patients with autoantibodies and recurrent disease.[59] Longitudinal evaluation of ADAMTS13 activity and autoantibody levels may help in monitoring patient response to treatment. Repeat treatment with rituximab should be considered when ADAMTS13 activity decreases and inhibitors reappear into the circulation, to prevent a relapse.

In patients who have TTP associated with congenital ADAMTS13 deficiency, ADAMTS13 is constitutively lacking and can be replaced by plasma infusions. During acute episodes, patients often require plasma exchange to restore a stable clinical and laboratory state. Providing enough ADAMTS13 to achieve 5% normal enzymatic activity may be sufficient to degrade large vWF multimers, which may be relevant to induce remission of the microangiopathic process, and this effect is sustained over time. Infused ADAMTS13 has a plasma half-life of 2 to 3 days *in vivo*,[60] and although plasma levels fall below 5% within 3 to 7 days after plasma administration, the effect of plasma on platelet count and clinical parameters may last up to 3 weeks, suggesting that ADAMTS13 remains available (e.g., on platelets and endothelial cells). Patients with congenital ADAMTS13 deficiency tend to relapse. Patients with frequent relapses, a severe clinical course with neurologic sequelae, or renal insufficiency, as well as patients who have siblings who died of TTP, should receive regular prophylactic plasma infusions every 2 to 3 weeks, a regimen shown to be effective in preventing acute TTP episodes and maintaining the patients in good health for years.

Other Forms of Thrombotic Microangiopathy, Associated with Systemic Disease or Drugs

Antiphospholipid Syndrome, Scleroderma, and Hypertensive Emergencies

Plasma therapy has often been attempted in patients with thrombotic microangiopathy associated with systemic diseases, even though its efficacy is poorly defined.[5] In the antiphospholipid syndrome, oral anticoagulation remains the only treatment of proven efficacy to prevent and to treat microvascular and macrovascular thrombosis, even if concomitant thrombocytopenia may increase the risk of bleeding. Preliminary reports suggest a potential efficacy of rituximab therapy, but further controlled studies are needed.[61]

Blood pressure control is fundamental in patients with TMA associated with scleroderma crisis and hypertensive emergencies.

Human Immunodeficiency Virus

Hemolytic uremic syndrome and thrombotic thrombocytopenic purpura are both possible complications of acquired immunodeficiency syndrome (AIDS), which may account for as many as 30% of hospitalized TMA patients in cities where AIDS is epidemic. Plasma therapy is the only feasible approach in these forms, although the prognosis is poor.[5]

Malignant Diseases

Spontaneous TMA complicates almost 6% of cases of metastatic gastric carcinoma, which in turn accounts for about 50% of all malignant disease–associated TMA. The prognosis is extremely poor. Therapy is minimally effective.[5]

Drugs

More often resembling HUS, TMA is described in 2% to 10% of cancer patients treated with mitomycin C.[62] Patients who develop mitomycin C–associated TMA are usually in remission from their malignant disease. Mortality is about 70%, and median time to death is about 4 weeks. Patients surviving the acute phase often continue to receive dialysis or die later of tumor recurrence or metastasis. The suggestion to administer corticosteroids during mitomycin treatment to prevent disease needs to be confirmed. Plasma exchange is usually attempted, but its effectiveness is unproved.

Platinum- and bleomycin-containing combinations have also been reported to induce HUS.[62]

Quinine is one of the most common drugs associated with TMA. It is generally used to treat muscle cramps but is also contained in beverages and nutrition health products (e.g., tonic water, herbal preparations). Quinine-dependent platelet, erythrocyte, granulocyte, lymphocyte, and endothelial antibodies may contribute to the pathogenesis. Severe renal impairment is frequent, and hemodialysis is required in most cases. High mortality and chronic renal failure have been reported.[62] Quinine cessation and plasma therapy should be initiated rapidly.

Thrombotic microangiopathy associated with interferon alfa is characterized predominantly by renal impairment. Patients typically recover with early discontinuation of the drug and prompt supportive therapy. However, kidney prognosis is usually poor, with ESRD in about 42% of patients.

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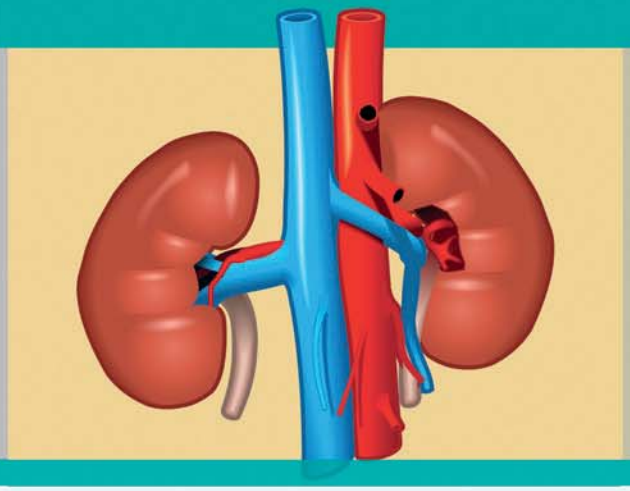


SECTION V

Diabetic Nephropathy

CHAPTER 30

Pathogenesis, Clinical Manifestations, and Natural History of Diabetic Nephropathy

Gunter Wolf and Kumar Sharma

DEFINITIONS

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD) in most Western societies. It can develop in the course of both type 1 and type 2 diabetes and as a consequence of other forms of diabetes mellitus (DM). *Type 1 diabetes* is an autoimmune disease characterized by antibody-mediated and cell-mediated destruction of pancreatic islets. Type 1 diabetes may occur at any age but is common in childhood, usually presenting before age 30 years. *Type 2 diabetes* is characterized by a combination of insulin resistance and insulin deficiency. The *metabolic syndrome* (insulin resistance, visceral obesity, hypertension, hyperuricemia, and dyslipidemia with high triglyceride levels and low amounts of high-density lipoprotein) is often followed by type 2 diabetes. For a long period, insulin resistance is compensated by increased insulin secretion, but a gradual decline in pancreatic β-cell function finally culminates in hyperglycemia, and type 2 diabetic patients require treatment with insulin. Type 2 diabetes was typically a disease of mostly elderly adults, but recently it is increasingly seen in adolescents and even in children. In addition, other types of DM include maturity-onset diabetes of the young, gestational diabetes, and diabetes secondary to various metabolic disorders or the result of corticosteroid treatment.

PATHOGENESIS OF DIABETIC NEPHROPATHY

Genetic and Environmental Factors

The risk of nephropathy is strongly determined by polygenetic factors. The risk for development of DN is equal in type 1 and type 2 diabetes, and only 30% to 40% of patients with type 1 or type 2 diabetes will ultimately develop nephropathy. The prevalence of nephropathy in diabetic patients varies among different racial and ethnic groups such that it is relatively increased in African Americans, Native Americans, Mexican Americans, Polynesians, Australian aborigines, and urbanized South Asian immigrants in the United Kingdom compared with Caucasians. Although barriers to care seem likely to account for some of these interpopulation differences, genetic factors may also contribute.

Familial clustering of DN has been reported in both type 1 and type 2 diabetes and in both Caucasian and non-Caucasian populations. In a type 1 diabetic patient who has a first-degree relative with diabetes and nephropathy, the risk for development of DN is 83%. The frequency is only 17% if there is a first-degree relative with diabetes but without nephropathy.[1] In type 2 diabetes, familial clustering has been well documented in Pima Indians,[2] and a familial determinant is also suggested by the observation that albumin excretion rates are higher in offspring of type 2 diabetic patients with nephropathy. The risk is particularly high in the offspring if the mother had been hyperglycemic during pregnancy, perhaps because this causes reduced formation of nephrons ("nephron underdosing") in the offspring,[3] as shown in experimental studies.[4] Low birth weight and nephron underdosing are also associated with hypertension, metabolic syndrome, and perhaps DN, although for DN the data are somewhat controversial. The hypothesis has been proposed that nephron underdosing[5] leads to compensatory glomerular hypertrophy and increased single-nephron glomerular filtration rate (GFR), thus aggravating glomerular injury if a renal insult such as diabetes occurs.

There is ongoing research to identify genetic loci for DN susceptibility through genomic screening and candidate gene approaches. However, risk for DN does not show simple mendelian inheritance, and multiple genes are presumably involved. Whole-genome scanning has identified several chromosomal regions that are linked with DN with susceptibility loci, for example, on chromosomes 3q, 7p, and 18q. At present, the pathophysiologic function of such genetic regions is mainly unknown. Gene polymorphisms may also contribute to familial clustering. A study suggested a genetic predisposition to DN caused by a polymorphism in the carnosinase gene, causing accumulation of carnosine with antioxidant properties.[6] Several studies also suggested some detrimental effect of the double-deletion (DD) polymorphism of the angiotensin-converting enzyme (ACE) genotype on disease progression,[7] although the finding has not been uniformly confirmed.[8,9]

Environmental factors, especially dietary factors, may also be involved in the pathogenesis of diabetes and DN. One of the strongest risk factors is the intake of soft drinks containing added sugars such as sucrose or high-fructose corn syrup. Added sugars contain fructose, which has been shown to induce features of metabolic syndrome in both humans and laboratory animals, and the mechanism may be mediated in part by the ability of fructose to increase uric acid level. In turn, an elevated serum uric acid level has been found to be a potent predictor for the development of type 2 diabetes as well as DN. The mechanism is linked to the ability of uric acid to induce oxidative stress and endothelial dysfunction. Recent studies suggest that one of the mechanisms by which low birth weight increases the risk for hypertension and diabetes later in life is because low birth weight results in an elevation of uric acid that persists from birth throughout childhood.

Hemodynamic Changes

Hyperfiltration is common in early diabetes but can be corrected with good glycemic control. Increased GFR involves glucose-dependent effects causing afferent arteriolar dilation, mediated by a range of vasoactive mediators, including insulin-like growth factor 1 (IGF-1), transforming growth factor β (TGF-β1), vascular endothelial growth factor (VEGF), nitric oxide (NO), prostaglandins, and

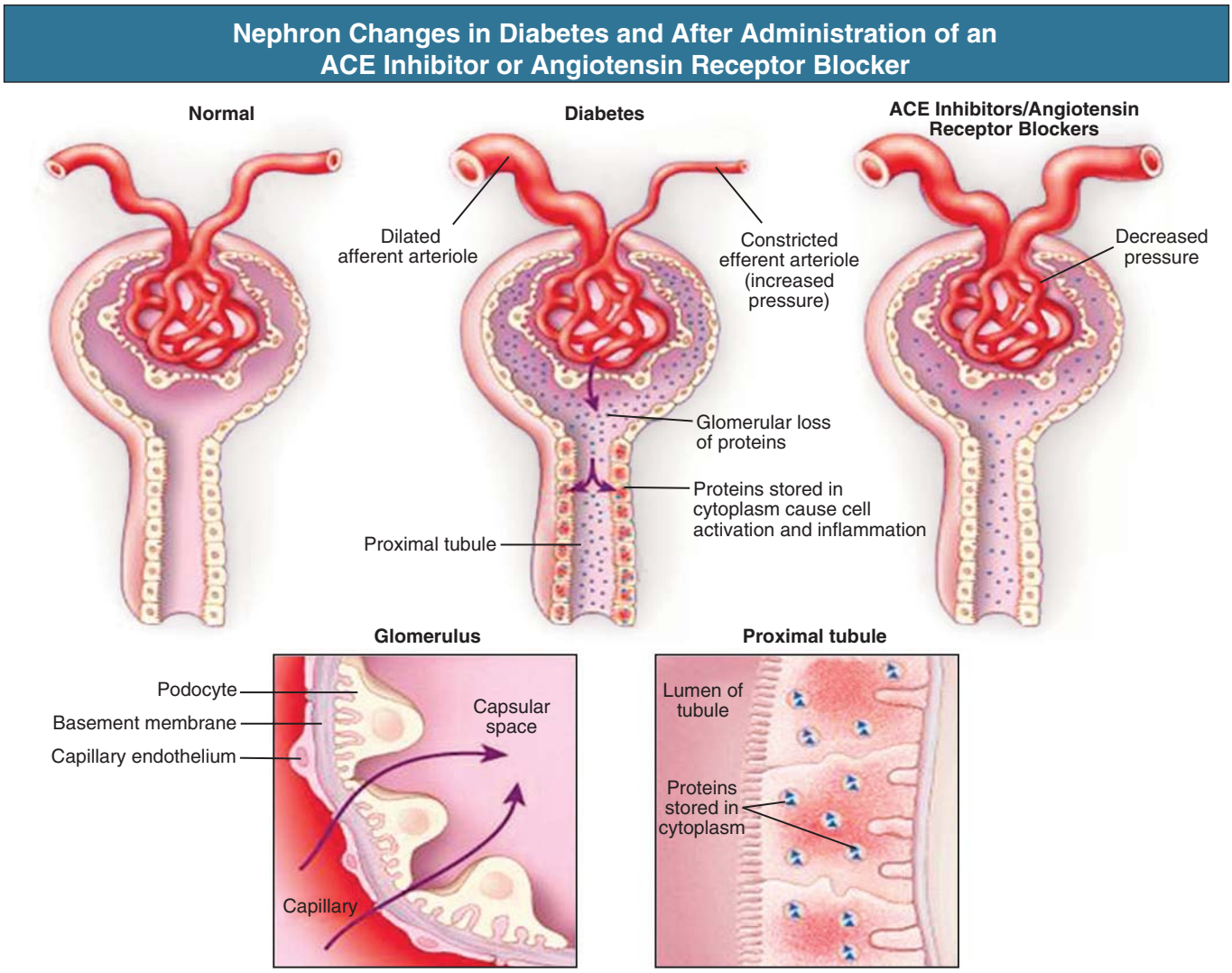


Figure 30-1 Schematic comparison of normal nephron, nephron in DN, and nephron in DN after ACE inhibitor/ARB administration. Note afferent vasodilation and efferent angiotensin II (Ang II)–mediated vasoconstriction in diabetic nephropathy (DN) causing glomerular hypertension, which is relieved by angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) therapy. Note also protein leakage into the filtrate and tubular loading, with endocytosed protein causing an inflammatory reaction that promotes interstitial fibrosis. This is reversed by ACE inhibitor/ARB treatment.

glucagon (Fig. 30-1). Over time, development of vascular disease of the afferent arteriole may result in permanent alterations in renal autoregulation that favor glomerular hypertension. Renal injury in DN is caused not only by hemodynamic disturbances (e.g., hyperfiltration, hyperperfusion) but also by disturbed glucose homeostasis, and the two pathways interact. For example, shear stress increases glucose transport into mesangial cells by upregulation of specific glucose transporters. Furthermore, shear stress and mechanical strain resulting from altered glomerular hemodynamics trigger autocrine and paracrine release of cytokines and growth factors in the glomerulus.

Diabetic nephropathy is also associated with tubular abnormalities (e.g., increased tubular reabsorption of sodium). Hyperfiltration increases the colloid osmotic pressure in postglomerular capillaries, facilitating reabsorption of sodium in the proximal tubule. In the presence of hyperglycemia, increased proximal sodium reabsorption may also result from increased activity of the glucose-sodium cotransporter. Angiotensin II (Ang II) also appears to have a role, causing hypertrophic proximal tubular growth and increased sodium reabsorption.[10]

Renal Hypertrophy

Renal growth is seen early after the onset of diabetes. The size of the kidney may increase by several centimeters. Glomerular enlargement is associated with an increase in the number of mesangial cells and of capillary loops, thus enhancing the filtration surface area. Enlargement of the glomeruli is the result of cellular hypertrophy, whereas the tubular epithelial cells undergo both proliferation and hypertrophy.

In animal experiments, avoidance of hyperglycemia prevents renal hypertrophy. Elevated serum glucose levels cause hypertrophy by stimulating growth factors in the kidney, including IGF-1, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), VEGF, TGF-β, and Ang II. The molecular mechanisms involved in glycemia-induced hypertrophy include induction of cell cycle inhibitors such as $p27^{Kip1}$. TGF-β stimulates protein synthesis (hypertrophy) but prevents cell proliferation and division by induction of cell cycle inhibitors.[11,12] It is overexpressed in the glomeruli and the tubulointerstitium both in experimental and in human DN. Glucose as well as glucose-derived *advanced glycation end products* (AGEs) and Ang II stimulate the production of TGF-β in mesangial cells,

podocytes, and tubular epithelial cells. Hyperglycemia also induces the expression of thrombospondin, a potent activator of latent TGF-β. Treatment of diabetic mice with neutralizing anti–TGF-β antibodies attenuated diabetes-related renal hypertrophy and extracellular matrix (ECM) accumulation and preserved renal function, but had minimal influence on proteinuria. Similarly, inhibition of VEGF prevented glomerular hypertrophy in models of DN and also reduced albuminuria.[12]

Mesangial Expansion and Nodule Formation

The hallmarks of DN are mesangial expansion, nodular diabetic glomerulosclerosis (the acellular Kimmelstiel-Wilson lesion), and diffuse glomerulosclerosis. The early mesangial lesion is characterized by a variable increase in mesangial cell number and size associated with an increased ECM deposition. In later stages, a general loss of mesangial cells occurs. Increasing evidence suggests that local NO deficiency contributes to these histologic lesions, in particular nodule formation. Indeed, endothelial cell nitric oxide synthase (NOS)–deficient mice made diabetic with streptozotocin represent one of the most promising models for DN.

Mesangial expansion is mediated by both glucose and glucose-derived AGEs. In experimental models, mesangial changes can largely be prevented by tight glycemic control or the use of AGE inhibitors such as aminoguanidine. The effects are presumably mediated by TGF-β.

Inflammation and Diabetic Nephropathy

Inflammatory processes and immune cells are involved in the development and progression of DN.[11] Glomerular and interstitial infiltration by monocyte/macrophages and activated T lymphocytes is observed both in human biopsy specimens and in animal models of DN. An inflammatory state is also suggested by the frequent elevation of serum levels of acute-phase proteins and elevated neutrophil counts. Chemokines and their receptors, in particular monocyte chemotactic protein 1 (MCP-1/CCL2), as well as adhesion molecules seem to contribute to this.[11,13] Fractalkine/CX3CL1 may function as an arrest chemokine in monocyte/macrophage adhesion before migration into the kidney. T lymphocyte recruitment is the consequence of glomerular and tubulointerstitial upregulation of RANTES/CCL5 structures as well as tubulointerstitial upregulation of inducible protein 10 (IP-10/CXCL10) (Fig. 30-2). Bardoxolone methyl, as an inducer of the KEAP1-Nrf2 pathway, exhibits anti-inflammatory effects and showed initially promising results as a novel therapeutic agent in patients with type 2 diabetes. However, a large Phase III trial was stopped after an interim analysis revealed significantly more adverse effects and increased mortality in the intervention group (see Chapter 31).

Mechanisms Underlying Proteinuria

Widening of the glomerular basement membrane (GBM) is associated with accumulation of type IV collagen and net reduction in negatively charged heparin sulfate. However, heparin sulfate cannot be the key factor underlying proteinuria, because selective reduction of GBM proteoglycans unexpectedly reduced rather than increased proteinuria. This supports the podocyte being more important in the genesis of proteinuria. Biopsies in patients with DN documented a correlation between the degree of proteinuria and the width of podocyte foot processes. The expression of one permeability-controlling protein, nephrin, is abnormally low in DN.[12] The transcription of nephrin is suppressed by Ang II and restored by inhibitors of the renin-angiotensin system (RAS). In addition, in DN, apoptosis of podocytes is triggered by various factors, including Ang II and TGF-β, and adhesion of podocytes to the GBM is reduced by AGE-induced suppression of neuropilin-1. Furthermore, migration of podocytes is also attenuated by the reduction of neuropilin-1, thereby preventing surviving podocytes from covering denuded areas of GBM, and thus causing formation of synechiae and development of focal segmental glomerulosclerosis (FSGS).

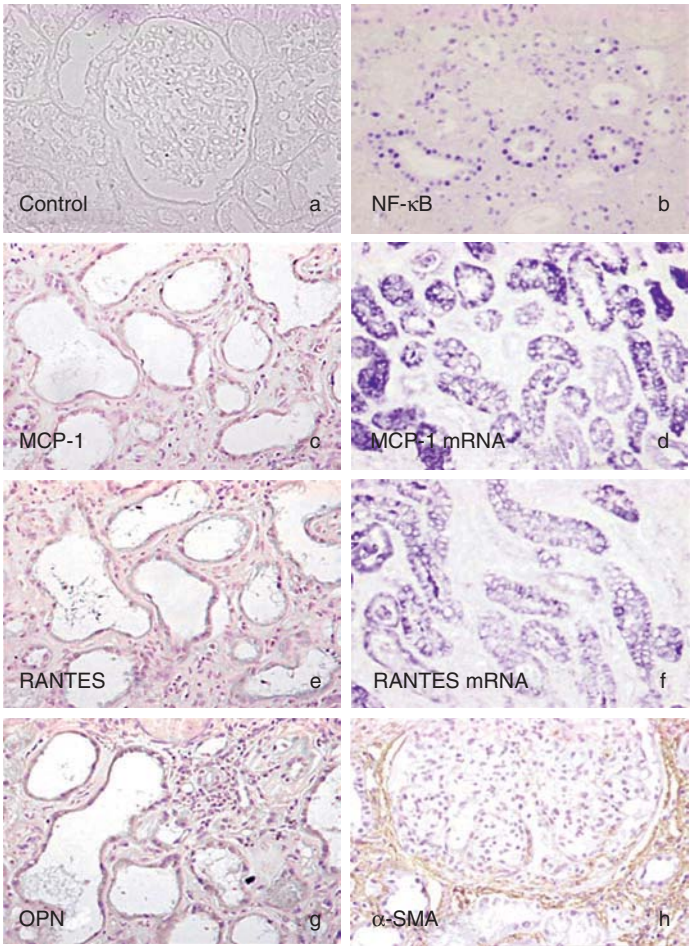


Figure 30-2 Activated nuclear factor (NF)-κB and overexpression of related chemokines in human diabetic nephropathy (DN). Overexpression of chemokines (MCP-1, RANTES), osteopontin *(OPN),* and activated NF-κB in human DN (**a,** normal, nondiabetic kidney; **b** to **h,** DN) indicating the inflammatory nature of DN. *MCP-1,* Monocyte chemotactic protein 1; *RANTES,* regulated on activation, normal T cell expressed and secreted (CCL5); *α-SMA,* α-smooth muscle actin. *(From reference 13.)*

Crosstalk between glomerular endothelial cells and podocytes involves activated protein C (APC). APC formation is regulated by endothelial thrombomodulin and is reduced in diabetic mice.[14] In DN, thrombomodulin-dependent APC formation inhibits podocyte apoptosis (Fig. 30-3).

In cultured podocytes, adiponectin administration reduced the permeability to albumin and caused podocyte dysfunction. Endothelial cell dysfunction associated with altered fenestrations and glycocalyx may also contribute to enhanced permeability. Because adiponectin levels are low in patients with the metabolic syndrome or type 2 diabetes, lack of adiponectin may further contribute to proteinuria.

In advanced stages of DN, high-molecular-weight serum proteins are able to escape across basal membranes with disrupted texture, gaps, and holes (nonselective proteinuria).

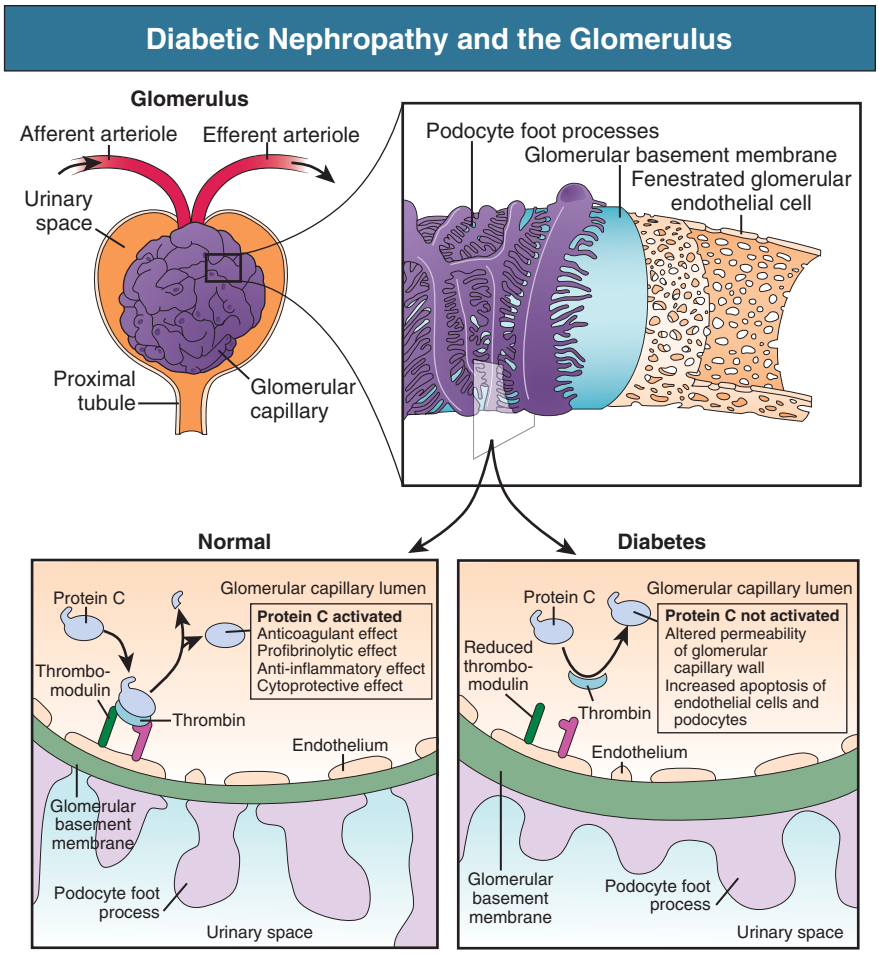


Figure 30-3 Crosstalk between endothelial cells and podocytes involving protein C. Under physiologic conditions, protein C is activated by the binding of thrombin to its receptor, called thrombomodulin, on glomerular endothelial cells. The formed complex catalyzes the conversion of protein C to its catalytically activated form, which has potent anticoagulant, profibrinolytic, anti-inflammatory, and cytoprotective effects. In diabetic nephropathy, the production of activated protein C in the glomerulus is reduced because of suppression of thrombomodulin expression. Decreased functional activity of activated protein C affects the permeability of the glomerular capillary wall and enhances apoptosis of glomerular endothelial cells and podocytes. *(From reference 69.)*

Tubulointerstitial Fibrosis and Tubular Atrophy

Tubulointerstitial pathology is seen early in DN and correlates with prognosis.[15] The pathogenic mechanisms underlying tubulointerstitial fibrosis and tubular atrophy are similar or identical to those in nondiabetic progressive renal disease (see Chapter 79): release of growth factors, in particular TGF-β, and other cytokines from the glomerulus and direct or indirect effects of proteinuria. Under the influence of mediators such as TGF-β and Ang II, tubular cells change their phenotype and become fibroblast-like.[15,16] High glucose concentration and AGEs further stimulate this process. One of the mechanisms by which glucose may promote tubular disease is by conversion through the polyol pathway to fructose, where it is degraded by local fructokinase to induce oxidative stress and local inflammation. Proapoptotic genes are expressed by tubular cells in DN, as promoted by Ang II.

Four different cell types may contribute to matrix accumulation along the glomerular and tubular basement membranes and within the interstitial space: glomerular cells, tubular epithelial cells, macrophages/lymphocytes, and fibroblasts/myofibroblasts. In renal fibrosis, the role of matrix-producing myofibroblasts, which contribute to the progression of fibrosis in DN by facilitating deposition of interstitial ECM, is widely accepted; however, their origin remains controversial. Up to 36% of all interstitial fibroblasts is derived from tubular epithelial cells by *epithelial-mesenchymal transition* (EMT).[16] In addition, endothelial cells and pericytes may also contribute to fibroblast-like transformation. EMT is a highly regulated process defined by four key events: (1) loss of epithelial cell adhesion (e.g., E-cadherin adhesion complex), (2) *de novo* α-smooth muscle actin (α-SMA) expression and actin reorganization, (3) disruption of tubular basement membrane, and (4) enhanced cell migration and invasion of the interstitium (Fig. 30-4). The third and fourth features are difficult to confirm in human disease. Several factors are known to be important in the induction of EMT and subsequently in tubulointerstitial fibrosis. Most important, the enhanced multifunctional cytokine TGF-β1 has been identified as a central mediator of the fibrotic response as a regulator for EMT. TGF-β1 is increased by hyperglycemia in glomeruli and tubulointerstitium of kidney specimens from patients with established DN, induces fibroblasts to synthesize ECM proteins, such as type I, III, and V collagen and fibronectin. We recently demonstrated that EMT in the diabetic kidney depends on the presence of collagen type VIII, a nonfibrillar collagen protein that exists as a heterodimer composed of two distinct polypeptide chains, α1(VIII) and α2(VIII).[17] However, recent findings render the contribution of EMT to renal fibrosis controversial (see Chapter 79).

Clinical studies showed that even mild anemia (hemoglobin level <12.5 g/dl for men, 11.5 g/dl for women) increases the risk of progression of DN. Treatment of anemia early in renal failure with erythropoietin (EPO) may slow the decline of renal dysfunction in DN. Anemia presumably causes renal hypoxia. Moreover, hypoxia is exacerbated by the progressive hyalinosis of the afferent and efferent arterioles and loss of peritubular capillaries. In experimental models of chronic renal injury, hypoxia is an important factor aggravating interstitial fibrosis, partly by the induction of factors such as TGF-β and VEGF. The transition of tubular epithelial cells into fibroblasts

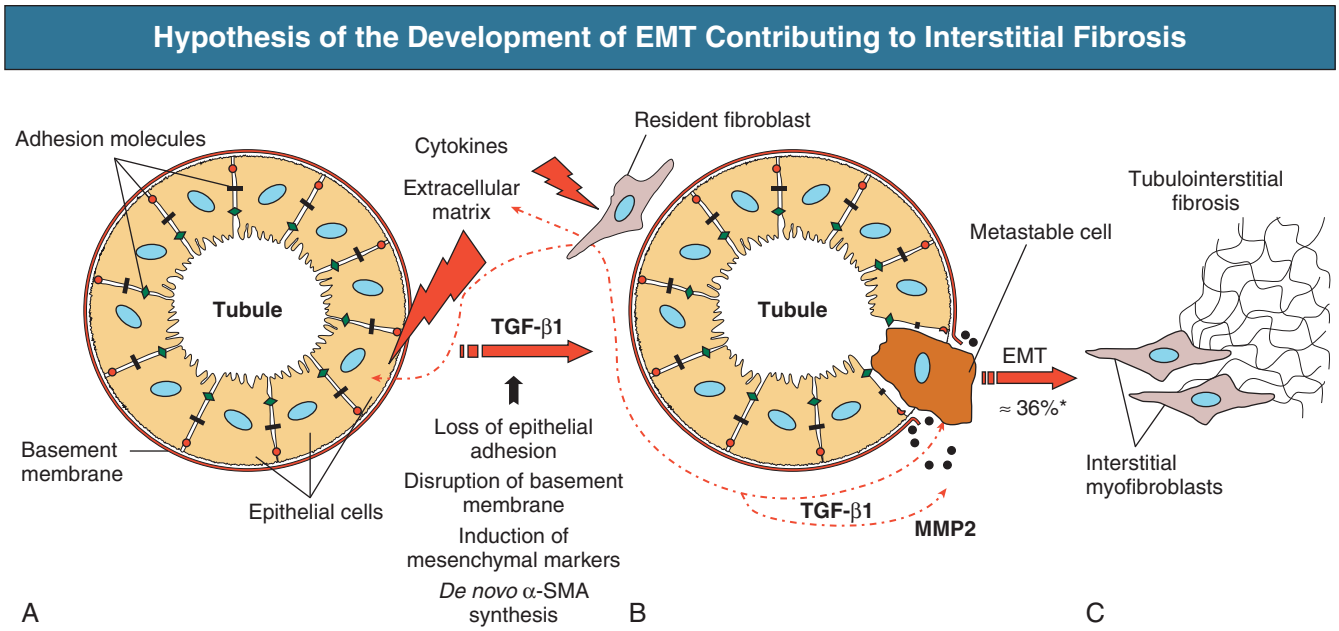


Figure 30-4 Hypothesis of the development of epithelial-mesenchymal transition (EMT) contributing to interstitial fibrosis. Initiated by external stimuli (e.g., cytokines), tubular cells lose their cell-cell contacts (e.g., E-cadherin) (**A**) and start to express mesenchymal markers (e.g., α-SMA, vimentin) (**B**). After disruption of tubular basement membrane (by MMP2) metastable cells disengage themselves from cell connective and transdifferentiate to interstitial myofibroblasts that synthesize extracellular matrix and contribute to fibrosis (**C**). *MMP,* Matrix metalloproteinase; *SMA,* smooth muscle actin; *TGF,* transforming growth factor. *Up to 36% of all interstitial myofibroblasts in diabetic nephropathy are thought to derive from EMT. *(Modified from reference 70.)*

is stimulated by cellular hypoxia.[18] The induction of growth factors and cytokines is mediated by hypoxia-inducing factor 1, which can be amplified by Ang II.

Hyperglycemia and Diabetic Nephropathy

Role of Glucose Control

Evidence of the role of tight glycemic control in retarding the development of DN includes the following:

- Studies suggest that with good glycemic control, as reflected by an average hemoglobin A_{1c} (HbA_{1c}) level of 7.0%, only 9% of type 1 diabetic patients will develop ESRD after 25 years, versus the historical prevalence of 40%.[19]
- Results from the Diabetes Control and Complications Trial (DCCT) showed a remarkable reduction in progression from normoalbuminuria to microalbuminuria and other microvascular complications, specifically retinopathy, in patients with type 1 diabetes with tight glycemic control.[20] At least for cardiovascular sequelae, the benefit of early aggressive reduction of glycemia persisted despite later deterioration of the glycemic control.[21]
- Euglycemia that followed isolated transplantation of the pancreas was associated with a regression of diabetic glomerulosclerosis after 10 years.[22]
- Evidence from the United Kingdom Prospective Diabetes Study (UKPDS) showed that reducing the HbA_{1c} level by approximately 0.9% in patients with type 2 diabetes reduces the risk for development of microvascular complications, including nephropathy.[23]
- The ADVANCE study randomly assigned 11,140 patients with type 2 diabetes to either intensive glucose control or standard glucose control. At the end of 5-year follow-up, HbA_{1c} level was 6.5% in the intensive group and 7.3% in the standard therapy group. Intensive glucose control was associated with a significant reduction in renal events and new-onset microalbuminuria. The trial did not show a significant effect of intensive control on major macrovascular events.[24]

The mechanisms by which hyperglycemia induces DN are complex and may involve not only effects of elevated glucose levels, but also the generation of AGEs and alcohol sugars (polyols) as a result of hyperglycemia.

Brownlee[25] proposed a unifying mechanism of how hyperglycemia leads to diabetic complications, including DN (Fig. 30-5). An increase in intracellular glucose concentrations stimulates glucose oxidation in the tricarboxylic acid cycle, pushing more electron donors (NADH, $FADH_2$) into the electron transport chain.[25,26] When a critical threshold is reached and electrons are donated to molecular oxygen, superoxide is generated. This mitochondrial overproduction of superoxide activates four major pathways that are involved in DN. Although this hypothesis is supported by studies in cell culture, validation in animal models remains inconclusive, partly because of the difficulty in measuring superoxide production accurately *in vivo.*

Protein Kinase C Pathway Many of the adverse effects of hyperglycemia have been attributed to activation of protein kinase C (PKC), a family of serine-threonine kinases that regulate diverse vascular functions. The activity of PKC, especially the membrane-bound form, is increased in the retina, aorta, heart, and glomeruli of diabetic animals. In short-term and long-term studies of diabetic rats, an orally effective PKC-β–selective inhibitor ameliorated glomerular hyperfiltration, albuminuria, and renal TGF-β overexpression as well as ECM accumulation.[12,26] PKC-α may represent an additional therapeutic target because albuminuria was virtually absent in diabetic PKC-α knockout mice.

Advanced Glycation End Products Pathway Chronic hyperglycemia can lead to nonenzymatic glycation of amino acids and proteins (Maillard or Browning reaction)[27] (Fig. 30-6). Over time, these products undergo rearrangement, including cross-linking, to become irreversible AGEs. Both circulating and tissue proteins as well as lipids and nucleic acids may thus be glycated. Although

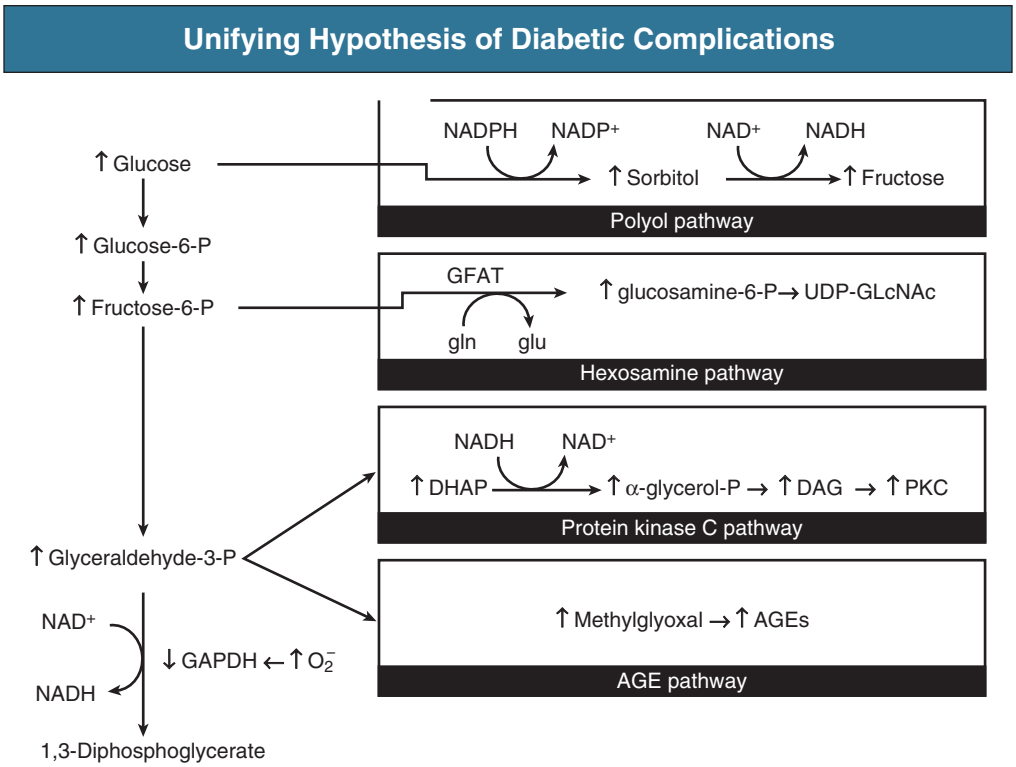


Figure 30-5 Unifying hypothesis of diabetic complications. Mitochondrial overproduction of superoxide activates four major pathways of hyperglycemic damage by inhibiting GAPDH. *DHAP,* Dihydroxyacetone phosphate; *DAG,* diacylglycerine (an activator of protein kinase C, *PKC,* and of triose phosphates to methylglyoxal), the main intracellular advanced glycation end products *(AGEs)* precursor. Increased flux of fructose-6-phosphate to UDP-*N*-acetylglucosamine increases modification of proteins by *O*-linked *N*-acetylglucosamine (GlcNAc) and increased glucose flux through the polyol pathway consumes nicotinamide adenine dinucleotide phosphate *(NADPH)* and depletes glutathione *(GSH). NAD,* Nicotinamide adenine dinucleotide; *UDP,* uridine diphosphate; *GAPDH,* glycerinaldehyde-3-phosphate-dehydrogenase; *GFAT,* glutamine fructose-6-phosphate amidotransferase; *gln,* glutamine; *glu,* glutaminic acid; *PARP,* poly [ADP-ribose] polymerase; *P,* phosphate. *(From reference 26.)*

primarily observed in diabetes, AGEs also accumulate in aging and in renal failure.[27]

The concentration of AGEs is increased in the serum of DN patients. AGEs have also been localized to diabetic glomeruli by immunohistochemistry. AGEs bind to a variety of cell types, including macrophages and mesangial cells, and mediate a variety of cellular actions, including expression of adhesion molecules, cell hypertrophy, ECM synthesis, EMT, and inhibition of NOS. AGEs injected *in vivo* induce albuminuria and glomerulosclerosis.[27] AGEs have profound effects on podocytes, including induction of hypertrophy, followed by apoptosis and suppression of nephrin synthesis. Among several binding sites, the most important is the putative receptor RAGE (receptor for AGE), a pattern recognition receptor. It is present in tubular cells and podocytes. Ang II stimulates upregulation of RAGE on podocytes.[28] This effect is mediated by angiotensin-2 (AT_2) receptors not blocked by sartanes.[28] One of the actions of RAGE is activation of nuclear factor-κB (NF-κB). sRAGE, the soluble extracellular domain of RAGE, acts as a decoy receptor and experimentally ameliorates the renal lesions in diabetes.[27]

Administration of aminoguanidine, an inhibitor of AGE formation, to diabetic animals reduces AGE deposition, mesangial matrix expansion, and albuminuria, but has inconsistent effects on GBM thickening. Preliminary clinical studies suggest beneficial effects on retinopathy, lipids, and proteinuria. The clinical experience with aminoguanidine has been disappointing and riddled with side effects. Newer, more specific agents have been developed that may be more potent blockers of AGE formation. For example, phenacylthiazolium bromide cleaves covalent, AGE-derived protein

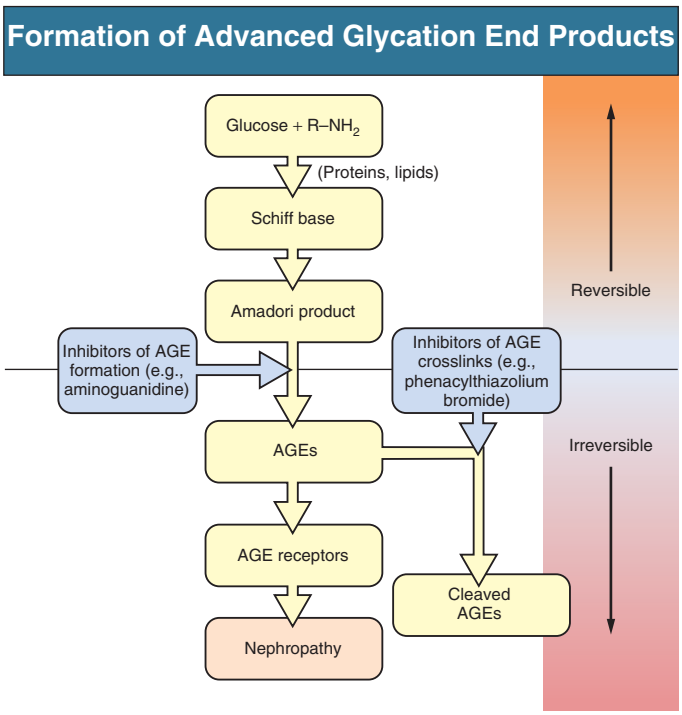


Figure 30-6 Mechanism of formation of advanced glycation end products (AGEs).

cross-links and provides a conceptual basis for the reversal of AGE-mediated tissue damage, which until now has been regarded as irreversible.

Polyol Pathway The polyol pathway involves the conversion of glucose to sorbitol and eventually fructose. The role of polyols in diabetic complications has been assessed with aldose reductase (AR) inhibitors such as sorbinil, tolrestat, and ponalrestat,[12] which have shown promise in preventing diabetic cataracts and improving or stabilizing DN. AR inhibitors also blunt hyperfiltration and have a mild effect on reducing albuminuria in both experimental and human diabetes. Overall, however, the experience with AR inhibitors in DN has been disappointing, and treatment was associated with hypersensitivity reactions and liver function abnormalities. More recently, laboratory studies have focused on blocking fructokinase, which is in the distal polyol pathway, with more promising results. However, fructokinase inhibitors have not yet been administered to humans.

Hexosamine Pathway Although most of the intracellular glucose is metabolized by the glycolytic pathway, some fructose-6-phosphate is diverted into the hexosamine pathway, increasing the concentrations of *N*-acetylglucosamine. This glucosamine modifies certain transcription factors, such as Sp1 activity, by post-translational *O*-linked glycosylation. In turn, Sp1 then leads to enhanced transcription of key mediators, such as TGF-β1 and plasminogen activator inhibitor 1. Glucosamine-mediated modification of the enzyme Akt/PKB reduces expression of endothelial NOS and promotes apoptosis of cells.

Adenosine Monophosphate–Activated Protein Kinase Pathway Recent studies suggest an alternative pathway that may also contribute to DN. The energy-sensing enzyme, 5′-adenosine monophosphate (AMP)–activated protein kinase (AMPK), appears to play an important role in many aspects of diabetic and obesity-related kidney disease.[29-31] Inhibition of AMPK in caloric-excess states has been linked to inflammation (NF-κB, NADPH oxidase, MCP-1 stimulation), vascular dysfunction (eNOS inhibition), stimulation of hypertrophy (mTOR activation), and profibrotic pathways (TGF-β signaling).[29-31]

Renin-Angiotensin-Aldosterone System and Diabetic Nephropathy

Studies in patients with type 1 and type 2 diabetes as well as in various animal models of diabetes suggest that ACE inhibitors or angiotensin receptor blockers (ARBs) retard progression of DN (see Chapter 31). Although plasma renin activity is low in DN, it is inappropriate in relation to increased extracellular volume and exchangeable sodium, suggesting activation of the RAS.[32] This has suggested that activation of the intrarenal RAS may play a critical role in the development of DN. In experimental diabetes, sites of local RAS activation have been identified in glomeruli (podocytes, mesangial/endothelial cells), renal vessels, and tubular cells.[32] High glucose concentration and AGEs stimulate angiotensinogen and renin expression in various renal cells, mainly through reactive oxygen species.[32] Proteinuria further activates the local RAS of tubular cells. A new mechanism of how high levels of glucose directly trigger the release of renin involves local accumulation of succinate and activation of the kidney-specific G protein–coupled metabolic receptor GPR91.[33] Adipocytes are another source of Ang II in obese patients.

In patients with DN, prorenin levels are elevated, possibly reflecting increased synthesis. Specific prorenin and renin receptors have been demonstrated in the kidney; ligand binding causes nonenzymatic activation of prorenin to yield renin activity and locally produced Ang II.[34] Moreover, prorenin as well as renin can directly bind to specific receptors on mesangial and tubular cells and induce proinflammatory and profibrogenic cytokines.[11] As a further complexity, in diabetes, chymase is strikingly expressed in the kidney; this enzyme generates Ang II but is not inhibited by ACE inhibitors.[35] On the other hand, the enzyme ACE2 generates peptides such as angiotensin 1-7, which antagonize the effects of Ang II.[35] ACE2 activity is reduced in DN, leading to a decrease in angiotensin 1-7 and further amplification of the effects of Ang II. Interestingly, 1,25-dihydroxyvitamin D_3 suppresses the RAS. Thus, in diabetic patients with advancing chronic kidney disease (CKD), decreasing calcitriol production further activates the RAS.

Ang II has many nonhemodynamic effects and mediates cell proliferation, hypertrophy, ECM expansion, and cytokine (TGF-β, VEGF) synthesis.[32] Therefore, ACE inhibitors and ARBs presumably act by hemodynamic as well as by nonhemodynamic actions.

Aldosterone accelerates progression in renal damage models independently of Ang II. In DN, aldosterone escape has been linked to progression of proteinuria (see Chapter 31). Aldosterone synthesis is stimulated in DN, and this steroid hormone stimulates the synthesis of other proinflammatory and profibrogenic cytokines (MCP-1, TGF-β).[12,35]

Other vasoactive agents may also be involved in the pathogenesis of DN, including alterations in systemic or intrarenal production of endothelin, NO, the kallikrein-kinin system, and natriuretic peptides.

Uric Acid and Fructose

As discussed earlier, there is also increasing evidence that uric acid may have a role in the pathogenesis of both diabetes and DN. Several studies have shown that an elevated uric acid level can predict the development of DN as well as diabetic CKD, and pilot studies have reported an early benefit of allopurinol therapy on diabetic albuminuria.[36]

Uric acid is generated during the metabolism of fructose, when it appears to induce oxidative stress in mitochondria. In addition to dietary sources of fructose from added sugars, there is increasing evidence that in diabetic patients, fructose is generated in the kidney, where it is metabolized to generate uric acid and oxidative stress that may mediate renal injury. Thus, both dietary fructose and endogenous production of fructose may be involved in the development of diabetes and its complications.[37]

EPIDEMIOLOGY

In most Western countries, diabetic nephropathy has become the leading cause of ESRD. According to the U.S. Renal Data System (www.USRDS.org), in 2006, DN was the most frequent primary diagnosis, with 159 cases per 1 million population per year. The proportion of diabetics among patients with ESRD varies considerably between countries but had consistently been on the rise in all countries until recently, when the incidence figures have stabilized. In patients starting renal replacement therapy (RRT), we found diabetes in 49%, but classic features of DN were observed in only 60% of these diabetic patients (i.e., normal kidney size despite ESRD; proteinuria > 1 g/24 h with or without retinopathy); 13% had an atypical presentation with ischemic nephropathy, and in 27%, a known primary renal disease coexisted with diabetes, including polycystic kidney disease (PKD), analgesic nephropathy, and glomerulonephritis (GN).[38] An important mode of presentation has become irreversible acute kidney injury (AKI), for example, after administration of radiocontrast media, cardiac events, and

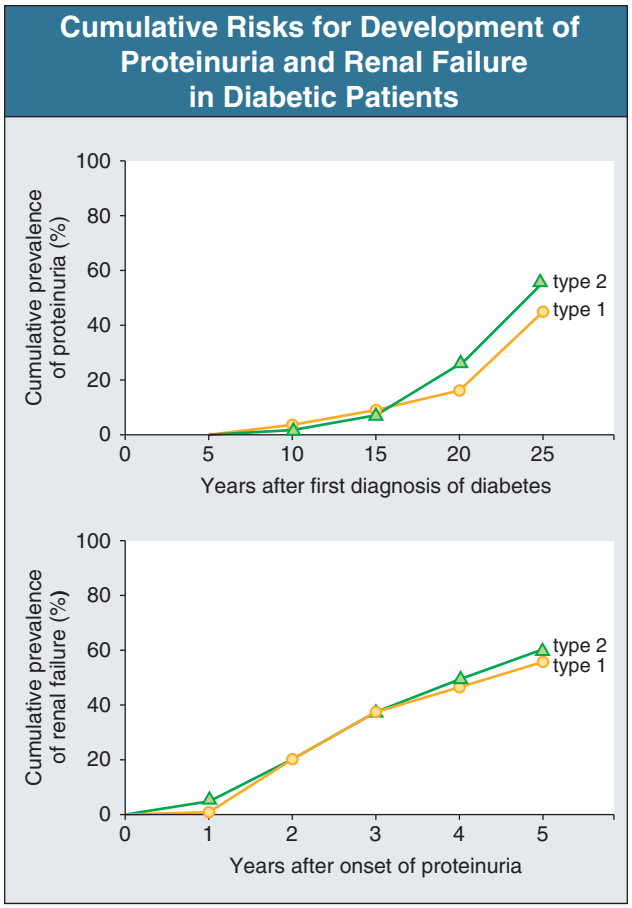


Figure 30-7 Cumulative risks for development of proteinuria and progression to renal failure in patients with type 1 and type 2 diabetes. *(From reference 38.)*

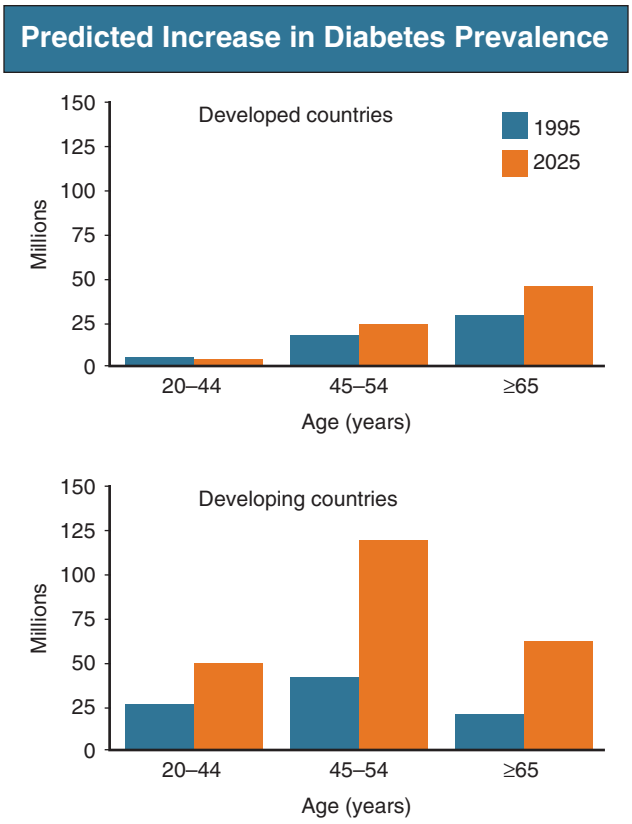


Figure 30-8 Predicted increase in diabetes prevalence. Number of patients by age group, region (developing versus developed countries), and year. *(From reference 42.)*

septicemia. Many patients also lose the clinical manifestations of overt diabetes (e.g., hyperglycemia) because of CKD-associated weight loss, impaired renal gluconeogenesis, or increased insulin half-life in CKD. This may explain why at least 5% of patients develop apparent *de novo* diabetes after the start of dialysis.

The great majority (in our experience >90%) of patients entering ESRD with diabetes as a comorbid condition have type 2 diabetes. In the past, few type 2 diabetic patients had a chance to live long enough to develop nephropathy.[38] Currently, with better treatment of hypertension and of coronary heart disease, an increasing proportion of type 2 diabetic patients survive and thus are exposed to the risk for development of DN and ESRD. The proportion of type 1 and type 2 diabetic patients who develop proteinuria and elevated serum creatinine concentration is related to the duration of diabetes. As shown in Figure 30-7, the cumulative risks for development of proteinuria and progression are practically superimposable on type 1 and type 2 diabetes.[38] Diabetes-related mortality (cardiovascular, related infections) amounted to almost 3 million, equivalent to 5% of worldwide all-cause mortality in 2000. There is a major increase in the prevalence of type 2 diabetes in the developing world compared with the developed world (Fig. 30-8). For example, in Asia, high mortality from diabetes is most prominent in patients age 50 to 60 years, which translates to a reduction in life expectancy of more than 1 decade. Up to 60% of Asian diabetic patients have microalbuminuria or macroalbuminuria, compared with 30% to 40% reported in Western diabetic populations in cross-sectional surveys.[39] Also, the incidence of diabetes-associated ESRD varies in Western countries, with very high numbers of patients in the United States. The reasons are complex and include genetic variability,[40] differences in lifestyle, and different national health care systems, with variable access to screening programs and early management for diabetes.[39] A targeted screening program may help in the early identification of individuals at high risk for DN.[41,42]

CLINICAL MANIFESTATIONS AND NATURAL HISTORY

Diabetic nephropathy is part of a generalized microvascular syndrome that is accompanied by macrovascular disease.

Obesity, Metabolic Syndrome, and Renal Disease

The metabolic syndrome—defined as having at least three of the five parameters of increased waist circumference, elevated triglycerides (TGs), decreased high-density lipoproteins (HDLs), elevated blood pressure (BP), and elevated fasting blood glucose concentration—is increasingly being recognized not only as a major contributor to cardiovascular diseases but also as a negative influence on renal function. The strong association of metabolic syndrome with kidney disease has been appreciated only relatively recently.[43,44] Obesity is often defined as body mass index (BMI) greater than 30, although different values define obesity in other countries (e.g. India, Japan). Obese individuals have large kidneys and glomerulomegaly, with increased renal blood flow, increased filtration fraction, and glomerular hyperfiltration.[45] Obese patients have microalbuminuria even in the absence of hypertension. The resemblance of obesity-related kidney disease to the early features of diabetic kidney disease

is striking. In addition, sleep apnea, which is common in obese individuals, leading to hypoxic episodes, may also contribute to kidney impairment. Visceral adipocytes are a potent source of deleterious factors[46] and could have an impact on renal function (Ang II, leptin, tumor necrosis factor α [TNF-α]). Thus, renal changes may occur years before the manifestation of type 2 diabetes during obesity and the development of the metabolic syndrome.

Evolution of Diabetic Nephropathy

One of the earliest changes of renal function in diabetes is an increase in GFR, or hyperfiltration, which is observed in patients with type 1 as well as many with type 2 diabetes and is accompanied by an increase in renal size. The next observable change is the development of albuminuria. Somewhat arbitrarily, albumin excretion rates between 0 and 30 mg/day are called *normo*albuminuria, and between 30 and 300 mg/day, *micro*albuminuria. Diabetic patients with persistent microalbuminuria are at greatly increased risk for development of overt DN, which is heralded by the development of proteinuria (albuminuria > 300 mg/day), on average 15 years after disease onset, with progressive increase in proteinuria and BP as well as development of progressive CKD.

Mogensen[47] proposed a scheme of the different stages of DN that is valid in type 1 diabetes but less reliable in type 2 diabetes (Fig. 30-9). In the later, CKD may occur in the absence of microalbuminuria, possibly as a result of macrovascular disease.

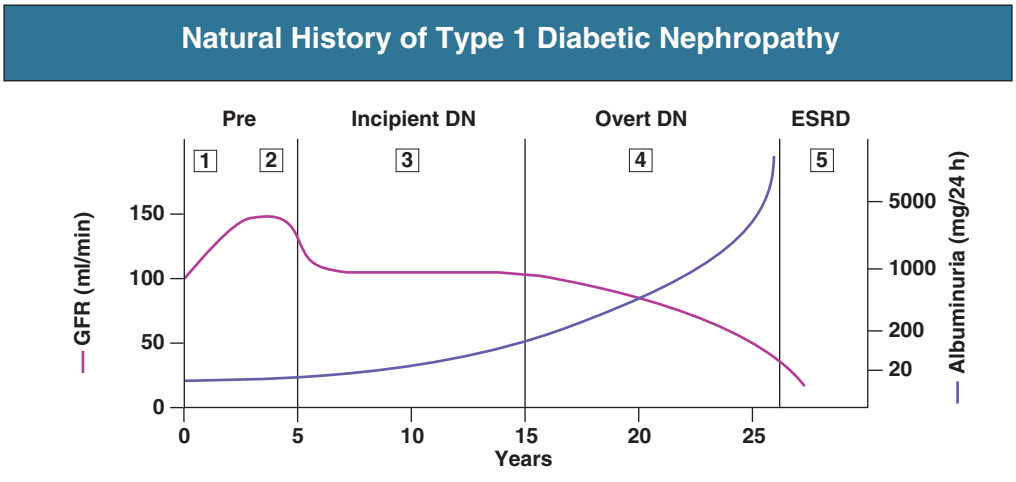
Hypertension and Diabetic Nephropathy

If hypertension develops in a patient with type 1 diabetes, it is almost always caused by renal parenchymal disease. At present, however, type 1 diabetic patients survive longer, and a minority of elderly type 1 patients develop primary hypertension with no evidence of nephropathy. In patients with type 2 diabetes, hypertension often precedes the onset of diabetes by many years and decades as a feature of the metabolic syndrome. At diagnosis of type 2 diabetes, an abnormal BP and an abnormal circadian BP profile are found in 80% of patients. Prediabetic hypertension increases the risk of onset and progression of DN. If patients with type 2 diabetes ultimately develop nephropathy, the prevalence of hypertension further increases, with greater BP elevation, but the relationship between hypertension and nephropathy is generally much less than in type 1 diabetes. The pathogenesis of hypertension in type 2 diabetes is complex and involves activation of the RAS, direct sympathetic nerve activation, and macrovascular changes.[48] Furthermore, there is evidence that genetic factors defining primary hypertension as well as diabetes are clustered (Fig. 30-10).

In DN, it has been well documented that the nocturnal BP decrease is frequently attenuated, or nondipping, which even precedes the onset of microalbuminuria.[48] Furthermore, the BP response to exercise tends to be exaggerated, even when the BP is normal under basal conditions. Diminished compliance of the central arteries with stiffening of the aorta increases the peak systolic pressure and decreases the diastolic pressure, resulting in increased BP amplitude. The great BP amplitude explains why isolated systolic hypertension is so common in patients with type 2 diabetes.[49] Low diastolic pressure increases the risk of coronary events because coronary perfusion occurs during diastole only.[50] Ambulatory pulse pressure and impaired nocturnal BP decline are independent predictors of nephropathy progression in type 2 diabetic patients (Fig. 30-11).

Associated Extrarenal Microvascular and Macrovascular Complications

Diabetic retinopathy is present in virtually all patients with type 1 diabetes and nephropathy. In contrast, only 50% to 60% of proteinuric patients with type 2 diabetes have retinopathy.[51,52] Consequently, the absence of retinopathy does not exclude the diagnosis of DN in patients with type 2 diabetes.[52] The risk of blindness because of



Stage	Pre	Incipient	Overt
Functional	GFR ↑ (25%–50%)	Microalbuminuria, hypertension	Proteinuria, nephrotic syndrome, GFR ↓
Structural	Renal hypertrophy	Mesangial expansion, GBM thickening, arteriolar hyalinosis	Mesangial nodules (Kimmelstiel-Wilson lesions) Tubulointerstitial fibrosis

Figure 30-9 Natural history of type 1 diabetic nephropathy (DN). Functional and structural manifestations of DN. Numbers *1* through *5* indicate the stages of nephropathy defined by Mogensen; *ESRD,* end-stage renal disease; *GBM,* glomerular basement membrane; *GFR,* glomerular filtration rate. *(From reference 47.)*

severe proliferative retinopathy is substantially higher in diabetic patients with nephropathy, but it has become rare today with better ophthalmologic care. In patients with DN, retinopathy tends to progress more rapidly so that yearly or half-yearly ophthalmologic examination is indicated.

Many patients with DN also have polyneuropathy. Sensory polyneuropathy is an important aspect of the "diabetic foot." There is a strong inverse correlation between the incidence of diabetic foot and renal function[53] (Fig. 30-12). Motor and sensory neuropathy may cause areflexia, wasting, and sensory disturbances such as paresthesia, anesthesia, and impaired perception of vibration and pain, but the most vexing clinical problems are the results of autonomic polyneuropathy. Because cardiac innervation is defective, pain and angina are frequently absent when the patient has coronary heart disease and myocardial infarction. Further consequences of autonomic polyneuropathy are gastroparesis (delayed emptying of gastric contents into the gut) and diarrhea or constipation (often alternating with each other). These problems are caused by impaired intestinal innervation, often complicated by intestinal bacterial overgrowth because of stasis. Also, urogenital abnormalities are common, including erectile impotence and detrusor paresis with delayed and incomplete emptying of the bladder.

The major macrovascular complications associated with DN are stroke, coronary heart disease, and peripheral vascular disease.[54,55] These complications occur up to five times more frequently in diabetic patients with than without DN.

Survival in Patients with Diabetic Nephropathy

The presence of DN greatly increases mortality in patients with both type 1 and type 2 diabetes. Compared with the background population, mortality in patients with type 1 diabetes and no proteinuria is elevated only twofold to threefold; in contrast, it is increased 20- to 200-fold in patients with proteinuria.[56,57]

The major increase in risk starts when microalbuminuria has developed (Fig. 30-13). An increased risk is found even in the upper-normal range of albuminuria (Fig. 30-14). Urinary albumin excretion is a good predictor of cardiovascular (CV) events the first 5 years after measurement, but repeating the measurement several years later also detects progression, which is also associated with increased CV risk.[57] The presence of albuminuria likely reflects generalized endothelial cell dysfunction, thus increasing the risk of atherosclerosis.[57] Albuminuria is also associated with many CV risk factors, such as elevated BP, dyslipoproteinemia, increased platelet aggregation, and increased C-reactive protein concentration. An added risk factor is presumably the association with autonomic polyneuropathy (as found in diabetic foot syndrome[58]), which is a predictor of death from myocardial infarction or arrhythmia.

RENAL PATHOLOGY

After the onset of diabetes, kidney weight increases by an average of 15%. Renal size remains increased until overt nephropathy is established. Most patients with type 1 diabetes have a sustained increase in glomerular volume and glomerular capillary luminal volume. Although atrophic ischemic glomeruli are present, some of the nonfunctioning glomeruli fill up with material staining with periodic acid–Schiff (PAS), thus preserving their increased dimensions. These changes are accompanied by hypertrophy of the interstitium.[59]

In patients with diabetes of more than 10 years' duration, whether or not nephropathy is present, GBM thickening up to three times the

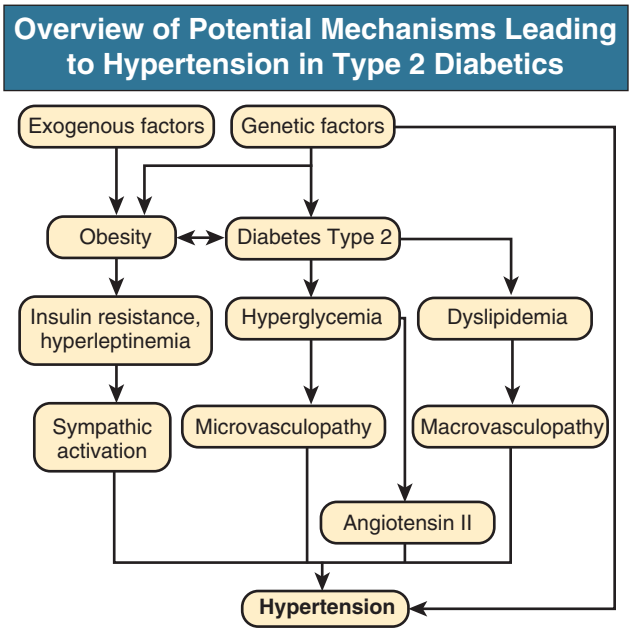


Figure 30-10 Overview of potential mechanisms leading to hypertension in type 2 diabetic patients. Genetic susceptibility factors for primary hypertension and diabetes may be clustered so that an individual patient may have a higher incidence of both diseases. Obesity and the metabolic syndrome lead to insulin resistance and hyperleptinemia associated with sympathic nerve activation. Hyperglycemia directly activates the renin-angiotensin system and, in addition, through renal microvasculopathy stimulates development of hypertension. Dyslipidemia leads through macrovasculopathic alteration to stiffness of vessels and hypertension.

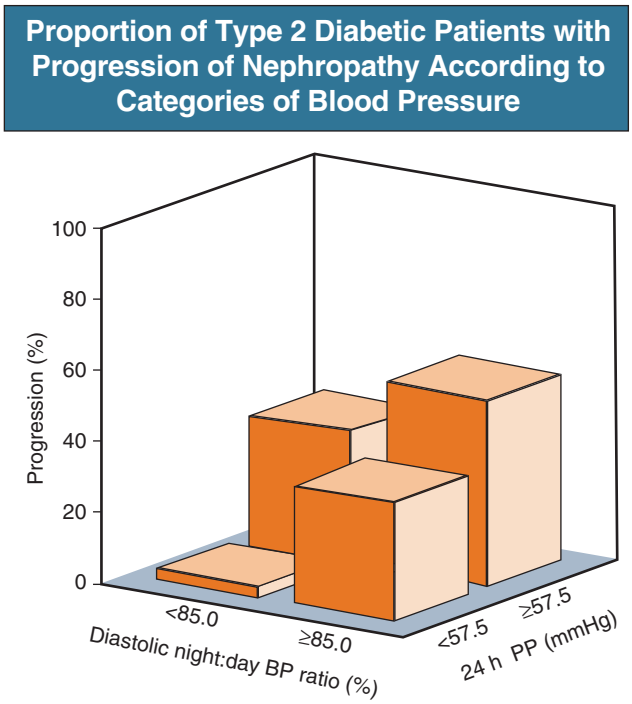


Figure 30-11 Proportion of type 2 diabetic patients with progression of nephropathy according to categories of blood pressure. Progression risk according to categories of night : day diastolic BP (median value < 85% or ≥ 85%), and 24 hour ambulatory pulse pressure *(PP)* (median value < 57.5% or ≥ 57.5%). *(From reference 54.)*

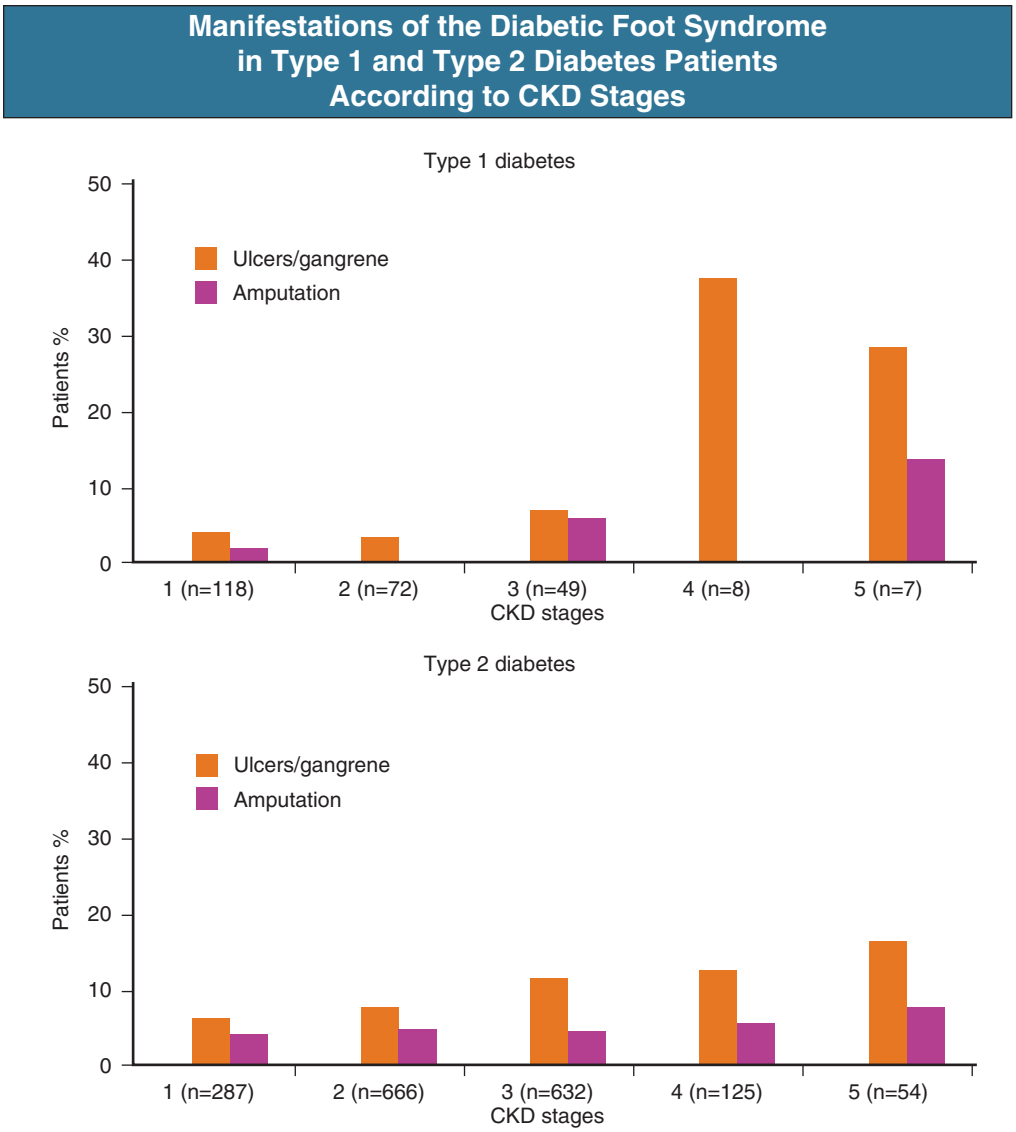


Figure 30-12 Association between manifestations of the DFS in type 1 and 2 diabetes patients classified according to CKD stages. Only patients with albuminuria were studied. All patients in a chronic kidney disease *(CKD)* stage were considered 100%. Diabetic foot syndrome *(DFS)* increases with higher CKD stages. *(From reference 58.)*

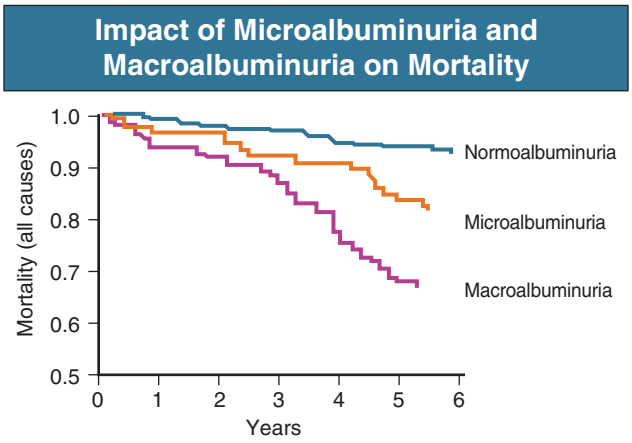


Figure 30-13 Impact of microalbuminuria and macroalbuminuria on mortality. The impact of microalbuminuria and macroalbuminuria on mortality was evaluated prospectively in 328 Caucasian patients with non–insulin-dependent diabetes mellitus (DM) observed for 5 years. Microalbuminuria and macroalbuminuria led to a significant increase in total mortality compared with patients who remained normoalbuminuric. *(From reference 56.)*

normal range of 270 to 359 nm is an almost universal feature (Fig. 30-15). In advancing DN, there is a consistent correlation between GBM thickness and fractional mesangial volumes with the urinary albumin excretion rate.

Nodular glomerular intercapillary lesions in advanced DN were described in 1936 by Kimmelstiel and Wilson (Fig. 30-16, *C*). The nodules are located in the central regions of peripheral glomerular lobules as well-demarcated eosinophilic and PAS-positive masses (Fig. 30-16, *C* and *D*). When they are not acellular, nodules contain pyknotic nuclei. It is suggested that nodules result from microaneurysmal dilation of the associated capillary followed by mesangiolysis and laminar organization of the mesangial debris with lysis of the center of the lobule. Foam cells often surround the nodules. These appearances are pathognomonic for diabetes but are reported in only 10% to 50% of biopsy specimens in both type 1 and type 2 diabetes. Nodules are also seen in membranoproliferative glomerulonephritis (MPGN) (see Chapter 21), in amyloidosis and light-chain deposition disease (see Chapter 27), and rarely, without diabetes (see Chapter 28); specific stains and immunofluorescence findings, respectively, will clarify the diagnosis. When no nodules are seen, specific staining should be used to exclude amyloid.

The diffuse glomerular lesion occurs more often than the nodular lesion, with an incidence of more than 90% in patients with type 1 diabetes longer than 10 years and an incidence of 25% to 50% in patients with type 2 diabetes. Diffuse glomerular lesions consist of an increase of mesangial matrix extending to involve the capillary loops (Fig. 30-16, *B*). In contrast to nodular lesions, which are of little functional significance, the degree of diffuse glomerulosclerosis correlates with the clinical manifestations of worsening renal function. Accumulation of mesangial matrix is the feature most consistently associated with progression.[60] In more severe disease, the capillary wall thickening and mesangial expansion lead to capillary narrowing (see Fig. 30-15, *B*) and hyalinization, with accompanying periglomerular fibrosis.

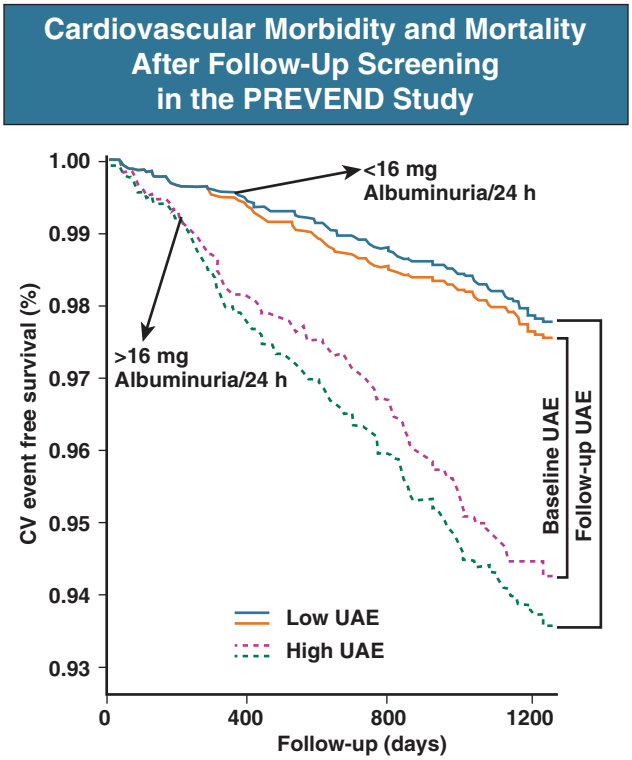


Figure 30-14 Event-free survival for cardiovascular (CV) morbidity and mortality after follow-up screening in the PREVEND study. Individuals are stratified according to the presence of a high or low urinary albumin excretion *(UAE)*. High and low UAE are defined by either the UAE measurement from the baseline screening *(orange and violet lines)* of approximately 4.2 years before follow-up screening or the repeated UAE measurement at time of the follow-up screening *(blue and green lines)*. To allow comparison, the survival curves for the 6800 individuals with either the baseline or follow-up measurement of UAE are plotted in the same graph. A high UAE *(dashed lines)* is defined as a UAE ≥ 16.2 mg/24 h, being the 75th percentile of UAE with use of the UAE measurement of the baseline screening. *(From reference 57.)*

Podocytes are involved early in the course of DN in type 1 and type 2 diabetes mellitus (Fig. 30-17), and an increase in foot process width is already observed in microalbuminuric type 1 diabetics.[61,62] Longitudinal studies in DN demonstrated a reduction in podocyte number that closely correlated with proteinuria.[61] Renal biopsy specimens from Pima Indians with type 2 diabetes showed a broadening in podocyte foot processes and a concomitant reduction in the number of podocytes per glomerulus.[63]

Arteriolar lesions are prominent in diabetes. Hyaline material progressively replaces the entire wall structure and involves both the afferent and efferent vessels, which is highly specific for diabetes.

A new classification of DN was introduced in 2007. This classification considers not only glomerular changes (Fig. 30-18), but also pathologic alterations of the tubulointerstitium and the vasculature.[64] Immunohistology is usually negative, but linear IgG can be seen occasionally because of passive trapping in the GBM (Fig. 30-19).

Tubulointerstitial leukocyte infiltration is often found in DN. Tubulointerstitial fibrosis and tubular atrophy may be the best pathologic correlates for the progressive decline in GFR. Tubulointerstitial fibrosis and renal arteriosclerosis are more prevalent in type 2 than type 1 diabetes. In fact, renal structure is heterogeneous in type 2 diabetic patients; only a subset of type 2 patients have typical diabetic glomerulopathy, whereas a substantial proportion have more advanced tubulointerstitial and vascular rather than glomerular lesions, or they have normal or near-normal renal structure.[64] Some patients with type 2 diabetes have a kidney appearance more suggestive of glomerular ischemia or tubulointerstitial disease.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of DN is based on the detection of proteinuria. In addition, most patients also have hypertension and retinopathy. The

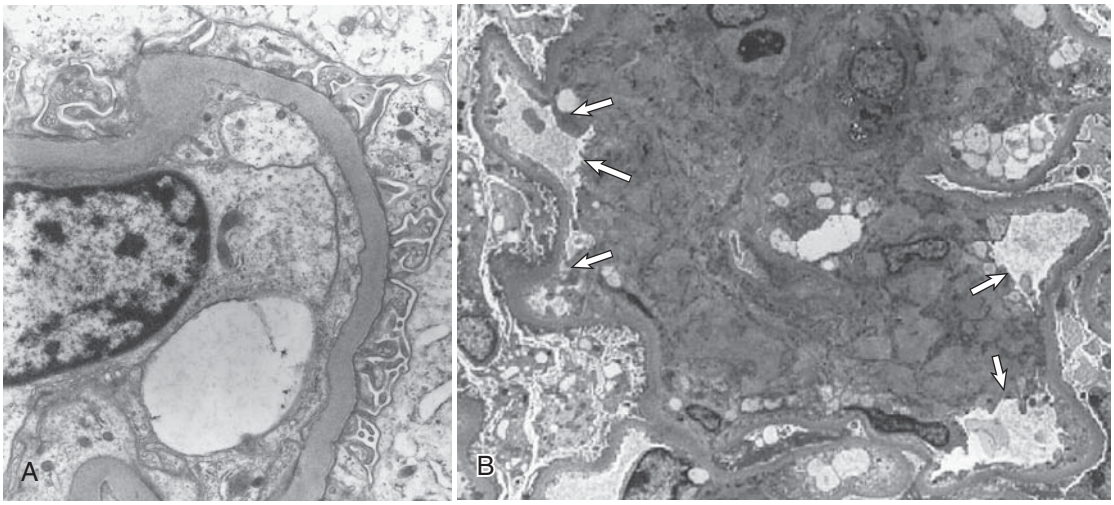


Figure 30-15 Electron microscopy of structural changes in diabetic nephropathy. A, Glomerular basement membranes are diffusely thickened. **B,** The expanded mesangium encroaches on the capillary spaces *(arrows)*.

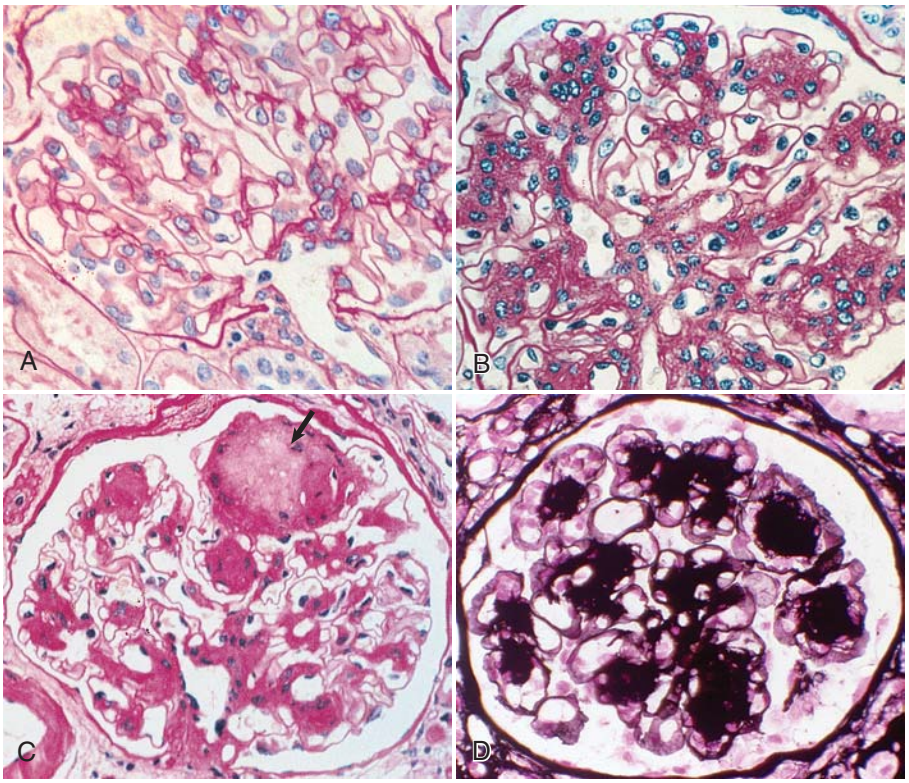


Figure 30-16 Light microscopy of structural changes in diabetic nephropathy (DN). A, Normal glomerulus. **B,** Diffuse glomerular lesion: widespread mesangial expansion. **C,** Nodular lesion as well as mesangial expansion: there is a typical Kimmelstiel-Wilson nodule at the top of the glomerulus *(arrow).* (**A, B,** and **C,** Periodic acid–Schiff reaction). **D,** Nodular lesion: methenamine silver staining shows the marked nodular expansion of mesangial matrix.

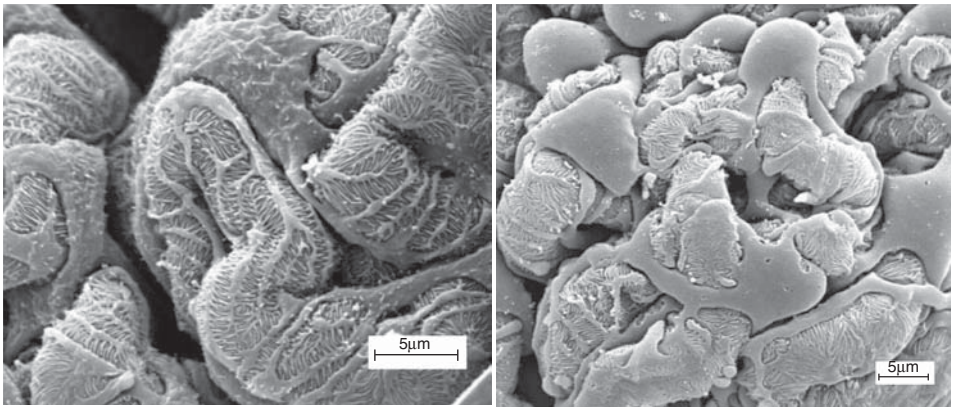


Figure 30-17 Electron micrograph of external surface of glomerular tufts from rats after removal of Bowman capsule by freeze-fracture. *Left,* Normal rat kidney with podocyte cell body; the primary processes and terminal foot processes resting on the glomerular capillary basement membrane are clearly seen. *Right,* In diabetic rat kidney, the decrease in the density of foot processes and the denuded glomerular capillary basement membrane are apparent. *(From reference 62.)*

main diagnostic procedures in the patient with suspected DN include the following:

- Measurement of urinary albumin or protein
- Measurement of serum creatinine concentration and estimation of GFR
- Measurement of blood pressure
- Ophthalmologic examination

Measurement of Albuminuria or Proteinuria

Microalbuminuria is arbitrarily defined as the excretion of 30 to 300 mg/24 h of albumin in at least two of three consecutive nonketotic sterile urine samples (Table 30-1). There is substantial

Urinary Albumin Excretion Rate

	UAER	
Condition	***24 hr (mg/day)***	***Overnight (µg/min)***
Normoalbuminuria	<30	<20
Microalbuminuria	30-300	20-200
Overt nephropathy	>300	>200

Table 30-1 Urinary albumin excretion rate (UAER). Levels of 24 hour and overnight UAE are diagnostic for microalbuminuria and overt diabetic nephropathy.

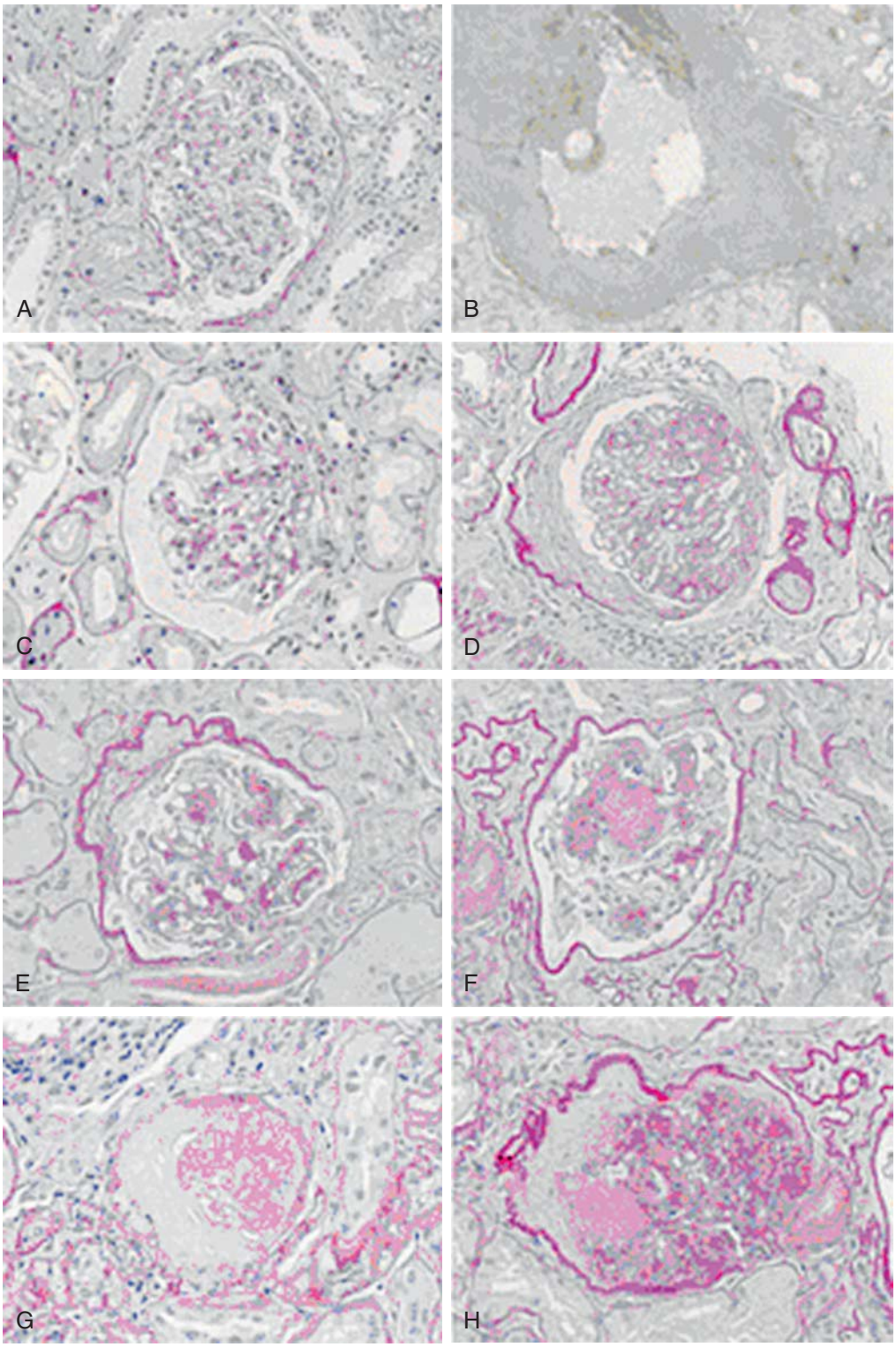


Figure 30-18 Pathologic classification of diabetic nephropathy (DN; according to Tervaert et al). Representative examples of the morphologic lesions in DN. **A,** Glomerulus showing only mild ischemic changes, with splitting of Bowman capsule. No clear mesangial alteration. **B,** Electron micrograph of this glomerulus: the mean width of the GBM was 671 nm (mean taken over 55 random measurements). Electron microscopy provides the evidence for classifying the biopsy with only mild light microscopy changes into class I**. C** and **D,** Class II glomeruli with mild and moderate mesangial expansion, respectively. In **C**, the mesangial expansion does not exceed the mean area of a capillary lumen (IIa), whereas in **D,** it does (IIb). **E** and **F,** A class III Kimmelstiel-Wilson lesion is seen in **F.** The lesion in **E** is not a convincing Kimmelstiel-Wilson lesion; therefore, on the basis of the findings in this glomerulus, the finding is consistent with class IIb. For the purpose of the classification, at least one convincing Kimmelstiel-Wilson (as in **F**) needs to be present. **H,** Signs of class IV DN consist of hyalinosis of the glomerular vascular pole and a remnant of a Kimmelstiel-Wilson lesion on the opposite site of the pole. **G,** Example of glomerulosclerosis that does not reveal its cause (glomerulus from same biopsy as **H**). For the purpose of the classification, signs of DN should be histopathologically or clinically present to classify a biopsy with global glomerulosclerosis in more than 50% of glomeruli as class IV. *(From reference 64.)*

individual day-to-day variation in albumin excretion (coefficient of variation, 30% to 50%) and also between day and night collections (Fig. 30-20). Even in the upper quantiles of so-called normoalbuminuria, however, the risk of progression and of CV events is definitely elevated. At concentration of 30 to 300 mg/24 h, albumin is normally not detected by nonspecific tests for protein (e.g., Biuret reaction). Albumin can be detected, however, by use of specific techniques such as dipstick, enzyme-linked immunosorbent assay, nephelometry, and radioimmunoassay. Instead of difficult-to-obtain 24-hour urine collections, the albumin concentration can be determined in spot urine or, better, first-void morning urine samples. The normal range is <20 mcg/min or <20 mcg/ml.

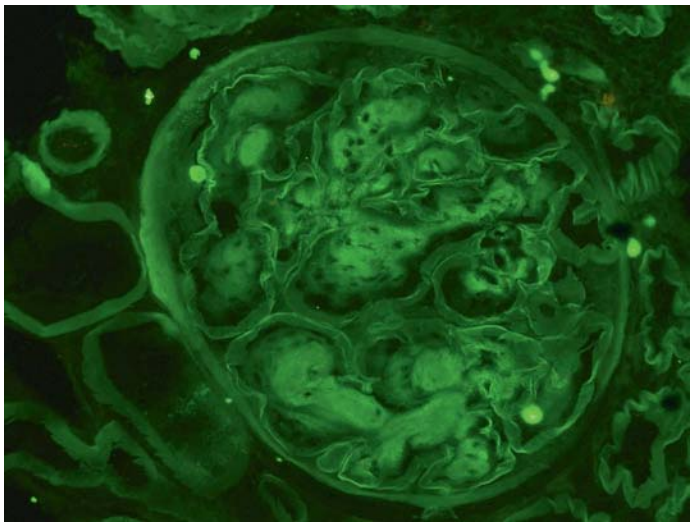


Figure 30-19 Immunofluorescence for glomerular IgG in diabetic nephropathy. Faint staining of the glomerular basement membrane for IgG results from passive trapping of IgG in the expanded GBM. *(Courtesy Prof. Peter Furness, Leicester, UK.)*

The detection of urinary albumin is a specific indicator of DN only if confounding factors such as fever, physical exercise, urinary tract infection, nondiabetic renal disease, hematuria from other causes, heart failure, uncontrolled hypertension, and uncontrolled hyperglycemia have been excluded.[65,66]

The main advantage of searching for microalbuminuria early in the course of diabetes is that it predicts a high renal and CV risk and thus allows targeted intervention. The American Diabetes Association (www.diabetes.org) and other societies recommend annual screening of all diabetic patients.

By definition, there is clinically overt DN (macroalbuminuria) if the rate of albumin excretion exceeds 300 mg/day. At this point, serum proteins other than albumin are usually excreted in the urine as well (nonselective proteinuria).

Although there are few guidelines regarding repeated measures of albuminuria or proteinuria after a diagnosis of diabetic kidney disease has been established, it is likely useful to repeat measures of albumin-creatinine ratio or protein-creatinine ratio annually to determine if there is progression of disease.[66]

Measurement of Blood Pressure

When measuring the BP in a diabetic patient, the following issues should be taken into account:

- In overweight patients with type 2 diabetes, the size of the cuff has to be adapted to the upper arm circumference. When this exceeds 32 cm, cuffs of 18-cm width are indicated.
- Patients with severe autonomic neuropathy tend to develop orthostatic hypotension, defined as a decrease of systolic BP by more than 20 mm Hg in the upright position. It is therefore advisable to measure BP after being in the upright position for a defined period (e.g., 30 minutes). However, such an approach may not always be feasible in a primary care setting.
- The circadian BP profile tends to be abnormal in early stages, and even a paradoxical increase in the nighttime BP is not rare.

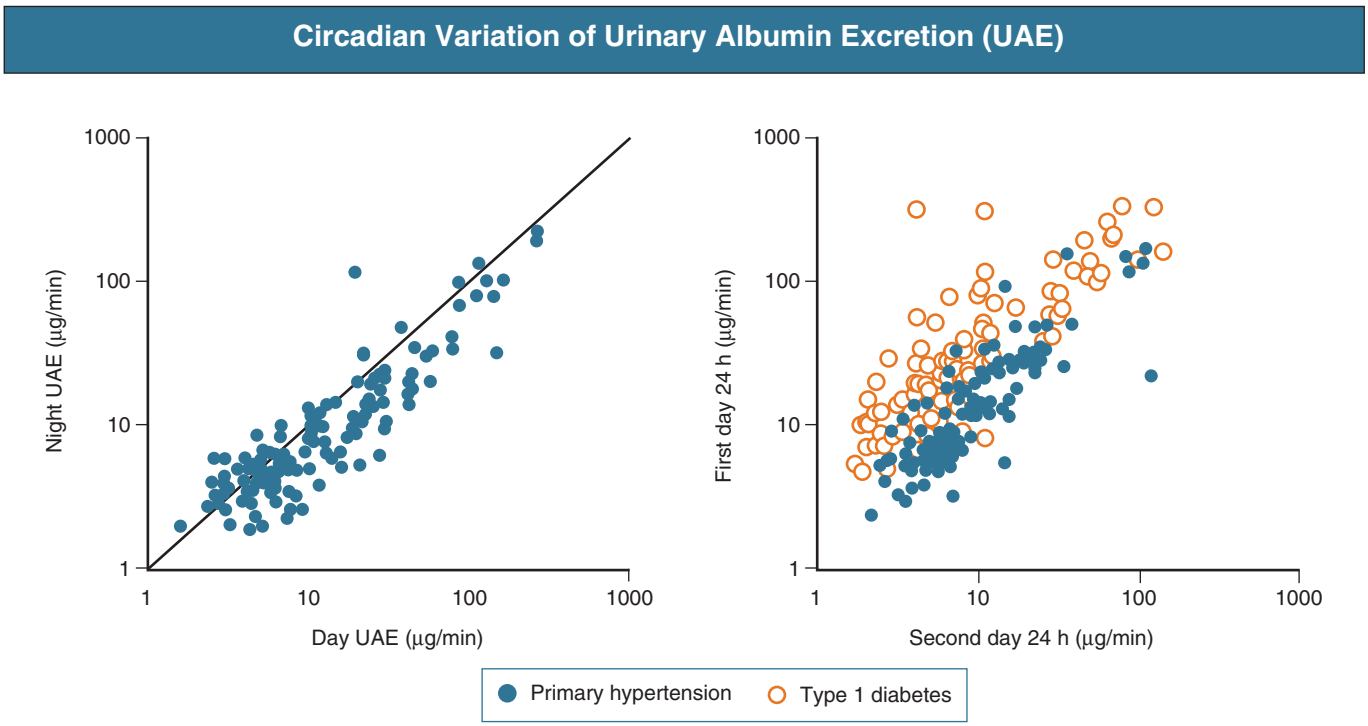


Figure 30-20 Circadian variation of urinary albumin excretion (UAE). UAE is lower in resting conditions at night than during daytime activity. Relationship between UAE assessed on two different days 1 week apart in patients with type 1 diabetes *(open circles)* and primary hypertension *(closed circles)*. There is substantial individual day-to-day variation of albumin excretion and also between day and night collections. *(From reference 66.)*

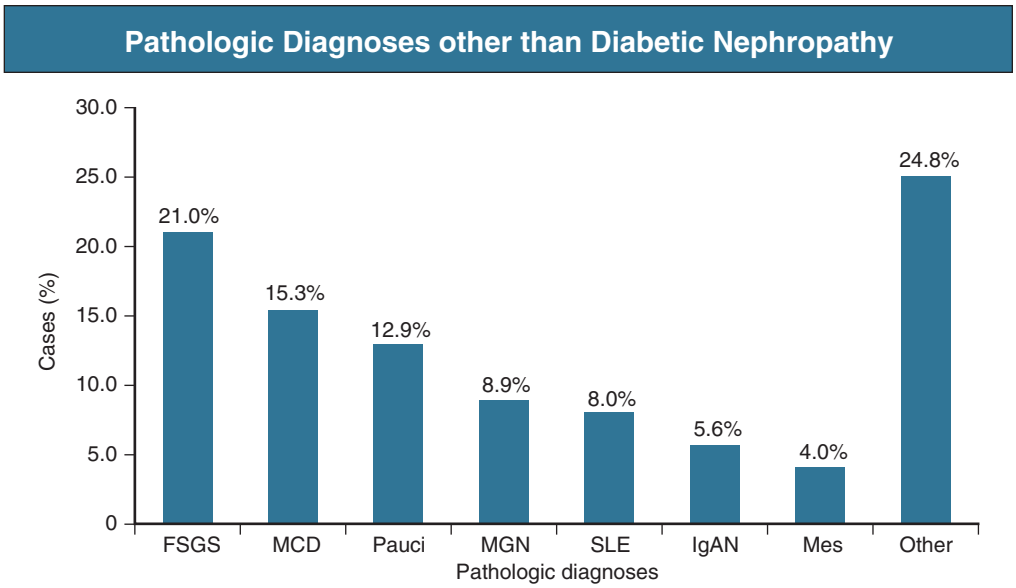


Figure 30-21 Pathologic diagnoses other than diabetic nephropathy are found in more than half of patients with type 2 diabetes with proteinuria. A total of 233 patients were studied; 53.2% (124 patients) had a diagnosis of nondiabetic renal disease; *FSGS,* focal segmental glomerulosclerosis; *IgAN,* IgA nephropathy; *MCD,* minimal change disease; *Mes,* mesangial immune complex glomerulonephritis; *MGN,* membranous nephropathy; *Pauci,* ANCA-positive pauci-immune glomerulonephritis; *SLE,* systemic lupus erythematosus. *(From reference 68.)*

In the diabetic patient with nephropathy, it has been shown that a nighttime increase in BP is independently associated with a 20-fold higher mortality and a higher risk of renal failure. Occasional measurements of ambulatory BP are particularly useful to assess the efficacy of antihypertensive treatment.

- In diabetic patients with sclerosis or calcification of the radial and brachial arteries, pseudohypertension, or "white-coat hypertension," may occasionally occur, that is, spuriously reduced BP values despite normotension established by intra-arterial BP measurements. This condition should be suspected if a discrepancy is found between modest target organ damage (e.g., left ventricular hypertrophy) and very high measured BP values. Such patients tend to develop marked hypotension even with relatively modest antihypertensive therapy.

Measurement of Serum Creatinine and Estimation of Glomerular Filtration Rate

In clinical practice, the serum creatinine concentration is most frequently used to assess renal function, but it may be grossly misleading in wasted patients when muscle mass is low. This problem is particularly frequent in elderly female patients with type 2 diabetes. Therefore, the Kidney Disease Outcome Quality Initiative (KDOQI) guidelines recommend that the GFR be estimated according to the Modification of Diet in Renal Disease (MDRD) study equation (see Chapter 3).

Differential Diagnosis

Although hematuria has been considered one of the atypical features indicating the presence of nondiabetic renal disease in patients with diabetes, the clinical significance of hematuria in the overall course of DN suggests that hematuria could be a sign of DN. Moreover, a study identified hematuric patients with pathologically defined DN, who had significantly lower renal function than nonhematuric patients with DN.[67] The prevalence of nephrotic syndrome and retinopathy was significantly higher in hematuric patients than in nonhematuric patients with diabetic glomerulosclerosis.

On the other hand, non-DN disease may be found in type 2 diabetic patients. Younger patients with diabetes, shorter duration of diabetes, and proteinuria in the absence of retinopathy strongly suggest nondiabetic renal disease.[68] Membranous nephropathy, FSGS, acute interstitial nephritis, postinfectious GN, and IgA nephropathy have all been described in type 2 diabetic patients in whom DN was clinically suspected (Fig. 30-21).

Indications for Renal Biopsy

Further investigation, including renal biopsy, should be considered in the following patient situations (Fig. 30-22):

- If retinopathy is not present in type 1 diabetes with proteinuria or moderately impaired renal function (absence of retinopathy does not exclude DN in type 2 diabetes).
- If the onset of proteinuria has been sudden and rapid, particularly in type 1 diabetes, and if the duration of type 1 diabetes has been less than 5 years. Alternatively, if the evolution has been atypical, for example, without transition through the usual stages, particularly the development of nephrotic syndrome without previous microalbuminuria.
- If macroscopic hematuria is present or active nephritic urinary sediment is found that suggests GN, such as acanthocytes and red blood cell casts; the sediment in DN typically is unremarkable apart from some occasional erythrocytes.
- If the decline in renal function is exceptionally rapid, or if renal dysfunction is found without significant proteinuria (first, renovascular disease must be excluded) (Fig. 30-23).

If renal ultrasound reveals small kidneys or a size difference, it is prudent not to perform a renal biopsy. Overall, renal biopsy is indicated only in a small minority of diabetic patients.

Approach to the Diabetic Patient with Impaired Renal Function

When seeing a diabetic patient with CKD, the nephrologist should do the following:

- Assess the cause of CKD (acute vs. chronic renal impairment; DN vs. alternative causes of renal damage).
- Assess the magnitude of proteinuria and the rate of progression.
- Search for evidence of the typical extrarenal microvascular and macrovascular complications of diabetes.

The majority of diabetic patients with heavy proteinuria or renal failure have DN. Renal ischemia (atherosclerotic renal artery stenosis

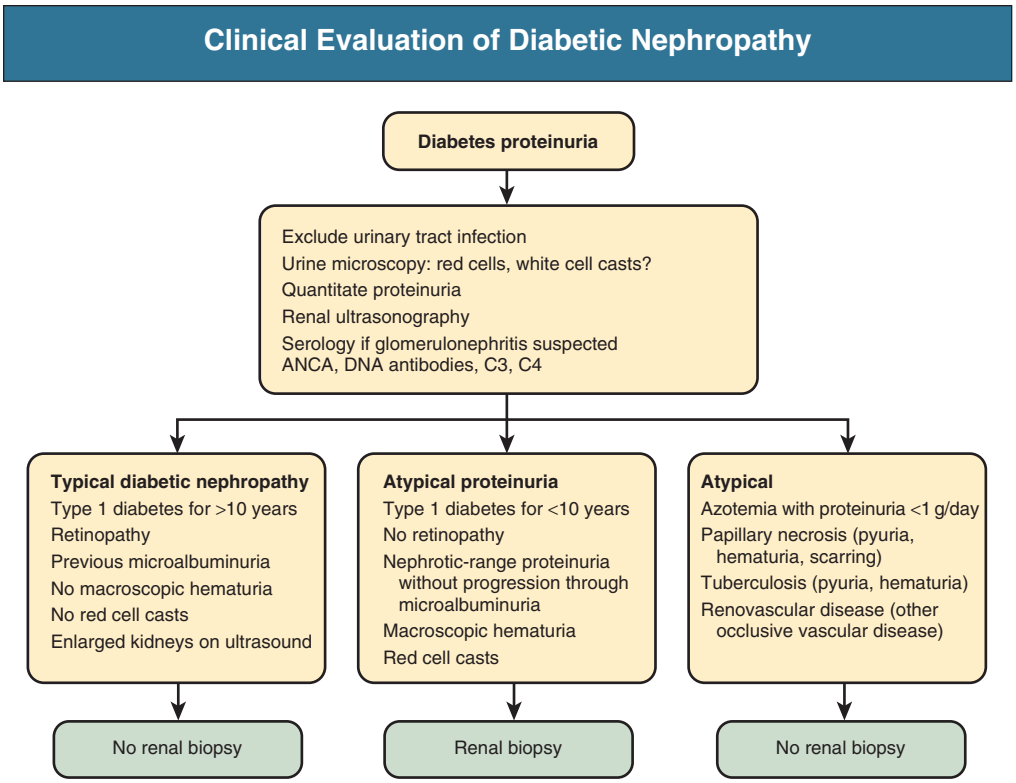


Figure 30-22 Clinical evaluation of diabetic renal disease. *ANCA,* Antineutrophil cytoplasmic autoantibody.

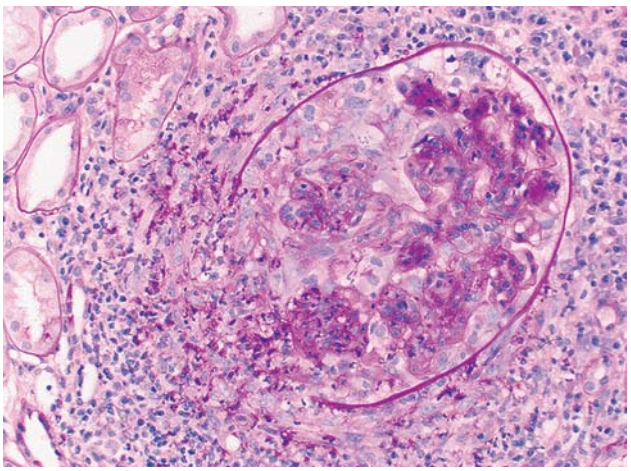


Figure 30-23 Glomerulonephritis superimposed on diabetic nephropathy (DN). A glomerulus showing a cellular crescent with rupture of Bowman capsule superimposed on nodular DN. The patient, known to have DN, presented with rapidly deteriorating renal function and red cell casts in the urine.

or cholesterol embolism) is common in diabetic patients, and a substantial proportion of type 2 diabetic patients have small kidneys and low GFR without albuminuria, possibly the result of macrovascular disease.

If urinary tract infection occurs, it is more severe in the diabetic than the nondiabetic patient. Purulent papillary necrosis and intrarenal abscess formation, however, have now become rare.

Diabetic patients with nephropathy are particularly prone to development of AKI after administration of nonsteroidal anti-inflammatory drugs (NSAIDs) or radiocontrast media, or after CV events or septicemia. Preventive measures for AKI are discussed in Chapter 73. AKI superimposed on preexisting DN carries a very poor renal prognosis.

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CHAPTER 31

Prevention and Treatment of Diabetic Nephropathy

Li-Li Tong and Sharon Adler

In diabetic patients, the development of diabetic nephropathy (DN) signifies the presence of a generalized microvascular syndrome that is frequently accompanied by macrovascular disease (see Chapter 30). Classically, DN evolves through several clinical stages based on urine albumin excretion (UAE) values: normoalbuminuria, microalbuminuria, and macroalbuminuria, or overt nephropathy. Regression of microalbuminuria to normoalbuminuria occurs spontaneously in a substantial proportion of patients with type 1 and type 2 diabetes. Without treatment, however, patients with persistent microalbuminuria are at high risk of progressing to overt nephropathy.

There is consensus that the level of UAE has predictive importance for both renal outcome and cardiovascular (CV) morbidity and mortality and affects the choice of therapeutic intervention. In patients with established DN, regression to normoalbuminuria and preservation of renal function, although difficult, is the ideal treatment goal. Strict blood pressure (BP) and glycemic control early in the disease course is vital. Aggressive lipid-lowering and lifestyle modifications, including adherence to low-protein and low-sodium diet, exercise, weight loss, and smoking cessation all are beneficial and likely to improve renal and CV outcome. Most patients with advanced-stage diabetic kidney disease, however, are likely to progress relentlessly to end-stage renal disease (ESRD), even though treatment may slow this progression.

This chapter reviews the current preventive and therapeutic strategies that promote renoprotection and cardioprotection in diabetic patients (Fig. 31-1). In general, the treatment principles for established DN are similar to those adopted for the prevention of DN, although multiple and more intensive strategies may be required for treatment. Special considerations are indicated in the management of the diabetic patient with advanced chronic kidney disease (CKD) (see Chapter 32). Many therapeutic issues discussed here are not specific for DN and thus are also relevant for CKD in general (see Chapter 80).

PREVENTION OF DIABETIC NEPHROPATHY

Prevention and early detection of DN improve patient outcome. General measures for prevention of DN include glycemic control and rigorous BP control. Because diabetes is associated with increased risk for CV morbidity and mortality, treatment of dyslipidemia as well as diet and lifestyle modifications, including physical activity and weight reduction as appropriate and smoking cessation, can significantly lower the CV risks.

Glycemic Control

In type 1 diabetic patients, strict glycemic control decreases the risk for microalbuminuria and impaired glomerular filtration rate (GFR). The Diabetes Control and Complications Trial (DCCT) compared the effects of intensive glucose control with conventional treatment on the development and progression of the long-term complications of type 1 diabetes (Fig. 31-2). During a 9-year period, patients receiving intensive therapy (mean hemoglobin A_{1c} 7%) had a 35% to 45% lower risk for development of microalbuminuria compared with the control group (mean HbA_{1c} 9%).[1] More recently, DCCT and Epidemiology of Diabetes Interventions and Complications (EDIC) trial data indicated that the long-term risk of an impaired GFR was lower by 50% in patients treated for an average of 6½ years with DCCT intensive glucose control than among those treated with conventional therapy. This effect was not evident until more than 10 years after randomization, beyond the period of the DCCT treatment intervention.[2] Moreover, the restoration of euglycemia with pancreas transplantation prevents recurrent DN in renal allograft of type 1 diabetic patients.[3]

For type 2 diabetic patients, several major studies have demonstrated a lower risk of nephropathy with stricter glycemic control. In a study design similar to the DCCT, the Kumamoto study found a 60% reduction in microalbuminuria in relatively young, nonobese type 2 diabetic patients receiving intensive glycemic treatment (HbA_{1c} 7.1%) compared with conventional treatment (HbA_{1c} 9.4%).[4] In the United Kingdom Prospective Diabetes Study (UKPDS) trial, newly diagnosed patients with type 2 diabetes were randomly assigned to intensive management (HbA_{1c} 7.0%) with a sulfonylurea or insulin or to conventional management (HbA_{1c} 7.9%) with diet alone. After 9 years of intensive therapy, relative risk reduction for the development of microalbuminuria was 24%.[5] After termination of the study, patients were observed for a further 10 years. The differences in HbA_{1c} were lost within 1 year, but a 24% lower risk of microvascular disease and myocardial infarction (−15%) persisted. All-cause mortality (−13%) was also reduced. This phenomenon of ongoing beneficial effects on diabetic complications after a period of improved glycemic control even if followed by a return to less intensive metabolic control has been described as representing "metabolic memory" by the DCCT/EDIC investigators and as a "legacy effect" by the UKPDS investigators. This observation underlines the importance of early glycemic control before complications develop.

Three recent major trials testing whether glycemic control reduced cardiovascular disease (CVD) risk in type 2 diabetic patients have refined our approach to establishing glycemic goals. The Action in Diabetes and Vascular Disease, Perindopril and Indapamide Controlled Evaluation (ADVANCE) study showed that intensive blood glucose control (HbA_{1c} 6.5% vs. 7.3%) yielded a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily because of a 21% relative reduction in nephropathy.[6] However, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, very tight glycemic control (lowering of HbA_{1c} to median of 6.4% vs. 7.5% with conventional control)

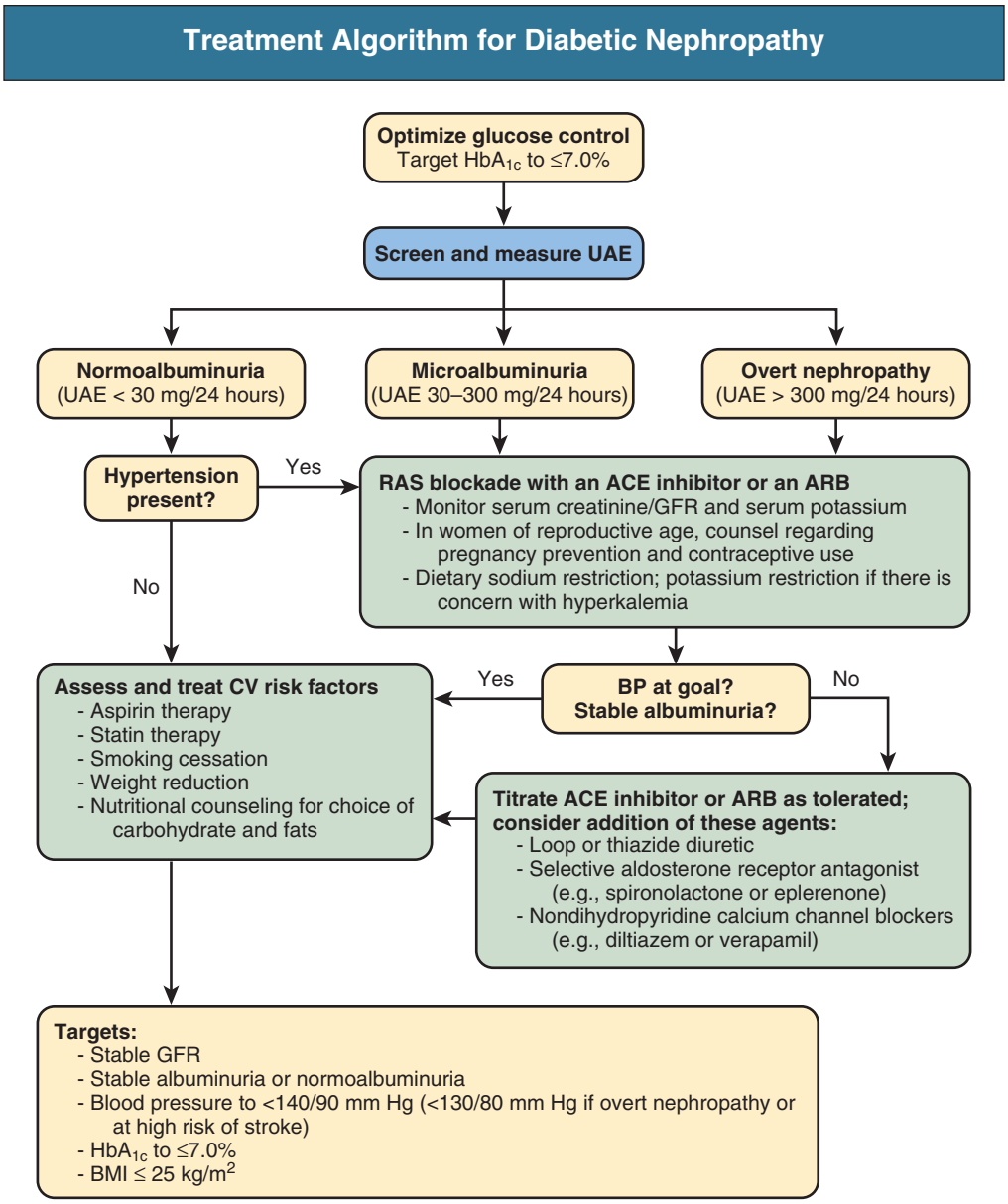

Figure 31-1 Treatment algorithm for diabetic nephropathy. In considering the management of patients with diabetes and chronic kidney disease (CKD), a global perspective is required, which includes therapy that retards progression of kidney disease as well as therapy that minimizes cardiovascular risk and addresses other major diabetic complications, including coronary artery disease, peripheral vascular disease, retinopathy, neuropathy, gastroparesis, and dyslipidemia. *Hb,* Hemoglobin; *UAE,* urine albumin excretion; *HTN,* hypertension; *RAS,* renin-angiotensin system; *ACE,* angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *GFR,* glomerular filtration rate; *CV,* cardiovascular; *LDL,* low-density lipoprotein; *CVD,* cardiovascular disease; *BMI,* body mass index.

was associated with 22% increase in mortality from any cause and did not significantly reduce major CV events.[7] A third major study of tight glucose control in type 2 diabetics, the Veterans Affairs Diabetes Trial (VADT), found no significant reduction in CV deaths or events during 7.5 years in high-risk patients treated aggressively for glycemic control (median HbA_{1c} 6.9%) compared with standard therapy (median HbA_{1c} 8.4%).[8]

It is apparent that glycemic control in type 2 diabetic patients must be individualized and take into account the patient's age, duration of diabetes, presence of CVD, presence of CKD, and microvascular risks and complications, as well as previous glycemic control and susceptibility to and awareness of hypoglycemia. In younger patients with recently diagnosed diabetes and no prior CVD events, strict glycemic control can reduce the risk of nephropathy and other microvascular complications. In patients with longstanding diabetes and known CVD, data do not support glycemic control to HbA_{1c} of less than 7% in reducing the risk of further CVD events or mortality. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guideline recommends lowering of HbA_{1c} levels to 7.0% for both type 1 and type 2 diabetic patients.[9] At even lower glycemic targets, any potential renoprotective effects of tight glucose control must be counterbalanced by the possibility of more frequent hypoglycemic episodes.

Blood Pressure Control

In patients with type 1 diabetes, microalbuminuria typically precedes hypertension. In patients with type 2 diabetes, however, as

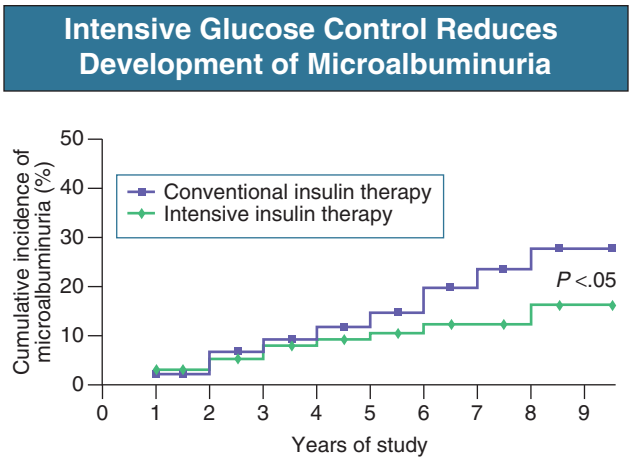

Figure 31-2 Microalbuminuria risk reduction with intensive versus conventional insulin therapy. Intensive glucose control was associated with a decreased risk for the subsequent development of microalbuminuria in patients with type 1 diabetes. *(Modified from reference 1.)*

many as 40% are hypertensive before the diagnosis.[10] In both type 1 and type 2 diabetic patients, higher BP is associated with increasing albuminuria and with more rapid progression and increased risk of kidney failure.[11] Early treatment of hypertension is critical for prevention of DN, retinopathy, and CVD. Major guidelines published before the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial have suggested that the target blood pressure in diabetic patients should be less than 130/80 mm Hg.[12] However, this BP target was challenged by findings of the ACCORD BP trial. Among diabetic patients with high CV risk randomized to goal systolic BP of less than 120 mm Hg or standard therapy aiming for under 140 mm Hg, there was no difference in the risks of composite major CV events.[13] A cross-sectional analysis of patients in the Swedish National Diabetes Registry also failed to show a reduction in mortality in patients with systolic BP below 130 vs. 130 to 139 mm Hg.[14] The recent Kidney Disease: Improving Global Outcomes (KDIGO) guideline for diabetic patients with CKD recommends a target BP of 140/90 mm Hg or less for all diabetic patients, and 130/80 mm Hg or less for patients with urine albumin excretion of greater than 30 mg per 24 hours.[15] For diabetic patients at highest risk for cerebrovascular accident (CVA, stroke), even lower systolic BP goals may provide greater protection against stroke, but the potential risks and burdens of serious adverse events attributable to antihypertensive therapy must be considered with such treatment goals.

Renin-Angiotensin System Blockade in Prevention

The role of blockade of the renin-angiotensin system (RAS) in normotensive, normoalbuminuric diabetic patients for the primary prevention of DN is unproved and cannot be recommended at this time. Most patients with diabetes do not develop DN, even after long periods of uncontrolled hyperglycemia, and there are hazards with the use of RAS-blocking drugs, including their potential teratogenicity in pregnancy. In a *post hoc* analysis of three randomized controlled trials (RCTs) conducted as part of the multicenter Diabetic Retinopathy Candesartan Trials (DIRECT) program, which included normotensive and normoalbuminuric type 1 diabetics and normoalbuminuric type 2 diabetics with or without hypertension, the ARB candesartan was found to have no effect on the development of microalbuminuria.[16] A recent study investigating whether olmesartan would prevent microalbuminuria in type 2 diabetic patients showed that the incidence of microalbuminuria was slightly reduced from 9.8% to 8.2% in the olmesartan arm, but this difference disappeared after adjusting for the lower BP in that arm. Of potential concern, was a higher rate of fatal CV events with this ARB among patients known to have preexisting coronary heart disease, especially those with lower BP.[17]

In hypertensive diabetic patients, an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) is effective as a first-line antihypertensive agent. The Bergamo Nephrologic Diabetes Complications Trial (BENEDICT), which randomized hypertensive normoalbuminuric type 2 diabetic patients to placebo, verapamil, trandolapril, or a combination of verapamil plus trandolapril, showed less progression to microalbuminuria in patients receiving trandolapril either alone or with verapamil.[18] Verapamil alone was no different from placebo. There were similar findings in smaller studies with other RAS inhibitors, implicating a class effect.[19] Longer-term studies would be required to demonstrate the effects of RAS blockade on the clinically important outcomes of death, dialysis, and doubling of serum creatinine level in normoalbuminuric patients. Therapy for the prevention of DN likely will be guided exclusively by studies using albuminuria as a surrogate.

Treatment of Dyslipidemia

Few clinical data are available on the effects of lipid lowering alone in preventing DN. In the Diabetes Atherosclerosis Intervention Study (DAIS), type 2 diabetic patients taking fenofibrate had a significantly lower rate of progression from normoalbuminuria to microalbuminuria at 3 years compared with the placebo group.[20] Earlier clinical practice guidelines had emphasized specific treatment targets for low-density lipoprotein (LDL) cholesterol of below 100 mg/dl (2.6 mmol/l) for diabetic patients in general and below 70 mg/dl (1.8 mmol/l) for diabetic patients with CVD. These targets, however, have not been proven beneficial in any clinical trial. Newer guidelines from the American College of Cardiology and the American Heart Association are shifting away from specific LDL cholesterol treatment targets.[21] Emphasis is now placed on assessing a patient's global risk for CVD and using maximum tolerated statin intensity for primary and secondary prevention of CVD.

Nonpharmacologic Interventions

For all diabetic patients, emphasis should be placed on lifestyle modification to lower the risk of diabetic kidney disease and CV events, including dietary restriction of salt and saturated fat, weight reduction and exercise as appropriate, and smoking cessation. Smoking in particular is an independent risk factor for the development of nephropathy in type 2 diabetes and is associated with an accelerated loss of renal function.[22]

TREATMENT OF DIABETIC PATIENTS WITH MICROALBUMINURIA OR OVERT NEPHROPATHY

For diabetic patients with incipient or established DN, the optimal therapeutic approach to reduce the rate of progression of nephropathy and to minimize the risk for CV events involves aggressive management of hypertension with emphasis on a RAS blocker, combined with management of dyslipidemia, hyperglycemia, and albuminuria, as well as diet modification, exercise, and smoking cessation. Such multifactorial therapy in the Steno type 2 trial in type 2 diabetics

included management of hyperglycemia and of hypertension, ACE inhibition, statins, aspirin, reduction of fat intake, light to moderate exercise, and cessation of smoking.[23,24] Impressive lowering of the risk of CVD, nephropathy, retinopathy, and autonomic polyneuropathy was noted after 7.7 years, and even a delayed reduction of mortality was seen.

In general, patients with DN require multiple antihypertensive agents (including RAS-blocking agents) to achieve BP goal, intensive insulin therapy in type 1 diabetes, two or more drugs for glucose control in type 2 diabetes, at least one lipid-lowering agent, and an aspirin or other antiplatelet agent for CV protection. One obstacle to achieving adherence is the number of medicines and the complexity of these regimens. Therefore, treatment of patients with DN needs to be individualized and requires considerations of the cost, side effects, and convenience of the drug regimen. Regular monitoring of UAE and serum creatinine concentration to assess response to therapy and progression of disease is required.

Antihypertensive Treatment

In type 1 and type 2 diabetic patients with overt nephropathy, hypertension is an almost universal finding and is associated with volume expansion and salt sensitivity. The absence of hypertension in an untreated patient with overt nephropathy should raise suspicion for underlying cardiac problems. Uncontrolled hypertension is associated with more rapid progression of DN[25] and increased risk of fatal and nonfatal CV events.[26] Thus, effective treatment of systemic hypertension is arguably the single most important strategy in the treatment of established DN (Fig. 31-3). Some have suggested that the overall effect of BP lowering may be more important than the type of antihypertensive used.[27] Antihypertensive therapies, regardless of agent used, reduce UAE, delay progression of nephropathy, postpone renal impairment, and improve survival in both type 1 and type 2 diabetic patients with DN.[28]

The optimal lower limit for BP control in DN though remains unclear. In a secondary analysis of the Irbesartan Diabetic Nephropathy Trial (IDNT), progressive lowering of systolic BP to 120 mm Hg was associated with improved renal and patient survival, an effect independent of baseline renal function.[29] However, mortality increased with systolic BP below 120 mm Hg, although a cause-and-effect relationship cannot be inferred from the data. From a safety perspective, diastolic pressure is also important. Low diastolic BP is poorly tolerated, and the incidence of myocardial infarction and mortality increases at values below 70 mm Hg, at least in patients with coronary heart disease, presumably because coronary perfusion occurs only during diastole. Indeed, in the IDNT study, CV mortality increased not only with higher systolic pressure but also with low diastolic pressure. The recent ACCORD BP trial failed to show reduced CV events, but found increased rates of hyperkalemia and renal dysfunction, when targeting a systolic BP less than 120 mm Hg compared with less than 140 mm Hg.[13] Thus, given the lack of strong evidence of benefit from reducing systolic BP to below 130 versus below 140 mm Hg, it is reasonable to strive for a BP target of 140/90 mm Hg or less for all diabetic patients. These recommendations are consistent with the KDIGO guideline and the Eighth Joint National Committee (JNC VIII) on BP management in diabetic patients.[15]

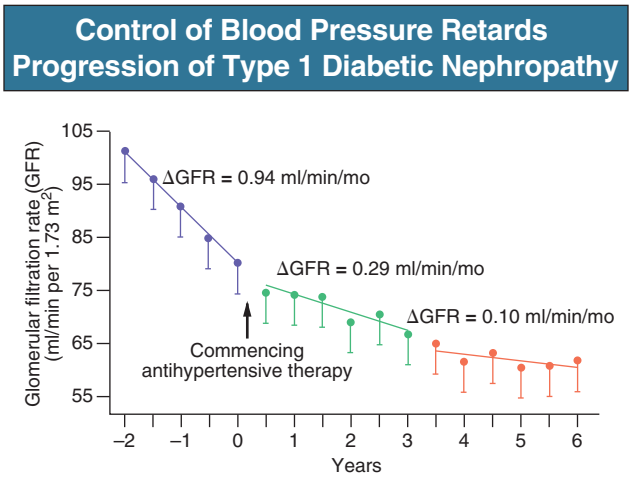

Figure 31-3 Control of blood pressure reduces the risk for progression in type 1 diabetic nephropathy. *(Modified from reference 25.)*

Renin-Angiotensin System Blockade in Treatment

In diabetic patients with established DN, RAS blockade with ACE inhibitors or ARBs confers preferential renoprotection that is independent of BP reduction. Intraglomerular hemodynamic and nonhemodynamic renal effects of angiotensin II (Ang II) best explain the observed renoprotection. Supporting this hypothesis, evidence-based *in vitro* models of DN show cellular effects of RAS inhibition that are consistent with benefit independent of BP effects (see Chapter 30).

Although many demonstrated a beneficial effect of ACE inhibitors and ARBs in retarding progressive renal disease, these studies did not differentiate between the relative contributions of the RAS blockade versus aldosterone system blockade. The renin-angiotensin-aldosterone system (RAAS) represents a hormonal cascade that functions in the homeostatic control of arterial pressure, tissue perfusion, and extracellular fluid homeostasis (see Chapter 7). In fact, plasma aldosterone levels are elevated in a subset of patients despite ACE inhibitor and ARB therapy (also known as aldosterone breakthrough; see Chapter 82). In studies that defined aldosterone breakthrough as any increase from an individual's baseline serum aldosterone level (i.e., before ACE inhibitor or ARB therapy), the incidence ranged from 40% during 10 months to 53% during 12 months.[30] In addition to its classic effects of promoting sodium retention and enhancing potassium and magnesium excretion, aldosterone promotes tissue inflammation and fibrosis.[31] Small studies have demonstrated considerably faster decline in glomerular filtration rate (GFR) in patients who experienced aldosterone breakthrough (median 5.0 ml/min/yr) than in those who did not (median 2.4 ml/min/yr). Aldosterone blockade, independent of RAS blockade, reduces proteinuria and retards progression of nephropathy. Current evidence is not strong enough to support widespread screening for aldosterone breakthrough. However, in select patients, additional aldosterone blockade with close monitoring of serum potassium levels may represent optimal therapy for patients who show aldosterone breakthrough during treatment with an ACE inhibitor or an ARB and who no longer show maximal antiproteinuric effects with these agents.

Type 1 Diabetic Patients

In type 1 diabetic patients with microalbuminuria, ACE inhibitors reduce the risk of progression to overt nephropathy.[32,33] In a meta-analysis of 12 placebo-controlled trials in 698 normotensive patients with type 1 diabetes and microalbuminuria treated with ACE inhibitors, the majority for more than 2 years, treatment was associated with a 60% reduction in progression to macroalbuminuria and a threefold increase in regression to normoalbuminuria.[34] Changes

in BP cannot entirely explain the antiproteinuric effect of ACE inhibitors.

In patients with macroalbuminuria or overt nephropathy, the Collaborative Study Group trial demonstrated that captopril reduced albuminuria, slowed the decrement in GFR, and delayed the onset of kidney failure compared with placebo.[35] The beneficial effect of captopril was greater in patients with reduced GFR at baseline largely because the end point, a doubling of baseline serum creatinine level, was achieved more quickly in these patients.

There are insufficient data and no large long-term clinical trials to demonstrate the efficacy of ARBs in type 1 DN. Nevertheless, based on the shared properties of ACE inhibitors and ARBs in inhibiting the RAS, there is reason to believe that both are effective in the treatment of type 1 DN.

Type 2 Diabetic Patients

In patients with type 2 diabetes, more data are available on the renoprotective effect of ARBs compared with ACE inhibitors. In the stage of microalbuminuria, the IRMA 2 study showed that the ARB irbesartan reduces progression to overt nephropathy by 70% in hypertensive type 2 diabetic patients during a 2-year follow-up period.[36] In the MARVAL trial, the ARB valsartan (80 mg/day) produced a greater reduction in UAE than did amlodipine (44% vs. 8%) with the same degree of BP reduction, suggesting that the antiproteinuric effect of ARBs is blood pressure independent.[37]

In type 2 diabetic patients with macroalbuminuria and decreased GFR, large RCTs (IDNT and RENAAL) have demonstrated that ARBs are effective in lowering proteinuria and decrease the relative risk of reaching the composite end point of death, dialysis, and doubling of serum creatinine level.[38,39] However, the risk reduction for reaching the composite end point was only 18% to 20% in these studies in patients with type 2 diabetes and nephropathy, compared with the more robust risk reduction of about 50% in patients with type 1 diabetes receiving captopril. ARBs did not decrease CV death in these trials but did decrease the incidence of heart failure.

Compared with ARBs, data on the efficacy of ACE inhibitors in type 2 DN are less strong, largely because the studies were underpowered by small sample size or short follow-up. Nevertheless, some studies did show that ACE inhibitor use results in greater reduction in albuminuria and slower decrease in GFR compared with other antihypertensive agents. Whereas both ACE inhibitors and ARBs are probably effective for treatment of DN in patients with type 2 diabetes, few studies have directly compared their efficacy. In a small RCT of type 2 diabetes and early nephropathy with 5 years' follow-up, the ARB telmisartan was not inferior to the ACE inhibitor enalapril in providing long-term renoprotection.[40] Some pharmaceutical companies marketing both ACE inhibitors and ARBs have attempted to make the argument that particular characteristics of individual agents within these classes, such as differences in tissue levels or differential effects on the metabolic syndrome, confer some with special beneficial properties. However, no high-quality prospective RCT has proved such superiority for any particular agent for DN.

Combination Therapy with Renin-Angiotensin System Antagonists

In both type 1 and type 2 diabetic patients with nephropathy, results of several earlier small trials suggested that the combination of an ACE inhibitor and an ARB is more effective in reducing BP and proteinuria than is either drug alone.[41,42] The Ongoing Telmisartan Alone and in Combination with Ramipril Global End-point Trial (ONTARGET), which included diabetic and nondiabetic patients with CV risk, failed to show improved CV outcomes from a combination of an ACE inhibitor and an ARB. Instead, it showed increased renal functional decline in some patients, a trend toward an increase in the development of ESRD that fell just short of statistical significance, and a possible increase in mortality.[43] Whereas most of the ONTARGET study population did not have overt DN, the more recent Veterans Affairs Nephropathy in Diabetes study (VA NEPHRON-D)[44] tested the effect of combination therapy with ACE inhibitor and ARBs in type 2 diabetic patients with overt nephropathy. The study showed no difference in the primary end point of CKD progression or death. There was, however, an impressive increase in hyperkalemia (6.3 vs 2.6 events/100 person-years; $P < 0.001$) and doubling of acute kidney injury events (12.2 vs 6.7 events/100 person-years; $P < 0.001$) with combination therapy compared to ARB alone. The VA NEPHRON-D study was in fact terminated early because of the unfavorable patient-risk benefit ratio.

ACE inhibitors and ARBs have also been studied in combination with a direct renin inhibitor (aliskiren). Further reductions in proteinuria have been reported with these combinations compared with the ACE inhibitor or ARB alone. However, as was seen in ONTARGET and VA NEPHRON-D study, an incremental antiproteinuric effect is not automatically translated into clinical outcome benefits. The large Aliskiren Trial in Type 2 Diabetics Using Cardio-Renal End-points (ALTITUDE) was also terminated prematurely because of findings that a combination of aliskiren and ACE inhibitors or ARBs caused considerable increase in nonfatal stroke, hypotension, hyperkalemia, and renal complications after 1½ to 2 years.[45] In summary, evidence from clinical trials suggest caution in the use of RAS antagonists in combination, which is presumably not superior to maximum tolerated dose of the monotherapies.

Dosing and Adverse Effects Associated with ACE Inhibitors and ARBs

The antiproteinuric effect of ACE inhibitors and ARBs is at least in part independent of blood pressure reduction, and in individual patients, proteinuria may continue to respond to dose escalations beyond those recommended for BP control.[46] Unfortunately, maximal dosing of ACE inhibitors or ARBs may be limited by side effects, including hyperkalemia, hypotension, and reduced GFR. In women of reproductive age, counseling about pregnancy prevention and contraceptive use should begin before ACE inhibitor or ARB is started.

Serum creatinine concentration may increase up to 30% in proteinuric patients with renal impairment after an ACE inhibitor is started. This rise in creatinine is associated with long-term renoprotection, and therefore the ACE inhibitor should not necessarily be stopped in these patients.[47] Increases in serum creatinine concentration above 30% after initiation of an ACE inhibitor should raise the suspicion of renal artery stenosis. Aggressive dose increments of ACE inhibitors or ARBs, especially in conjunction with diuresis, can precipitate acute kidney injury (AKI). In advanced CKD and aggressive sodium restriction, although ACE inhibitors and ARBs are not contraindicated, the *de novo* introduction of these agents or injudicious dose increments may precipitate the need for dialysis prematurely, so some caution is appropriate.

Other Antihypertensive and Antiproteinuric Agents

Diuretics and Low Sodium Intake

The antiproteinuric effects of RAS blockade are enhanced by sodium restriction and diuretic use. Patients receiving ACE inhibitors or ARBs should be instructed to take a low-sodium diet (e.g., <2 g sodium/day). The combination of a loop diuretic or a thiazide diuretic with agents that block the RAS may be more effective than

either type of treatment alone for lowering blood pressure and proteinuria.

Selective aldosterone receptor antagonists (e.g., spironolactone, eplerenone) have been shown to reduce proteinuria when used alone and have an additive effect on proteinuria when used with ACE inhibitor or ARB.[48] As discussed earlier, aldosterone blockade may be especially beneficial in patients demonstrating aldosterone escape. The risk of hyperkalemia, however, frequently limits the use of combined aldosterone receptor antagonists with ACE inhibitors or ARBs, especially in patients with reduced GFR.

Calcium Channel Blockers

Dihydropyridine calcium channel blockers (dCCBs; e.g., nisoldipine, nifedipine, amlodipine) may be used as additional antihypertensive agents, but they have not been shown to reduce albuminuria or to slow the progression of renal disease.[49] In the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, the long-acting calcium antagonist nisoldipine was compared with the ACE inhibitor enalapril as first-line antihypertensive therapy in 470 hypertensive type 2 diabetic patients. The incidence of fatal and nonfatal myocardial infarction was significantly higher among those receiving nisoldipine compared with those receiving enalapril during a 5-year study period.[50]

Nondihydropyridine calcium channel blockers (ndCCBs; e.g., diltiazem, verapamil) have been shown in some studies to have beneficial antiproteinuric effects. A meta-analysis of randomized trials of ndCCB and dCCB in hypertensive patients with proteinuric renal disease found that at comparable BP control, ndCCB reduced proteinuria by approximately 30% as compared with baseline, whereas dCCB had no appreciable effects on urinary proteins.[51] Taken together, these findings suggest ndCCBs are reasonable agents for BP control and can be used in combination with a RAS antagonist in patients with DN.

β-Blockers

Classic β-adrenergic blockers have adverse metabolic effects and are therefore undesirable in diabetic patients, but this is no longer true for the novel β-blockers (e.g., carvedilol, nebivolol). Despite insufficient controlled evidence, β-blockade appears to be useful because of the extremely high CV risk in diabetic patients with nephropathy and can be used in combination with ACE inhibitors or ARBs but not ndCCBs to achieve optimal BP control.

Glycemic Control

Most of the evidence favoring strict glycemic control comes from studies of patients with normoalbuminuria or early stages of DN. Fewer studies addressed intensive glycemic control in patients with advanced stages of DN, in whom it may be difficult to show a benefit because the results are confounded by the effects of concomitant hypertension and CVD. Even so, evidence supports glycemic control in reducing the risk of worsening albuminuria and renal functional decline.[52,53] Furthermore, in type 1 diabetic patients with DN, glycemic control may also improve renal histology. Renal biopsy specimens from pancreatic transplant recipients in whom true euglycemia is restored showed stabilized glomerular structure at 5 years' follow-up and improved glomerular and tubular structure at 10 years after transplantation.[54]

For type 2 diabetic patients with established DN, large trials (e.g., Kumamoto study, ADVANCE, ACCORD trial) suggest that strict glycemic control may provide some renoprotection but does not protect against macrovascular complications (see section under Prevention of Diabetic Nephropathy).[4,6,7] Thus, glucose-lowering treatment must be individualized in type 2 diabetes. It should be more aggressive in young patients with short duration of diabetes, high life expectancy, and low risk of hypoglycemia. A more cautious approach is sensible in the elderly patient who has longstanding diabetes, has preexisting CV problems, gains weight with insulin, and is susceptible to hypoglycemic episodes. Current guidelines recommend lifestyle intervention first and suggest the addition of basal insulin (most effective), sulfonylurea (least expensive), or thiazolidinediones (no hypoglycemia) if HbA_{1c} values still exceed 7%.

Treatment of Dyslipidemia

Most patients with DN have dyslipidemia, characterized by low levels of high-density lipoprotein (HDL) cholesterol, high triglyceride (TG) levels, and a shift from larger toward smaller LDL cholesterol.[55] Dyslipidemia in diabetic patients may contribute to the development of glomerulosclerosis and progressive renal disease.[56,57]

In type 2 diabetic patients with non–dialysis-dependent DN, treatment with statins provides substantial CV benefit.[58,59] The recently published KDIGO Clinical Practice Guideline for Lipid Management in CKD recommends treatment with statin in adult diabetic patients with CKD who are not treated with chronic dialysis. Furthermore, existing evidence does not support a specific on-treatment LDL cholesterol target. Once a patient is placed on a maximum tolerated dosage of statin, follow-up measurement of lipid levels is usually unnecessary except in instances in which the results would modify management. In contrast, statin therapy in ESRD may come too late to translate into improved CV outcomes (see Chapters 32 and 82).[59a]

In diabetic patients, LDL cholesterol is not the sole lipid that defines CV risk. As major statin trials have demonstrated, lowering of LDL cholesterol does not prevent the majority of adverse CV events and does not bring the CV risk in diabetics down to the level of nondiabetic patients. This has been referred to as residual CV risk. Atherogenic dyslipidemia, specifically elevated TG, low HDL cholesterol, elevated apolipoprotein B, and elevated apolipoprotein C-III, are thought to be key factors associated with residual CV risk in diabetic patients.[60] In the UKPDS, elevated TG was independently associated with albuminuria in type 2 diabetic patients. Thus, interventions aimed at improving all lipid targets are required. However, it is not clear whether this is best achieved by intensification of statin therapy or by supplementation of statin therapy with a fibrate, niacin, or omega-3 fatty acids. In the ACCORD Lipid trial, routine use of combination therapy with statin plus a fibrate did not reduce CV risk in patients with type 2 diabetes.

Nonpharmacologic Interventions

Dietary protein restriction may alleviate uremic symptoms in patients at or approaching ESRD. However, it is of uncertain benefit in the treatment of DN. Small trials have shown low-protein diet (0.8 g/kg/day) to reduce proteinuria significantly with increased plasma albumin in macroalbuminuric type 2 diabetic patients.[61] A recent meta-analysis, however, concluded that although low-protein diet improved proteinuria, it is also associated with lower serum albumin concentrations and was not associated with a significant improvement of renal function in patients with either type 1 or type 2 DN.[62] Nutritionist counseling is advised for all patients with advanced CKD to avoid protein-calorie malnutrition before renal replacement therapy, which has been shown to be a strong predictor for subsequent increased morbidity and mortality during maintenance dialysis. Furthermore, all patients with DN should be given counseling on salt, potassium, and phosphate restriction as well as choice of carbohydrates and fats.

Lifestyle modifications such as smoking cessation and weight reduction can provide additive renal benefits and lower the risk of CV events in patients with established DN. There is evidence that smoking cessation ameliorates progression of microalbuminuria to macroalbuminuria and improves renal prognosis.[63] Weight reduction may also improve renal outcome. In a small RCT of obese (BMI >27 kg/m^2) diabetic and nondiabetic patients with proteinuric renal disease, patients who lost weight through dieting had marked improvement in proteinuria compared with those who lost no weight.[64]

EMERGING TREATMENTS FOR DIABETIC NEPHROPATHY

The pathophysiology of diabetes and DN is complex (see Chapter 30). A number of therapeutic agents, some experimental and others in clinical use for other indications, have been tried with the goal of preventing or treating DN. Specific new targets for therapeutic intervention include drugs that interfere with the formation and action of advanced glycation end products (AGEs) or receptor for AGE (RAGE), drugs that inhibit inflammatory cytokines, and antifibrotic agents (Table 31-1). These heterogeneous compounds are increased in diabetic patients and are associated with diabetic complications. Preclinical trials evaluating the effects of the AGE inhibitor pimagedine on renal function in diabetic animals yielded promising results. Unfortunately, early clinical trials of pimagedine were suspended because of side effects.[65] Other AGE inhibitors (e.g., pyridoxamine)[66] and AGE cross-link breaker (e.g., alagebrium)[67] have been studied, but their efficacy in preventing or treating DN remains to be established.

Bardoxolone methyl is an inducer of the Nrf2 pathway, which can suppress oxidative stress and inflammation. In the Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 Diabetes (BEAM) trial, diabetic patients with stage 3 or 4 CKD given bardoxolone methyl had significantly increased eGFR (by 6 to 10 ml/min) at 52 weeks of follow-up compared to placebo. However, bardoxolone methyl therapy also resulted in significantly increased albuminuria, weight loss, and dose-dependent adverse events, including muscle spasms and nausea. There was also a trend toward increased systolic BP with bardoxolone therapy.[68] A Phase III trial of bardoxolone methyl in DN patients was recently halted because of excess serious adverse events in the treated group.[68a]

Peroxisome proliferator-activated receptor (PPAR) agonists, such as thiazolidinediones (e.g., pioglitazone, rosiglitazone) are glucose-lowering agents that appear to have beneficial effects in animal models of DN. Pioglitazone in combination with the ARB losartan seems to offer greater renoprotection than does losartan alone in short-term studies.[69] Unfortunately, thiazolidinedione use has decreased because of higher rates of CV complications in a recent

Selected Emerging Treatments of Diabetic Nephropathy

Drug	Proposed Mechanism of Action	Clinical Trials and Comments
Pyridoxamine	Vitamin B_6 derivative known to be effective scavenger of reactive oxygen species and potent inhibitor of AGE	Small RCT found that pyridoxamine may be of benefit in patients with type 2 diabetes who have minimal renal impairment.[66]
Alagebrium	AGE cross-link breaker with antioxidative properties	Preclinical evidence in DN models suggests treatment with alagebrium has favorable effects on biochemical, structural, pathologic, and functional hallmarks of DN.[67] Clinical trial data are lacking.
Bardoxolone methyl	Inducer of Nrf2 pathway that can suppress oxidative stress and inflammation	In type 2 diabetic patients with stage 3-4 CKD, bardoxolone methyl significantly increased eGFR (by 6-10 ml/min) at 52 weeks' follow-up compared to placebo. Dose-dependent adverse events include muscle spasms and nausea.[68] Phase III trial of bardoxolone methyl in DN was recently halted because of excess serious adverse events in the treated group.[68a]
Thiazolidinediones	Peroxisome proliferator-activated receptor (PPAR) agonist; may improve endothelial function and have anti-inflammatory properties	Pioglitazone in combination with ARB losartan seems to offer greater renoprotection than losartan alone in short-term studies.[69] Use of thiazolidinediones has declined due to higher rates of CV complications reported in a large observational trial.[70]
Avosentan	Endothelin A receptor blocker	Phase III clinical trial showed antiproteinuric effect of avosentan, but terminated early after median of 4 months due to drug-related adverse events including fluid retention.[71]
Atrasentan	Endothelin A receptor blocker	In short-term study, atrasentan reduced albuminuria when used with RAS inhibitor in patients with type 2 diabetes; significant risk of peripheral edema noted in subgroup of patients receiving higher dose of atrasentan (1.75 mg).[72]
Pirfenidone	Inhibitor of TGF-β production with antifibrotic and anti-inflammatory properties	In small RCT, pirfenidone 1200 mg/day significantly increased eGFR versus placebo after 1 year; at 2400 mg/day, dropout rate too high to detect a significant change; no difference in albuminuria.[73]
Doxycycline	Matrix metalloproteinase inhibitor with antifibrotic properties	Small studies in patients with DN have shown significant proteinuria reduction with no effect on serum creatinine.[74]
Allopurinol	Purine analogue and inhibitor of xanthine oxidase that decreases uric acid formation	Limited short-term studies have shown improved blood pressure control and slowing of CKD progression after serum uric acid lowering with allopurinol.[75]
Paricalcitol	Agonist for vitamin D receptor	RCT (n = 281) found that addition of paricalcitol to RAS inhibition lowered albuminuria in type 2 patients with DN.[76]

Table 31-1 Select emerging treatments of diabetic nephropathy (DN). *AGE,* Advanced glycation end product; *RCT,* randomized controlled trial; *CKD,* chronic kidney disease; *eGFR,* estimated glomerular filtration rate; *ARB,* angiotensin receptor blocker; *CV,* cardiovascular; *RAS,* renin-angiotensin system; *TGF,* transforming growth factor.

observational trial.[70] Currently, it is premature to suggest routine therapy with a thiazolidinedione in DN patients.

The renal endothelin system is activated in patients with DN as well as in rat models of diabetes-induced damage. The antiproteinuric effect of an endothelin A receptor blocker was shown in the Avosentan on Doubling of Serum Creatinine, End stage Renal Disease and Death (ASCEND) Phase III clinical trial. Drug-related adverse events such as fluid retention led to early termination of the ASCEND trial.[71] Another endothelin A receptor blocker, atrasentan, was shown to reduce albuminuria when used in conjunction with a RAS inhibitor in patients with type 2 diabetes. Unfortunately, significant risk of peripheral edema was noted in the subgroup of patients receiving higher dose of atrasentan (1.75 mg).[72] Thus, the cumulative evidence from trials using endothelin receptor blockers shows that these drugs may lower albuminuria, but the side effects of sodium retention and peripheral edema may ultimately limit their clinical use.

Pirfenidone is an antifibrotic agent that exerts its effect through inhibition of transforming growth factor β (TGF-β) in animal studies. In a small, double-blind RCT, pirfenidone at 1200 mg/day significantly increased estimated GFR (eGFR) compared with placebo after 1 year. At 2400 mg/day, the dropout rate was too high to detect a significant change.[73] Thus, pirfenidone may have dose limitations in the treatment of DN. Doxycycline is also proposed to have some antifibrotic properties and has been shown to significantly reduce proteinuria in patients with DN.[74]

Recent epidemiologic studies suggest an independent association between asymptomatic hyperuricemia and increased risk of arterial hypertension, CKD, CV events, and mortality.[75] A small number of short-term single-center clinical studies have shown improvements in BP control and slowing of CKD progression following serum uric acid lowering with allopurinol. A Phase IV pilot study to determine whether allopurinol can be used to prevent or delay the loss of kidney function in type 1 diabetes is currently under way.

The effect of vitamin D administration has also been investigated in patients with type 2 diabetes. In a placebo-controlled RCT (n = 281), the addition of paricalcitol 2 μg/day to RAS inhibition safely lowered albuminuria in type 2 DN.[76] Limitations of the study include the use of albuminuria reduction as the primary end point and its 24-week follow-up. Further investigation is required to evaluate the relationship between vitamin D and DN.

Several other agents, including sitagliptin (a dipeptyl-peptidase-4 inhibitor), ruboxistaurin (a protein kinase C inhibitor), FG-3019 (anti–connective tissue growth factor monoclonal antibody), AST-120 (an oral adsorbent with antifibrotic properties), and several drugs currently in clinical use for other indications (e.g., pentoxifylline, fenofibrate), have all been evaluated for treatment of proteinuric renal disease, including DN. The role of micro-RNAs in the pathogenesis of DN is an emerging field and may also provide additional novel treatment approaches. There are insufficient data on any of these agents at this time for their use to be advocated in the prevention or treatment of DN. New insights into the molecular mechanisms that underlie the origin and progression of DN are emerging from large-scale genetic and molecular studies in experimental models and humans. It is anticipated that strategies for the prevention and treatment of DN will continue to improve as newer agents become available.

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CHAPTER 32

Management of the Diabetic Patient with Chronic Kidney Disease

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Diabetes mellitus is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) (Fig. 32-1). Diabetes is also the most common primary diagnosis in patients receiving renal replacement therapy (RRT).[1] After the diagnosis of diabetic nephropathy (DN) has been established, the focus of care must be as follows:

- Aggressive management of diabetes and other risk factors, which are essentially the same for both type 1 and type 2 diabetes mellitus, to prevent or delay the progression of DN (Table 32-1).
- Management of the complications arising from diabetes-induced CKD, with the recognition that their presentation and management may differ from nondiabetic CKD.
- The associated morbidity and mortality from the microvascular and macrovascular complications of diabetes mellitus, especially with these rates potentially even higher in patients with DN.
- Timely institution and correct choice of RRT, with recognition of how diabetes impacts the management of ESRD.

This diabetic CKD patient population will benefit from a multidisciplinary approach, first and foremost with the involvement of nephrologists and diabetologists, but also with input from other specialists, such as cardiologists, renal or diabetes nurse specialists, podiatrists, and dieticians. Early referral to nephrology is also important to rule out other causes of renal disease, especially in patients without evidence of microvascular disease elsewhere (e.g. diabetic retinopathy) or with rapid progression of disease despite well-controlled diabetes. The primary goal in these patients should be stabilization of underlying kidney disease and preventing further progression. Regular follow-up is recommended, from a minimum of yearly appointments, to quarterly appointments in those with progressive CKD. As diabetic CKD progresses through various stages, from normoalbuminuria to microalbuminuria, frank proteinuria, and eventual deterioration in plasma creatinine levels, the risk of cardiovascular death increases (Fig. 32-2).

HYPERGLYCEMIA

Assessment

The reliability of glycosylated hemoglobin (HbA_{1c}) as a marker of glycemic control diminishes as CKD progresses. Anemia, iron deficiency, hemolysis, and reduced red blood cell (RBC) life span cause reductions in the measured HbA_{1c} regardless of actual plasma glucose levels, thus underestimating the degree of hyperglycemia. The use of erythropoiesis-stimulating agents can also interfere, generating younger RBCs with reduced exposure to plasma glucose. Therefore, using the "usual" measures for glucose averages and variability is challenging. For example, analysis of data from the Diabetes Control and Complications Trial (DCCT) showed a correlation coefficient of 0.82 with mean plasma glucose in type 1 diabetic patients,[2] whereas the correlation coefficients from various studies assessing how closely HbA_{1c} levels relate to mean plasma glucose in patients with CKD have been found to be generally much lower than this (correlation coefficients ~0.5).

Despite these limitations, HbA_{1c} remains a marker of mortality in patients with diabetes-induced CKD, even up to ESRD. The recent Dialysis Outcomes and Practice Patterns Study (DOPPS) data, looking at more than 9000 dialyzed type 1 and type 2 diabetic patients in 12 countries, found that HbA_{1c} strongly predicted mortality as levels increased beyond the range of 7% to 7.9%, which was associated with the lowest mortality rates.[3] Lower HbA_{1c} levels were associated with increased mortality as well, particularly in patients with indicators of poor nutritional status.

Other markers of hyperglycemia include glycated albumin and fructosamine, although these are less readily available than HbA_{1c} and are affected by conditions that alter protein metabolism. Newer glycated albumin assays free from the interference of other glycated molecules suggest that it may correlate more accurately than HbA_{1c} with mean plasma glucose, especially in the patient with advanced CKD.[4]

Treatment

Progressive CKD leads to changes in insulin and carbohydrate metabolism. As glomerular filtration rate (GFR) continues to decline, especially below 60 ml/min/1.73 m^2, regular review of the patient's oral antidiabetic agents or insulin doses is essential because these may need to be reduced or even stopped altogether, a result of accumulation of the drugs and their metabolites, which can have various adverse effects.

Biguanides

The only drug in the biguanide class in contemporary use is metformin, which works as an insulin sensitizer. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) state that the use of metformin is safe down to an estimated GFR (eGFR) of 30 ml/min/1.73 m^2, with dose reductions advised with eGFR less than 45 ml/min/1.73 m^2, based on the guidelines issued by the UK National Institute for Clinical Excellence (NICE).[5,6] These guidelines help to minimize the risk of lactic acidosis in a population with multiple comorbidities and an increased risk of cardiovascular disease (CVD) and hospitalization. Despite this, lactic acidosis remains extremely rare in clinical trials and cohort studies on metformin therapy, with a Cochrane meta-analysis showing only 4.3 cases per 100,000 patient-years (which was actually less than the nonmetformin group).[7]

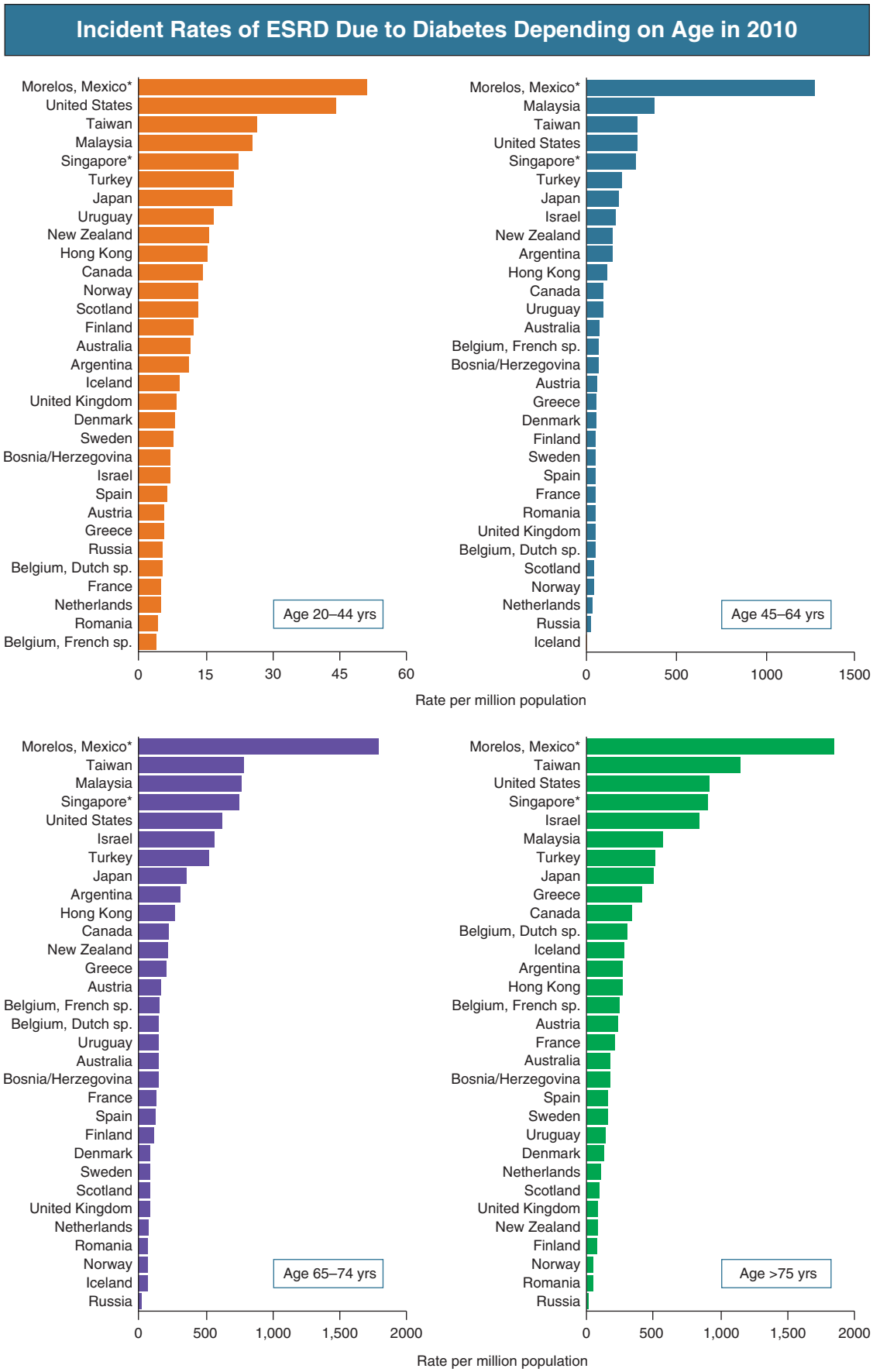

Figure 32-1 End-stage renal disease (ESRD) resulting from diabetes. Incident rates of ESRD caused by diabetes according to patient age (20-44, 45-64, 65-74, >75 years) throughout the world in 2010. Data for France include 23 regions in 2010.*Latest data for Singapore and for Morelos, Mexico are for 2009. *(Modified from reference 1.)*

Standard Care and Target Values Proposed for Diabetic CKD Patients

Parameter	CKD 3 and 4	CKD 5 and Dialysis
Metabolic Control		
Glycosylated hemoglobin	>6.5-7.5%	>7.0-8.0%
Preferred agents	Meglitinides, sulfonylureas, insulin	Insulin
Blood Pressure		
Systolic/diastolic BP	130/80 mm Hg	
Preferred agents	ACE/ARBs	?
Lipid Treatment		
LDL cholesterol	<100 mg/dl	?
Preferred agents	Statins	?
Anemia Treatment		
Hemoglobin level	11.0-12.0 g/dl	11.0-12.0 g/dl (avoid >13)
Preferred agents	Iron/ESA	Iron/ESA
Vitamin D Supplements*		
	Vitamin D_3/ 1,25-OH D_3	1,25-OH D_3/vitamin D_3
Supportive Treatment		
Smoking cessation	++	NP
Hypoglycemia awareness	++	+++
Low-dose aspirin	++	+
Exercise (daily/weekly)	+	+
Foot care	+++	+++
Prevention of falls	+	+++

Table 32-1 Standard care and target values proposed for patients with diabetes mellitus who have chronic kidney disease (CKD). *ACE,* Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *ESA,* erythropoiesis-stimulating agent; *LDL,* low-density lipoprotein; *?,* benefit unknown; +/++/+++, moderately/very/highly indicated. *In case of vitamin D supplements, the therapeutic approach should be reversed from native vitamin D first in CKD 3/4 to vitamin D analogues first in CKD5.

Annual Transition Rates Through the Stages of Nephropathy and to Death from Any Cause

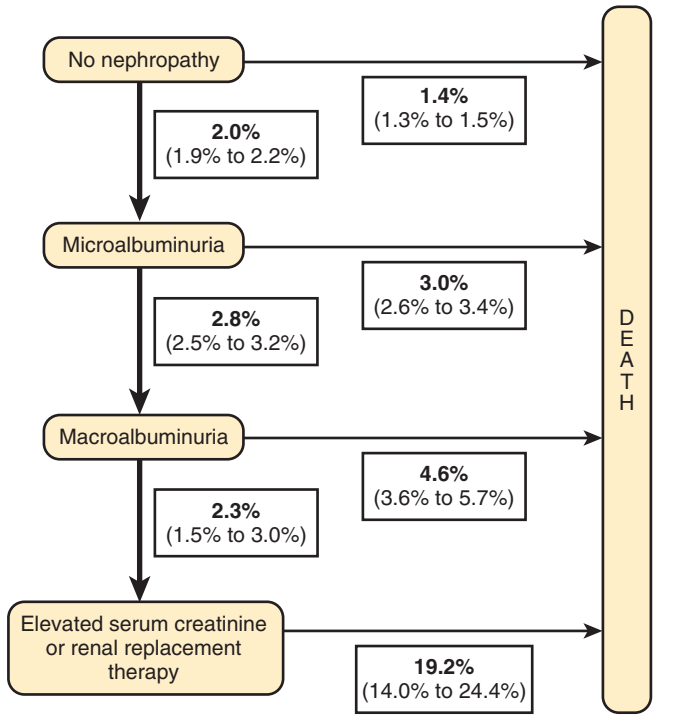

Figure 32-2 Stages of nephropathy and mortality. Annual transition rates with 95% confidence interval through the stages of nephropathy and to death from any cause in diabetic patients. *(Modified from reference 12.)*

Sulfonylureas

A class of insulin secretagogues, the older generation of sulfonylureas (tolbutamide, glibenclamide) are long acting and almost exclusively excreted by the kidneys and thus are best avoided in CKD patients. Newer agents are of shorter duration and primarily metabolized by the liver, although most metabolites are subject to renal clearance. The metabolites of gliclazide and glipizide are inert or only weakly active, so these particular sulfonylureas can be used even in patients with ESRD receiving dialysis. Their use does carry the risk of hypoglycemia, especially as GFR declines and insulin clearance decreases. Sulfonylureas are highly protein-bound but can be displaced into circulation by other drugs used in diabetic patients (e.g., salicylates, β-blockers, fibric acid derivatives), further contributing to hypoglycemia.

Thiazolidinediones

The thiazolidinediones are peroxisome proliferator-activated receptor (PPAR) modulators, which work to increase insulin sensitivity. Their use is limited by resultant weight gain and fluid retention through transcriptional upregulation of amiloride-sensitive sodium (Na^+) channels in renal tubules, which is problematic in a population already prone to CVD and heart failure. Rosiglitazone was withdrawn from the market because of the suggestion of an increased risk of myocardial infarction with its use, although pioglitazone remains in use.

Meglinitides

The main drugs in the meglinitide class, nateglinide and repaglinide, are primarily metabolized in the liver and act as insulin secretagogues. Repaglinide is safe to use in diabetic patients with advancing renal failure because it is converted to inactive metabolites and mainly excreted in bile, with less than 10% of the parent drug appearing in the urine, so no dose adjustments are deemed necessary. More than 80% of nateglinide is excreted in the urine, and thus it should only be used cautiously, if at all, in advanced CKD.

Glucagon-like Peptide-1 Analogues

Glucagon-like peptide-1 (GLP-1) analogues such as exenatide and liraglutide work by enhancing glucose-mediated insulin secretion in response to food entering the gut and maintaining the integrity of insulin-producing beta cells. The GLP-1 analogues help stimulate weight loss by appetite suppression, both centrally and by affecting gastric motility. Exenatide and liraglutide are not recommended if GFR falls below 30 and 60 ml/min/1.73 m^2, respectively.

Gliptins

The gliptin class inhibits the effect of dipeptidyl peptidase-4 (DPP4), a cellular membrane protein expressed in a variety of tissues whose function is to rapidly degrade incretin hormones such as GLP-1.

Sitagliptin is excreted mostly unchanged (70% to 80%) in the urine, requiring dose reductions as GFR drops below 50 ml/min/1.73 m^2 (50% reduction) and 30 ml/min/1.73 m^2 (75%). Newer agents such as linagliptin are primarily metabolized by the liver and excreted in the bile, not needing dose reduction in CKD. The gliptins have the advantage of being weight neutral, unlike insulin secretagogues.

Insulin

Exogenous insulin, unlike endogenously secreted insulin, which undergoes first-pass metabolism in the liver, is primarily eliminated by the kidneys through free filtration and secretion into the renal tubules, before reuptake and degradation by peritubular cells. In terms of endogenous insulin handling, the kidneys extract up to 40% of all plasma insulin down to GFR of 20 ml/min/1.73 m^2, with less than 10% extraction at ESRD.[8]

As GFR falls below 60 ml/min/1.73 m^2, insulin requirements in both type 1 and type 2 diabetic patients progressively fall, by up to 40% to 50%, regardless of residual insulin secretion in type 2 patients. This decline is especially marked as GFR falls below 20 ml/min/1.73 m^2 and approaches ESRD.[9] This helps to explain the phenomenon of hypoglycemia in nondiabetic patients with advanced CKD, although importantly, the kidney is an important site for gluconeogenesis, which can fail as CKD progresses.

Insulin resistance itself results from CKD. Uremia induces insulin resistance, thought to be caused by a defect in post–receptor signaling, with reduced glucose uptake and metabolism after insulin receptor activation peripherally. In skeletal muscle tissue, insulin-mediated glucose metabolism is mediated through phosphatidylinositol-3 kinase (PI3K-AKt) secondary messenger pathways, which are adversely affected by many factors associated with renal impairment, such as metabolic acidosis, uremia, anemia, elevated levels of proinflammatory cytokines, and low vitamin D levels.

In terms of the types of insulin used, available data favor the use of analogues, where the insulin molecule has been modified for both rapid-acting and long-acting forms so as to possess pharmacokinetics more in keeping with physiologic insulin secretion, in contrast to traditional human insulins. In a comparative study of insulin lispro versus human insulin in diabetic patients on hemodialysis, insulin was injected just after starting a 4-hour dialysis session. Insulin lispro was shown to have a faster rate of absorption with a shorter time to peak concentration (which was also of greater overall magnitude) and elimination.[10]

Another study on the pharmacodynamics and pharmacokinetics of insulin lispro versus human insulin in type 1 diabetic patients found that both attained a higher peak concentration and prolonged clearance in patients with overt DN, with an average reduction of insulin clearance by 30% to 40%.[11] However, despite higher circulating levels, human insulin was found to have a paradoxically lower peak effect with reduced overall metabolic activity in diabetic patients with DN than in those with normal GFR. Insulin lispro maintained a similar metabolic profile, regardless of whether DN was present. Insulin aspart, another rapid-acting analogue, has also been found to have a metabolic profile largely unaffected by various stages of CKD, along with long-acting analogues such as glargine and detemir.

Although there is no formal insulin regimen recommended in the setting of CKD, for type 1 diabetic patients, the basal bolus regimen of 3 daily injections of short-acting insulin with meals combined with 1 or 2 injections of long-acting insulin, as used in DCCT, is the standard treatment regimen, with the added benefit of greater flexibility over a regimen with fewer injections. Type 2 diabetic patients, when requiring insulin, usually start on once-daily or twice-daily, long-acting or intermediate-acting insulin, if necessary moving onto mixed formulations (fixed percentages of short-acting and longer-acting insulins) or the basal bolus regimen as in type 1 patients. Again, as CKD progresses, this may need regular adjustment.

HYPERTENSION

The most common blood pressure (BP) target, set by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) and other major societies, was a BP below 130/80 mm Hg for patients with CKD caused by diabetes mellitus,[12] with the cutoff derived from observational studies such as the MRFIT study and the Okinawa Screening Programme, with risk of developing ESRD beginning to increase significantly beyond the 130/80 mm Hg target (see Chapter 80).

Despite this, there is a lack of strong evidence from randomized controlled trials (RCTs) to support this target in secondary prevention of renal disease, with systemic review of relevant trials showing no benefit for tight BP control on renal outcomes such as the rate of decline of GFR and progression to ESRD.[13] Some benefit was found in patients with frank proteinuria, but this required more antihypertensive agents, with a slightly increased risk of adverse events. This must be taken with the caveat that the numbers of patients involved were quite small and the trials short in duration, possibly limiting their ability to detect differences.

The recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on managing hypertension in CKD patients with diabetes reflects this information, with a more conservative target of 140/90 mm Hg or less in patients with GFR below 60 ml/min/1.73 m^2, but with normal urinary albumin excretion rates, based on the conclusion that insufficient high-quality evidence from RCTs is available to recommend a lower target based on observational studies.[14] However, KDIGO also recommends a lower target of 130/80 mm Hg or less in patients with CKD and microalbuminuria or macroalbuminuria, because of the enhanced risk of CVD. Lower BP targets than this (e.g., systolic BP <120 mm Hg in ACCORD trial) are of uncertain benefit, possibly with increased risk of adverse events, and are not recommended.

The recommended first agents of choice in the DN population are either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), with evidence of significant reductions in both cardiovascular (CV) and all-cause mortality, especially if albuminuria is present. They have also been shown to have protective effects on renal outcomes in preexisting DN (progression to ESRD and doubling of serum creatinine), with a possible effect independent of BP lowering.

Long-term use of ACE inhibitors and ARBs is associated with lower hemoglobin (Hb) levels, with losartan doses of 50 to 100 mg shown to reversibly lower Hb by about 1 g/dl, thought mainly to result from lower levels of angiotensin II, known to have a proerythropoetic effect on RBC precursors.[15] Anemia as a result of renin-angiotensin-aldosterone system (RAAS) inhibition does not mitigate their renoprotective effects.

Patients with diabetic CKD will usually require more than one antihypertensive agent to achieve BP targets.[16] Aldosterone antagonists can reduce target organ damage as well as surrogate end points such as proteinuria and left ventricular hypertrophy (LVH). The addition of spironolactone to an ACE inhibitor exerts a greater renoprotective effect on DN than dual ACE inhibitor/ARB therapy. Given the risk of hyperkalemia, spironolactone must be used cautiously. Aliskiren improves albuminuria in short-term studies, although the ALTITUDE study showed an increased rate of adverse events when aliskiren was combined with RAAS blockade. The use of other

antihypertensive agents, such as calcium channel antagonists and thiazide-like diuretics (e.g., indapamide), has also been shown to be beneficial in reducing the risk of CVD in diabetic patients, with some evidence of benefit in the diabetic CKD population. β-Blockers, although beneficial in the setting of CVD as add-on therapy, may mask hypoglycemia and are not usually used as first-line therapy.

There are no guidelines recommending specific drug classes after use of an ACE inhibitor or ARB. Medical management should thus be tailored to the patient's comorbidities.

HYPERLIPIDEMIA

Given the elevated risk of CVD in diabetic patients, it is generally recommended that hyperlipidemia be treated (see Chapter 82). KDOQI recommends that all patients with diabetes mellitus and CKD 1 to 4 should receive treatment if low-density lipoprotein cholesterol (LDL-C) is greater than 100 mg/dl, with a target of less than 70 mg/dl. NICE UK guidelines, however, stipulate a total cholesterol less than 4 mmol/l and LDL-C less than 2 mmol/l for optimal prevention of microvascular and macrovascular complications of diabetes.[6,12]

In nondialysis CKD patients, a beneficial effect on lowering cholesterol was finally confirmed by the SHARP RCT, which included more than 9000 patients with a wide range of CKD but no prior history of CVD. They were randomized to either a combination of simvastatin and ezetimibe or to placebo. A 17% reduction in CV outcomes was found for every 0.85 mmol/L reduction in LDL-C (in nonhemorrhagic strokes, coronary revascularization events), with similar results in all subgroups, regardless of whether diabetic or nondiabetic.[17]

In diabetic patients on dialysis, the evidence is less clear, with the AURORA and 4D trials not showing significant reductions in CV events or mortality despite LDL-C falling by up to 42%. Subgroup analysis of the SHARP trial also found a nonsignificant reduction in primary CV end points for the cohort of patients on dialysis.

In terms of lipid-lowering agents available, statins are first-line agents. If insufficient, other drugs can be added, depending on the nature of the hyperlipidemia, with ezetimibe added to treat LDL-C, or fibric acid derivatives for hypertriglyceridemia. Other types can be added if the previous treatment is insufficient or if the patient is intolerant of statins or other medications. For statins, as renal function declines into CKD 4, dose reductions may be necessary if rosuvastatin or simvastatin is used; this is not necessary for atorvastatin or pravastatin. Multiple trials of statins in hemodialysis patients have not reported significantly increased adverse events relating to liver function or muscle enzymes. Dose reductions in fibric acid derivatives may be required as well. There is no need for dose adjustment for bile acid sequestrants, niacin, or ezetimibe.

ANEMIA

Anemia is common in patients with DN and acts as a risk multiplier for all-cause mortality in patients with diabetes mellitus and CKD, and as an independent risk factor for LVH, CVD, and heart failure (see Chapter 83).

A prospective 5-year study of type 2 diabetic patients in Australia found that 13% were already anemic, with an additional 13% developing anemia at the end stage.[18] The best predictors of developing anemia were significant albuminuria, baseline renal function, and preexisting macrovascular disease. Diabetic patients have lower Hb levels at every stage of renal impairment than patients with CKD from other causes; one study found a prevalence of 41% in diabetic versus 17% in nondiabetic CKD patients, and this fall can be seen even before renal function begins to decline.[19] As a result, diabetic patients should be screened for anemia when GFR begins to decline below 60 ml/min/1.73 m^2. Patients with DN have increased levels of proinflammatory cytokines (from low-grade systemic inflammation), which causes resistance to the effects of erythropoietin (EPO) in various tissues of the body, as well as impairing the efficient use of iron in the generation of new erythrocytes. Other contributing factors include autonomic neuropathy, use of ACE inhibitors or ARBs, and possible microvascular damage in the bone marrow impairing responses to EPO as well.

Earlier studies on anemic patients with ESRD requiring RRT found that the use of erythropoiesis-stimulating agents (ESAs) to correct low hemoglobin led to increased quality-of-life scores and reduced frequency of blood transfusions, but current data do not suggest that this can be extrapolated to earlier stages of CKD. In the CHOIR and CREATE studies, non–dialysis-dependent CKD patients receiving ESAs were randomized to higher or lower Hb targets, with the higher target Hb greater than 13 g/dl. In these studies, use of larger doses of ESA in the higher-Hb target group was associated with increased quality-of-life scores, but led to an increased incidence of CV events. This would suggest ESA resistance itself is a marker for poorer outcomes. Progression to ESRD had a higher incidence in the high-Hb group in CREATE but not CHOIR.

The TREAT study was a landmark study in the use of ESAs for correcting anemia secondary to CKD in type 2 diabetic patients. Over a median follow-up of 29 months, type 2 patients with GFR or 20 to 60 ml/min/1.73 m^2 and Hb of 11.0 g/dl or lower were randomized either to treatment with darbepoetin alfa, to achieve a target Hb of 13 g/dl (mean achieved value 12.5 g/dl), or to a control group with rescue darbepoetin treatment only if Hb fell below 9.0 g/dl (mean value 10.6 g/dl). The treatment group had fewer CV revascularization procedures but had significantly increased risk of both fatal and nonfatal nonhemorrhagic strokes. Those treated also had an increased risk of arteriovenous thromboembolic events compared with the placebo group, and no effect on progression to ESRD was noted.[20] In fact, the TREAT cohort showed (despite BP/glycemic/lipid control measures), a 31% progression to dialysis and death.

The KDIGO guidelines recommend that for CKD patients not receiving RRT, ESAs should only be used if Hb levels drop below 10.0 g/dl, with other factors such as the rate of decrease and presence of symptoms to be considered before initiation (for adult hemodialysis patients, given the faster rate of fall of Hb, ESAs are recommended when Hb is 9.0 to 10.0 g/dl, to avoid the need for transfusions).[21] It is also recommended that Hb not be maintained above 11.5 g/dl. Other measures to correct anemia, such as intravenous iron and improved dialysis technique, should be considered especially if patients are asymptomatic, only moderately anemic, or have a history of previous stroke (see Chapter 83).

ANTIPLATELET AGENTS

It is well known that hyperglycemia has a procoagulant effect on platelet aggregation independent of insulin levels, and hyperinsulinemia itself carries an inhibitory effect on fibrinolysis, with these two phenomena in tandem significantly increasing the risk of thrombosis. Platelet reactivity is known to increase as CKD progresses into stage 3 and beyond. ADA guidelines recommend the use of antiplatelet therapy as primary prevention in diabetic patients at significant risk of CVD with risk factors such as albuminuria, hypertension, and hyperlipidemia (see Chapter 84). This stipulates that almost all patients with DN should receive antiplatelet therapy.

Although DN patients are at an increased risk of CVD compared to other patient groups, dual-antiplatelet therapy has not shown any benefit. *Post hoc* analyses of data from the CHARISMA and CREDO trials found that there was no benefit in adding clopidogrel to aspirin in patients with dual-antiplatelet therapy in patients with DN and may actually lead to worse outcomes independent of bleeding risk.

A recent Cochrane review on the use of antiplatelet agents in CKD patients found that although CVD was reduced, all-cause mortality was not, with an increased risk of both minor and major bleeding events, with the recommendation that antiplatelet therapy only be used in those at higher risk of CVD. This would surely include diabetic patients, even at earlier stages of CKD. There was also little evidence to suggest any preference for one agent over another.

BONE DISEASE

It has been suggested that disordered mineral metabolism and bone disease occur across the whole range of CKD, even in patients with normal renal function (see Chapter 85). Markers of altered bone metabolism, such as hyperphosphatemia, elevated fibroblast growth factor 23 (FGF-23) and reduced Klotho concentrations, have been linked to an increased risk of progression to ESRD, CVD, and mortality.[22] Observational follow-up studies on both type 1 and type 2 diabetic patients found that those with vitamin D levels below the 10th centile had a significantly increased risk of CV or all-cause mortality independent of other CV risk factors.[23]

Bone disease in diabetic patients with ESRD on dialysis is usually a low-turnover (adynamic) state, with lower overall levels of parathyroid hormone than in their nondiabetic counterparts. Adynamic bone disease in turn is a recognized risk factor for cardiovascular calcification (see Chapters 82 and 85), as is diabetes itself. In non–dialysis-dependent CKD, evidence suggests that secondary hyperparathyroidism occurs at an earlier stage in diabetic patients.

Preventive and therapeutic approaches to CKD-related bone and mineral disease do not differ substantially between diabetic and nondiabetic patients (see Chapter 85). However, given the increased prevalence of low-turnover bone disease in diabetic patients with CKD, care should be taken to avoid calcium loading. These patients also appear to accumulate aluminum more readily and are more susceptible to aluminum-induced bone disease. Aluminum-containing phosphate binders should always be avoided in the diabetic patient with advanced CKD.

EXTRARENAL COMPLICATIONS OF DIABETES MELLITUS

Even the asymptomatic diabetic patient with advanced CKD must be monitored at regular intervals for timely detection of microvascular and macrovascular complications, with at least yearly ophthalmologic examination along with assessing the patient, both clinically and through the use of appropriate investigations if necessary, for CVD (see Chapter 82).

In particular, problems related to the diabetic foot are a major cause of hospital admission and nontraumatic amputation (Fig. 32-3). For this reason, at least yearly inspection of the feet and examination of peripheral pulses and sensation is an essential part of the diabetic patient's consultation, along with general foot care (Box 32-1). Diabetic microvascular disease of the foot is frequently complicated by diabetic and uremic polyneuropathy, both of which respond poorly to conventional treatment (see Chapter 86).

Figure 32-3 The diabetic foot. Gangrenous ulcers in a diabetic caused by a combination of large-vessel and small-vessel disease and neuropathy.

Prevention of Diabetic Foot Complications

- Identification of patients at risk
- Education about foot care
- Regular examination of the feet at clinic
- Provision of appropriate footwear
- Provision of podiatry services

Box 32-1 Therapeutic measures to prevent diabetic foot complications

In the diabetic patient, due to a combination of neuropathy and poor peripheral blood supply, foot ulcers can develop suddenly with a rapid rate of enlargement, with potential bone involvement. If osteomyelitis is present, ulcers can be intractable and difficult to treat medically, often requiring very long courses of antibiotics. Patients with ulcers may need vascular intervention in the form of angioplasty, stenting, or bypass surgery as part of their treatment. Amputation may also be necessary, however, especially for refractory infections from methicillin-resistant *Staphylococcus aureus* (MRSA) or other multiresistant organisms.

Diet and Malnutrition

Diabetic patients with CKD are often severely catabolic and tend to develop malnutrition (see Chapter 87). This risk is particularly high during periods of intercurrent illness and fasting but may also be the result of ill-advised recommendations to restrict protein intake. Anorectic obese patients with type 2 diabetes and advanced CKD often undergo massive weight loss, leading to normalization of fasting glucose concentration and even of hyperglycemia after a glucose load. Low muscle mass because of wasting is an important reason for misjudging the severity of renal failure, leading, for example, to delayed start of RRT. Therefore, creatinine clearance should be measured, or at least GFR should be estimated, rather than relying on serum creatinine.

Prevention and Treatment of Cardiac Disease

In diabetic patients, the likelihood of death from CVD greatly exceeds that of reaching ESRD, and thus the population of diabetic patients on dialysis represents a "positive selection." Similar observations have been made in the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) trial in type 1 diabetic patients[23] and in particular in the Steno-2 population, in whom 27 deaths (14 from CVD) occurred during a mean follow-up of 7.8 years, whereas

mean GFR decreased by about 30 ml/min/1.73 m^2, and no patient reached ESRD.[24,25]

Once a diabetic patient has reached ESRD, CV mortality rate is still excessive. This may relate to the fact that in diabetics, coronary heart disease is often amplified by the coexistence of more severe LVH, congestive heart failure, disturbed sympathetic innervation, and microvascular disease. How and when best to intervene in the progressive course of CVD in diabetic patients with CKD has not been precisely defined. In the absence of data, recommendations for the formal workup of coronary heart disease in diabetic patients with CKD should be no different from those for nondiabetic CKD patients.

In nondialysis patients, both coronary intervention and bypass surgery can be associated with significant risk of acute renal deterioration, which must be weighed against the potential outcome benefits in the individual patient. In general, to preserve residual renal function, bypass grafting might be favored in nondialysis CKD stages, whereas interventional stenting procedures might be assumed to be more appropriate for dialysis patients with limited life span, if risks of cerebrovascular complications are assessed and treated adequately (see Chapter 82).

DIALYSIS AND TRANSPLANTATION

Diabetes mellitus is the most common cause of ESRD in developed countries. Diabetes is also an independent risk factor for developing ESRD from nondiabetic causes, possibly from accelerated atherosclerotic disease. The most recent data reports from the U.S. Renal Data System (USRDS) show that patients with ESRD either on dialysis or with renal transplant as a result of diabetes have the highest annual mortality compared with ESRD patients requiring RRT secondary to any other cause.[1] The main cause of death is again CVD. Infections are the other important contributor to increased mortality in diabetic patients. Other contributing factors are impaired immunity, malnutrition, lower limb ulceration, hospitalization, and long-term indwelling catheters.

Diabetic patients receiving dialysis are also at increased risk of foot complications, with higher amputation rates. Diabetic eye disease is also highly prevalent in this population.

The management of hyperglycemia in the patient receiving renal replacement therapy can present many challenges. Note that even in nondiabetic patients receiving RRT, plasma glucose concentrations can be abnormal and unpredictable, if glucose-free dialysates are used, with about 80% of all episodes of hypoglycemia and mean nadir glucose levels occurring within 24 hours of a session of hemodialysis.[26] The usual systemic symptoms that occur in response to hypoglycemia may well be attenuated by the prevalence of neuropathy. Thus it is recommended that glucose-containing dialysates be used.

The general metabolic milieu in ESRD patients, as previously outlined, predisposes to increased insulin resistance. During and after dialysis, this can be temporarily reversed through correction of uremia, acidosis, and phosphate handling, leading to greater efficacy of antidiabetic treatments. Importantly, the pharmacokinetics of the various treatments are altered during dialysis, coupled with impaired renal gluconeogenesis and insulin clearance.

Symptomatic uremia and fluid overload occur in diabetic patients at higher GFR than in ESRD from other causes. Earlier initiation of dialysis was thought to have survival benefit over later initiation, with the better control of volume-dependent hypertension especially relevant in the patient with ischemic heart disease, heart failure, and strokes. However, the IDEAL study comparing early to late initiation (with 34% of both groups having diabetes as the primary cause of ESRD) found no significant benefit with adverse events (e.g., CVD, sepsis) or for survival[27] (see Chapter 81).

The best modality of RRT for survival and rehabilitation of the patient with diabetes-induced ESRD is living-related renal transplantation, with better courses of neuropathy and retinopathy, although not for CVD and ischemic heart disease.[28] Prior USRDS data showed 5-year survival rates of 29% in diabetic patients starting dialysis versus 75% and 85% with cadaveric and living-donor renal transplants, respectively.[29] Ideally, the transplant should be timed to avoid an interim period of dialysis, preferably at a stage where uremic symptoms are minimal. For patients with type 1 diabetes, the ideal form of transplantation is simultaneous pancreas and kidney transplantation (SPKT); the additional restoration of normoglycemia carries a significant survival advantage over isolated kidney transplants, although with the caveat of higher rates of allograft rejection and hospitalization[30] (see Chapter 110). Another option is sequential living-donor kidney transplantation, followed by deceased-donor pancreas transplants, reducing the waiting time to transplantation. Although there were concerns with this approach due to possible worse outcomes in terms of survival and the pancreas graft itself, outcomes have improved in recent years.[31]

For diabetic patients, in whom there are advantages and disadvantages to either form of dialysis, outcomes in terms of survival and CV mortality/morbidity are similar in hemodialysis and peritoneal dialysis (PD).[32] Some evidence suggests that PD has an initial advantage in terms of survival, but this decreases over time. Younger diabetic patients have better survival with PD as well, with PD potentially serving as a staging interval while preparing for transplantation (Table 32-2).

Hemodialysis

Hemodialysis as RRT is associated with a general improvement in morbidity from retinopathy, neuropathy, and peripheral vascular disease (although to a lesser degree than patients with renal transplant or on CAPD). If hemodialysis is the chosen modality, vascular access should be prepared for 3 to 6 months, given that atherosclerotic disease in these patients poses a challenge to the vascular surgeon, with calcific atherosclerosis causing inadequate arterial inflows and problems with venous runoff. Early failure of fistulas resulting from impaired maturation is also more common in diabetic patients.

The process of hemodialysis is not without its risk, especially in a population with a preexisting burden of CVD. Regular hemodialysis, with its rapid removal of fluid and solutes in combination with exposure to an extracorporeal circuit, can precipitate hypotension, arrhythmias, and heart failure, with a general deterioration in CV status caused by the recurrent circulatory stress. This is compounded by the presence of diabetic autonomic neuropathy, with impaired compensatory reflexes such as increasing peripheral vascular resistance and reflex tachycardia. As a result, there is an increased frequency of intradialytic hypotension in diabetic patients in response to rapid fluid shifts across different compartments. Such hypotension can precipitate myocardial ischemia (although conversely, hypotension can result from silent infarction). Systolic dysfunction is common, but the diastolic dysfunction of diabetic cardiomyopathy associated with reduced left ventricular compliance and filling can also contribute to this phenomenon. With lower blood pressures, underdialysis can occur with reduced access blood flow.

Patients also have a higher incidence of hypertension requiring medical therapy despite amelioration of volume-dependent hypertension with dialysis. Paradoxical rises in BP during dialysis sessions

Comparison of Dialysis Options for the Diabetic Patient				
	Peritoneal Dialysis		Hemodialysis	
Parameters	*Advantages*	*Disadvantages*	*Advantages*	*Disadvantages*
Technique	No need for vascular access; better preservation of residual renal function	Low technique survival rate; high hospitalization rate; higher rate of infections	Better technique survival rate; lower hospitalization and infection rate	Frequent difficulty in obtaining good vascular access
Blood pressure	Good control, slow ultrafiltration, and fewer episodes of cardiovascular instability			Difficult control; more frequent hypotensive episodes (esp. in patients with autonomic neuropathy)
Nutritional factors	Fewer dietary restrictions	Excessive weight gain, poor nutrition		Difficulty with fluid and dietary restrictions
Biochemical and metabolic control	Steady-state biochemical parameters	Worsening of blood glucose control and hyperlipidemia; increased insulin requirements	Efficient solute and water extraction	
Social factors	Maintains independence		Better medical surveillance	In most diabetic patients, cannot be performed at home

Table 32-2 **Advantages and disadvantages of peritoneal dialysis versus hemodialysis options for the diabetic patient**

can occur, possibly from activation of RAAS and increased peripheral vascular resistance from reduced intravascular plasma volumes (clinically inapparent hypervolemia can also contribute); ACE inhibitors can attenuate this effect. Other agents, such as calcium channel antagonists and central vasodilators (e.g., clonidine), can be used in tandem. The tendency to high intradialytic weight gain is related to the degree of hyperglycemia with resultant thirst and excessive fluid intake.

Peritoneal Dialysis

Given the slower ultrafiltration rate in PD compared with hemodialysis (see Chapter 96), PD carries less hemodynamic instability and mitigates the risk of hypotension or precipitating CVD with large fluid shifts or BP changes, which is especially relevant in diabetic patients with preexisting CVD burden or autonomic neuropathy. Also, PD is associated with better preservation of residual renal function and urine output along with increased clearance of advanced glycation end products, one of the pathways by which diabetic complications occur. Issues with vascular access, such as thrombosis, local infection, and transfer of blood-borne diseases, are also avoided.

Another advantage of PD is better outcomes for retinopathy, with stabilization and reduced rates of progression, possibly from less heparin and CV instability. Various reports of improvement in peripheral neuropathy are thought to result from increased clearance of middle molecular proteins thought responsible for uremic neuropathy.

Intraperitoneal insulin (soluble human insulin) can be injected through the connecting tubing before starting dialysis or can be added to dialysate bags. Note that requirements are often higher than when subcutaneous injections of insulin are used, because intraperitoneal insulin is adsorbed onto plastic surfaces of the delivery systems, and bioavailability does depend on the solution used as well. This has the advantage of being more physiologic because intraperitoneal insulin is absorbed through portal circulation, with decreased amplitude of glucose excursions and improved mean plasma glucose, predominantly by inhibition of hepatic gluconeogenesis. However, soluble human insulin does carry a risk of subcapsular hepatic steatosis, linked to the dosage of intraperitoneal insulin used.

Peritoneal dialysates contain supraphysiologic concentrations of glucose, which can diffuse down a concentration gradient into the bloodstream, with up to 80% of glucose from the dialysate potentially absorbed. This can obviously worsen glycemic control, and hyperlipidemia, leading to weight gain or worsening of obesity. In some patients a vicious cycle can occur, in which patients with poor diabetic control and the resultant thirst and fluid consumption require dialysate solutions with higher glucose concentrations to off-load the volume excess. While glucose degradation products in PD solutions are known to cause leukocyte apoptosis, no difference in PD-related catheter infections seems to exist between diabetic and nondiabetic patients.

Non–glucose-containing solutions (e.g., icodextrin) avoid both the risk of hyperglycemia and the damaging effects of glucose degradation products, leading to better ultrafiltration volume, blood pressure control, and preservation of residual function (see Chapter 97). Note that some metabolites of icodextrin can act as substrate for the glucose dehydrogenase present in blood glucose meters, resulting in potential overestimation of blood glucose levels. Up to 15% of patients can experience skin reactions to icodextrin, which can be serious in up to one third of all cases.[33]

As peritoneal clearance declines over time as a result of progressive peritoneal membrane impermeability or fibrosis, longer dialysis sessions are needed. Malnutrition can result from large protein loss in the dialysate, as well as high glucose loads and increased intra-abdominal pressures, reducing appetite.

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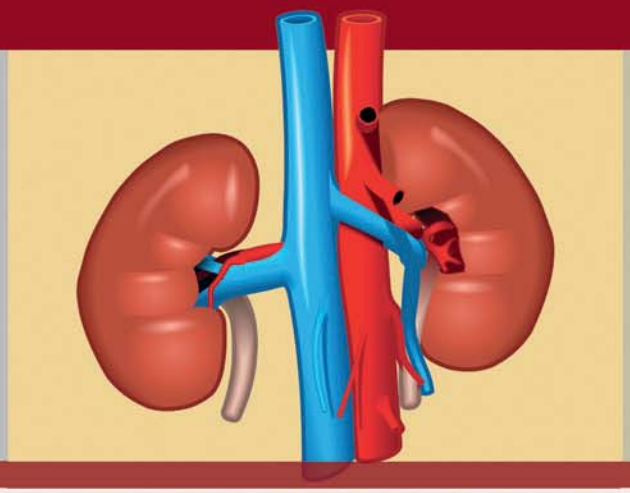

SECTION VI

Hypertension

CHAPTER 33

Normal Blood Pressure Control and the Evaluation of Hypertension

William J. Lawton, Gerald F. DiBona, Ulla C. Kopp, and Friedrich C. Luft

NORMAL BLOOD PRESSURE CONTROL

Systemic arterial blood pressure (BP), or the pressure of the blood within the arteries exerted against the arterial wall, is produced by the contraction of the left ventricle (producing blood flow) and the resistance of the arteries and arterioles. *Systolic* blood pressure (SBP), or *maximum* BP, occurs during left ventricular systole. *Diastolic* blood pressure (DBP), or *minimum* BP, occurs during ventricular diastole. The difference between SBP and DBP is the pulse pressure.[1] The mean arterial pressure (MAP) is clinically defined as the DBP plus one third of the pulse pressure.

Blood flow, *Q*, as defined by Ohm's law, varies directly with the change in pressure, *P*, across a blood vessel and varies inversely with the resistance, *R*, defined as $Q = P/R$. Rearrangement shows that pressure varies directly with blood flow and resistance, $P = QR$. Ohm's law suffices for an overall view of the circulation. However, for a more detailed picture of the resistance to flow in any given vessel, the relationship of Hagen-Poiseuille should be applied, as follows:

$$Q = \Delta P \times (\pi r^4/8L) \times (1/\eta)$$

Here, *r* is the radius of the pipe, *L* is its length, and η is the coefficient of viscosity. Thus, as the lumen of a vessel decreases, the pressure increases to the fourth power of the radius for the same blood flow. In other words, a 50% reduction in radius results in a 16-fold increase in pressure to maintain equivalent flow.

Normal BP is controlled by cardiac output and the total peripheral resistance and is dependent on the heart, the blood vessels, the extracellular volume, the kidneys, the nervous system, humoral factors, and cellular events at the membrane and within the cell (Fig. 33-1). Cardiac output is determined by the stroke volume in liters per minute (l/min) and the heart rate. In turn, stroke volume is dependent on intravascular volume regulated by the kidneys as well as on myocardial contractility. Myocardial contractility involves sympathetic and parasympathetic control of heart rate, intrinsic activity of the cardiac conduction system, complex membrane transport and cellular events requiring influx of calcium that lead to myocardial fiber shortening and relaxation, and effects of humoral substances (e.g., catecholamines) on stimulating heart rate and myocardial fiber tension.

Total peripheral resistance is regulated by baroreflexes and sympathetic nervous system (SNS) activity, response to neurohumoral substances and endothelial factors, myogenic responses, and intercellular events mediated by receptors and mechanisms for signal transduction.[2] Baroreflexes are derived from (1) high-pressure baroreceptors in the aortic arch and carotid sinus and (2) low-pressure cardiopulmonary baroreceptors in ventricles and atria. Aortic baroreceptor nerve fibers travel via the vagus nerve (cranial nerve X), and carotid sinus fibers travel via the glossopharyngeal nerve (cranial nerve IX). These receptors respond to stretch (high pressure) or filling pressures (low pressure) and send tonic inhibitory signals to the brainstem. If BP increases and tonic inhibition increases, inhibition of sympathetic efferent outflow occurs and decreases vascular resistance and heart rate. However, if BP decreases, less tonic inhibition occurs, and heart rate and peripheral vascular resistance (PVR) increase, thereby increasing BP.

The brainstem cardiovascular centers are localized in the dorsomedial medulla. Neural afferents from cranial nerves IX and X are integrated in the nucleus tractus solitarius (NTS). From here, vasoconstriction and increased heart rate are mediated through the caudal and rostral ventrolateral medulla by the SNS. NTS efferents communicate with the nucleus ambiguus (vagal nucleus) to decrease heart rate through the vagus nerve. Also, the central neural control of renal function modulates renal blood flow, glomerular filtration rate (GFR), excretion of sodium and water, and renin release. These factors in turn regulate intravascular volume, vascular resistance, and BP.[3]

Inhibitory reflexes also originate in the kidney. Increases in urine flow rate increase renal pelvic pressure, which stretches the renal pelvic wall, leading to activation of mechanosensory nerves in the renal pelvic wall. Activation of these sensory nerves decreases renal sympathetic nerve activity and induces diuresis and natriuresis, an inhibitory renorenal reflex response.[4] The responsiveness of the renal sensory nerves is modulated by dietary sodium. A high sodium intake enhances the responsiveness of the afferent renal mechanosensory nerves in rats, thereby achieving sodium balance during increased dietary sodium intake.[5] Rats lacking intact afferent renal innervation only achieve sodium balance at the cost of increased MAP. Afferent renal denervation leads to salt-sensitive hypertension.[6]

Numerous vasoactive substances have effects on blood vessels, the heart, the kidneys, and the central nervous system (CNS) to regulate BP (Table 33-1). The renin-angiotensin-aldosterone system (RAAS) regulates volume and PVR (Fig. 33-2). Angiotensin II (Ang II) constricts vascular smooth muscle; stimulates aldosterone secretion; potentiates SNS activity; stimulates salt and water reabsorption in the proximal tubule; stimulates prostaglandin, nitric oxide (NO), and endothelin release; increases thirst; and stimulates vascular remodeling and inflammation. Increased renal angiotensin activity has also recently been linked with salt-sensitive hypertension, even in the volume-expanded state, and may have a role in blocking pressure natriuresis, in part by increasing renal sympathetic nerve activity and local oxidative stress.[7] Aldosterone stimulates sodium channels in distal renal tubular epithelium, leading to sodium retention and potassium excretion. It also exerts inflammatory and fibrotic effects through the mineralocorticoid receptor in vascular cells and in the heart. Plasma concentrations of renin and aldosterone are both inversely related to salt intake and are influenced by various medications.

A second major effector system is the SNS. Sympathetic nerve endings release the vasoconstrictor (norepinephrine) that binds the

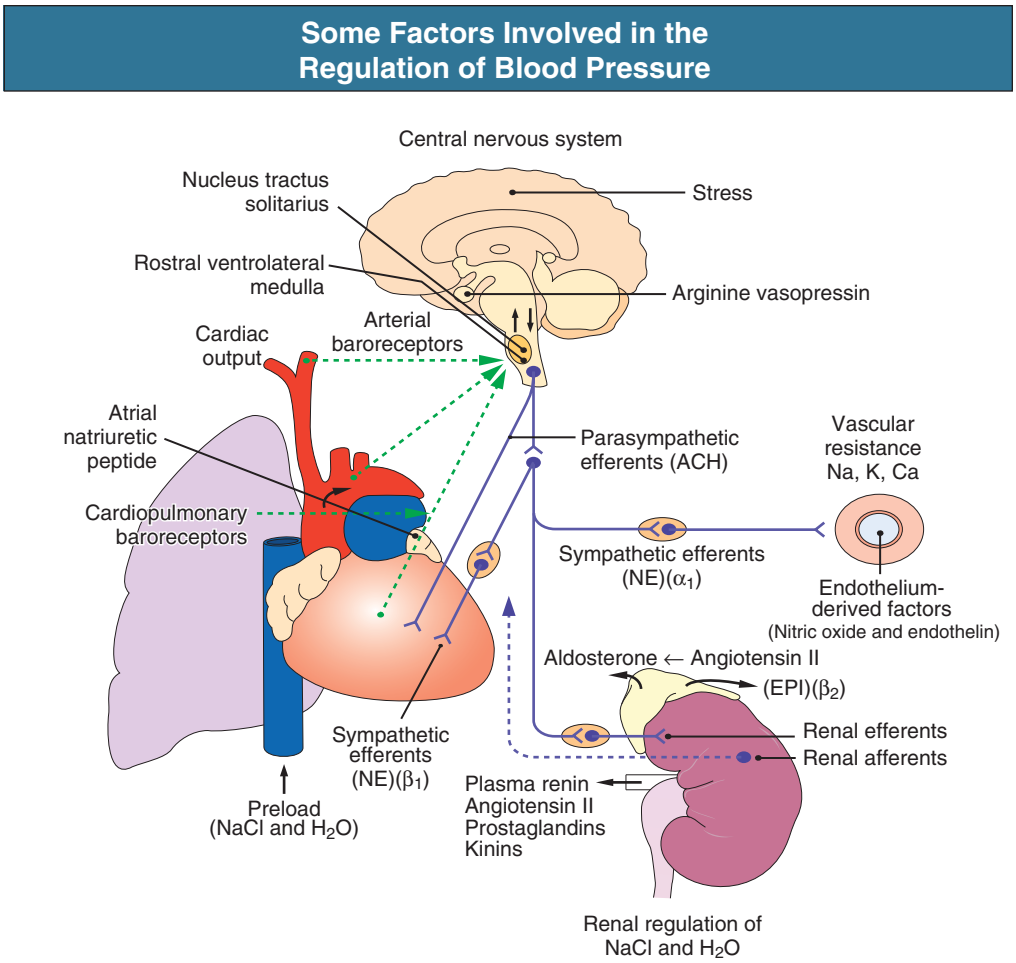

Figure 33-1 Factors in regulation of blood pressure. *ACH,* Acetylcholine; *EPI,* epinephrine; *NE,* norepinephrine; α_1, β_1, β_2, adrenergic receptors. Dashed lines refer to feedback to the central nervous system from cardiovascular *(green dash)* or renal *(purple dash)* sites.

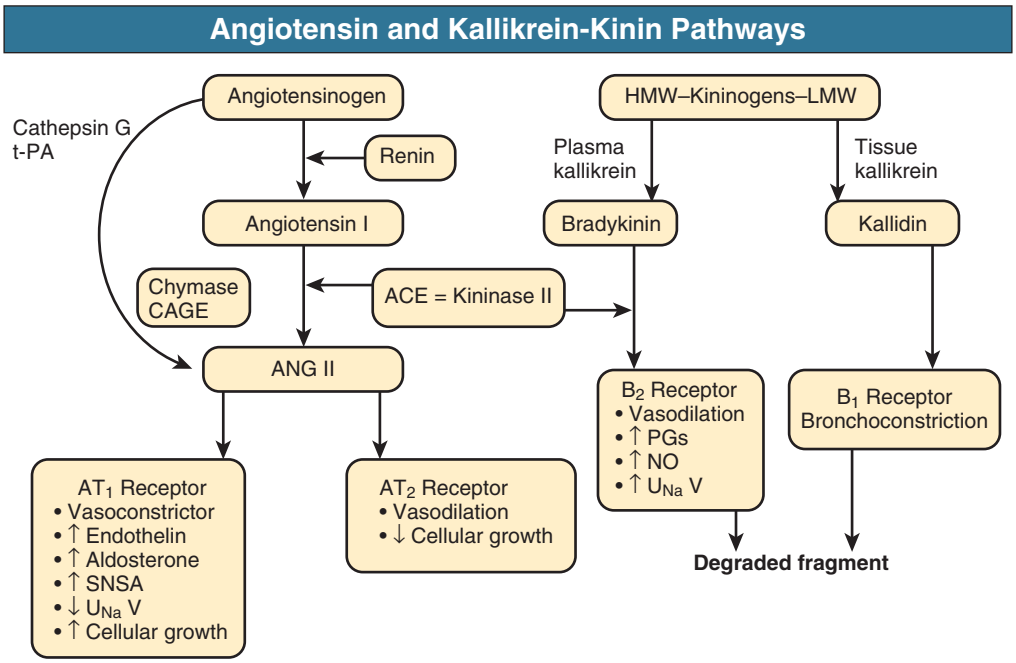

Figure 33-2 Interactions and functions of renin-angiotensin and kallikrein-kinin systems. *ACE,* Angiotensin-converting enzyme; *ANG II,* angiotensin II; AT_1, AT_2, angiotensin receptors; B_1, B_2, bradykinin receptors; *CAGE,* chymostatin-sensitive angiotensin II–generating enzyme; *HMW,* high molecular weight; *LMW,* low molecular weight; *PGs,* prostaglandins; *NO,* nitric oxide; *SNSA,* sympathetic nervous system activity; *t-PA,* tissue plasminogen activator; U_{Na} *V,* urinary sodium excretion.

Vasoactive Substances that Modulate Blood Pressure		
Group	**Compound**	**Cellular Effects**
Catecholamines	Norepinephrine, epinephrine, dopamine	Adrenergic receptors (α_1, α_2, β_1, β_2) causing protein phosphorylation and increased intracellular calcium through G proteins linked to ion channels or second messengers (cyclic nucleotides, phosphoinositide hydrolysis)
Renin-angiotensin system (RAS)	Angiotensin II (Ang II)	Angiotensin receptors (AT_1, AT_2, AT_4) causing increased intracellular calcium and protein phosphorylation through second messenger, phosphoinositide hydrolysis, and activated protein kinases Aldosterone stimulation
Mineralocorticoids	Aldosterone	*Genomic:* Binds to cytoplasmic mineralocorticoid receptor (MR), translocates to nucleus, modulates gene expression, and signals transduction and effectors (S_gK, CHIF, K_i-Ras), which increases transport proteins (increasing ENaC number and open probability) *Nongenomic:* Effects through separate membrane or cytosolic proteins
Kallikrein-kinin system	Bradykinin	Bradykinin receptors (B_1, B_2), B_2-G protein coupling cause activation of phospholipase C, increased inositol phosphates, and intracellular calcium
Arachidonic acid products	Prostaglandins: prostaglandin E, prostacyclin, thromboxanes Lipoxygenase enzyme products: leukotrienes, hydroxyeicosatetraenoates	Nine prostaglandin receptors coupled to G proteins: (e.g., PGI_2 [Receptor IP], PGE_2 [Receptors EP_1, EP_2]); PGF_{2a} (Receptor FP)
Endothelium-derived factors	Endothelium-derived relaxing factor (nitric oxide) Endothelins (ET-1, ET-2, ET-3)	Increased levels of cyclic guanosine monophosphate cause activation of protein kinases G proteins activate phospholipase C and L-type calcium channels Class 2 G protein–coupled receptor
Natriuretic peptides	Atrial, brain, and C-type	Activation of three receptor types; further effects mediated by cGMP
Posterior pituitary hormones	Arginine vasopressin	Vasopressin receptors (AVPR 1A; AVPR 1B) mediated by second messenger system, phosphatidyl inositol/calcium; AVPR2 effects via adenylate cyclase (cAMP)
Cyclic vasoactive peptides	Urotensin II (UT II)	UT II binds to G protein receptor GPR 14
Other substances	Acetylcholine, adenosine, insulin, neuropeptide Y, serotonin, sex hormones (estrogens, progesterone, androgens), glucocorticoids, other mineralocorticoids, substance P, vasopressin, renalase, heme oxygenase 1	

Table 33-1 Vasoactive substances that modulate blood pressure.

α-adrenergic receptor (adrenoceptor) on vascular cells, renal cells, and other cells (e.g., adipocytes). Epinephrine increases heart rate, stroke volume, and SBP through α- and β-adrenoceptors. The hormone is released from the adrenal medulla. Increased sympathetic tone has long-term influences on cardiovascular regulation and may cause hypertension.[8] In the kidneys, sympathetic nerves mediate renin release. Furthermore, innervation of each individual nephron affects sodium reabsorption. Thus, the SNS regulates both effective circulating fluid volume and PVR.

The kallikrein-kinin system counters the RAAS and produces vasodilator kinins, which stimulate prostaglandins and NO (see Fig. 33-2). Prostaglandin E and prostacyclin block the vasoconstriction by Ang II and norepinephrine. Two endothelium-derived factors have opposite effects on the blood vessels: NO is a vasodilator, whereas the endothelins are vasoconstrictors. Natriuretic peptides that include atrial (ANP), brain (BNP), and C-type induce vasodilation and natriuresis and inhibit other vasoconstrictors (renin-angiotensin system [RAS], SNS, endothelin). Renalase is a flavin adenine dinucleotide–dependent amine oxidase that is secreted by the kidney, circulates in the blood, and modulates cardiac function and systemic BP by metabolizing catecholamines.[9] Heme oxygenase (HO) is another important intrarenal and systemic BP modulator and inhibits oxidants, resulting in decreased BP.[10] Endogenous digitalis-like factors, which inhibit cell surface Na,K-ATPase and include an ouabain-like factor and marinobufagenin, also appear to regulate BP, cardiovascular (CV), and renal function.[11] Urotensin II is a locally expressed vasoconstrictive cyclic vasoactive peptide that stimulates proliferation of vascular smooth muscle cells and fibroblasts, inhibits insulin release, and modulates GFR. Despite urotensin II having these actions, high plasma urotensin II levels predict reduced CV complications in patients with chronic kidney disease (CKD, stages 2 to 5).[12,13]

Other mediator systems recently discovered include leptin, which in obese persons may increase BP by activating the CNS through a melanocortin pathway.[14] Uric acid may also be important by activating the RAS, inducing intrarenal oxidative stress, blocking endothelial NO, and directly affecting the vasculature.[15] Recent studies suggest a role for T cells in primary hypertension, possibly in response to heat shock protein 70, which may cause intrarenal vasoconstriction through release of Ang II and oxidants.[16] Chemoreceptors in the brain medulla and in the carotid and aortic bodies respond to changes in carbon dioxide and oxygen tension, resulting in renal vasoconstriction and dilation of the CNS and coronary vasculature.[17] Pain can also activate the SNS, although deep pain from crush injuries, testicular trauma, joint disruption, or abdominal distention leads to decreased sympathetic and increased parasympathetic outflow and decreased BP.[17] Postreceptor signaling events also regulate PVR. For example, the small guanosine triphosphatase Rho and its effector, Rho-associated kinase (Rho-kinase), stimulate vascular constriction and may have a role in cerebral artery spasm.[18]

Guyton and Hall[1] provide a model of the BP regulation in which CNS mechanisms (e.g., baroreflexes) provide short-term regulation of the circulation (seconds to minutes), with the RAAS and fluid shifts altering BP over minutes to hours and the kidneys responsible for long-term adjustments in BP, predominantly by regulating extracellular fluid volume[1] (Fig. 33-3). Indeed, the critical role for the kidney in the long-term control of BP received strong support from kidney cross-transplantation experiments[19] and bilateral nephrectomy in patients with end-stage renal disease (ESRD) and severe hypertension. However, activation of CNS and renal SNS pathways are now recognized as important in long-term BP control, in part by the later effects on the kidneys.[20] Renal sympathetic denervation by radiofrequency ablation through the renal arteries leads to substantial reduction in blood pressure in patients with resistant hypertension (see Chapter 38).[21,22] Furthermore, both intrarenal and extrarenal mechanisms are involved in the long-term regulation of blood pressure.[23]

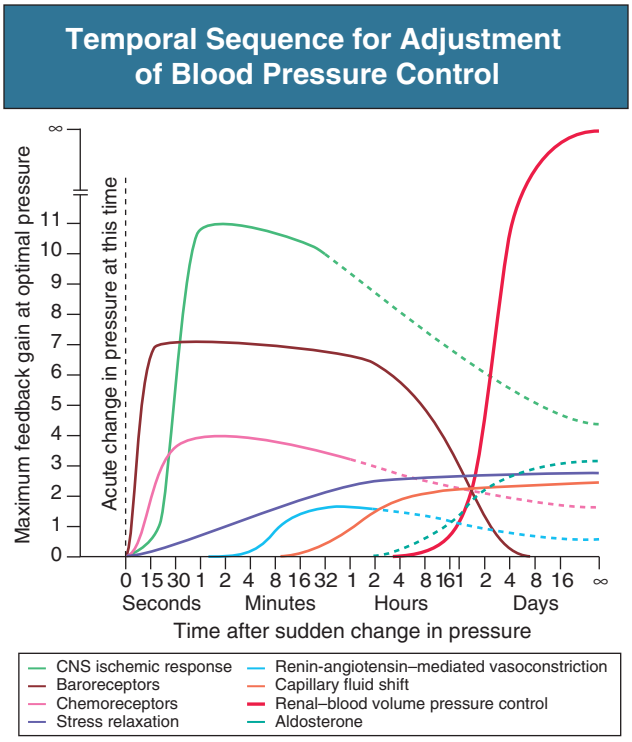

Figure 33-3 Temporal sequence for adjustment of blood pressure control. Degree of activity, expressed as feedback gain, of several arterial blood pressure control systems at various times after a sudden change in arterial BP. Note the infinite gain of the renal-volume mechanism for BP control. *CNS,* Central nervous system. *(From reference 1.)*

DEFINITION OF HYPERTENSION

Blood pressure is normally distributed in the general population. Thus any definition of hypertension is arbitrary. Hypertension is usually asymptomatic, and most symptoms, if present, are more from the sequelae of hypertension or its treatment. Hypertension may be defined by its associated morbidity and mortality, as increases over arbitrary cutoff points, or by thresholds defining therapeutic benefit.

Blood Pressure in Relation to Morbidity and Mortality

The first approach defines hypertension by relating BP levels to the risk of morbidity and mortality. The association of SBP and DBP with CV and renal complications is continuous over the entire BP range.[24] Death from both coronary heart disease and cerebrovascular accident (stroke) increases progressively and linearly from BP as low as 115 mm Hg SBP and 75 mm Hg DBP upward in all age groups ranging from 40 to 89 years (Figs. 33-4 and 33-5). For every increase of 20 mm Hg SBP or 10 mm Hg DBP, the mortality from both coronary heart disease and stroke doubles. On the basis of these data, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7 Report) introduced the term *prehypertension* for those with BP ranging from 120 to 139 mm Hg SBP or 80 to 89 mm Hg DBP.[25] After the 2003 JNC 7, the Writing Group of the American Society of Hypertension (WG-ASH) proposed a new definition of hypertension not based on BP values alone but considering hypertension as a complex cardiovascular disorder that includes target organ damage, early disease markers, and CV risk factors[26] (Table 33-2). This risk-based approach seeks to identify individuals with an increased likelihood of future CV events at any BP level. The WG-ASH stage 1 includes the prehypertension category in JNC 7. It should be noted that JNC 8 has recently been published but focuses on BP management and not on classification.[26a]

Elevation of Blood Pressure by Arbitrary Cutoff Points

A second approach defines hypertension by the frequency distribution within a population. This statistical approach arbitrarily designates values above a certain percentile as "hypertensive" and is used in defining hypertension in children. The values defining hypertension vary according to age, gender, body size, and race.[27] This frequency distribution method is not helpful for determining a value for initiation of antihypertensive treatment but is useful in epidemiologic studies, for example, defining the prevalence of hypertension in various age groups or the changing prevalence

WG-ASH Definition and Classification of Hypertension

Class	BP Elevation		CV Disease*	CV Risk Factors	Early Disease Markers	Target Organ Disease
Normal	Normal or rare	or	None	None or few	None	None
Hypertension						
Stage 1	Occasional intermittent	or	Early	Several	Usually present	None
Stage 2	Sustained	or	Progressive	Many	Overtly present	Early signs present
Stage 3	Marked and sustained	or	Advanced	Many	Overtly present with progression	Overtly present with or without CV disease events

Table 33-2 Working Group–American Society of Hypertension (WG-ASH) definition and classification of hypertension. *Cardiovascular *(CV)* disease determined by constellation of risk factors, early disease markers, and target organ disease.

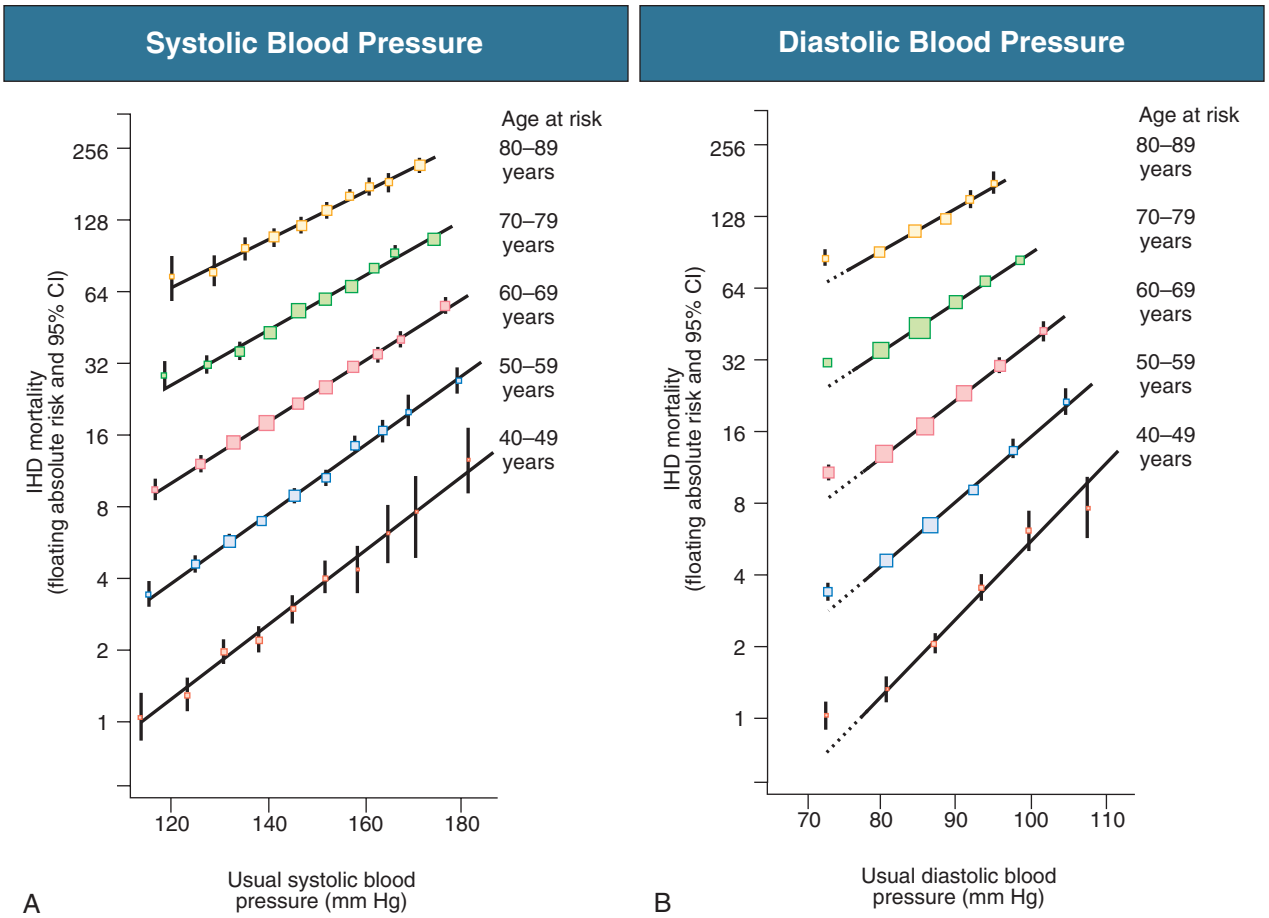

Figure 33-4 Ischemic heart disease (IHD) mortality rate in each decade of age versus usual blood pressure at start of that decade. A, Systolic blood pressure. **B,** Diastolic blood pressure. Floating absolute risk is a relative risk score that corrects for a baseline group, in this case the absolute death rate within a particular community. The size of the squares correlates inversely with the variance of the data collected for that data point. *CI,* Confidence interval. *(From reference 24.)*

of hypertension in a given population over time. The prevalence of hypertension in adults in the United States, defined as BP of 140/90 mm Hg or higher, has increased progressively from 11% of the population in 1939 to 29.3% in 2004.[28] The reported prevalence of hypertension in six European countries is 44%, and 66.3% in those older than 60.[29]

Threshold of Therapeutic Benefit

The third concept for defining hypertension is derived from randomized controlled trials (RCTs) that have demonstrated reductions in mortality and morbidity. As a result of clinical RCTs, consensus has been reached on intervention levels for moderate and severe hypertension but not for lower levels of hypertension. The Hypertension Optimal Treatment (HOT) study showed benefits of lowering BP to 138/83 mm Hg in hypertensive patients in the absence of diabetes mellitus, CKD, coronary heart disease risk, or target organ damage.[30] For patients with these complications, a treatment goal below 130/80 mm Hg is recommended (JNC 7).[25]

Operational Definitions

The European Society of Hypertension (ESH) divides "normotension" into three categories (optimum, normal, high-normal) and describes hypertension as mild, moderate, or severe[31] (Table 33-3). The ESH also provides values for automated 24-hour BP measurements, divided into daytime and nighttime.

In the United States, JNC 7 defined hypertension for individuals 18 years and older.[25] The committee settled on normal, prehypertension, and stage 1 and stage 2 hypertension (Table 33-4). For children, JNC 7 considers that BP at the 95th percentile or higher at each age is elevated.

Clinicians evaluate hypertensive patients and treatment goals on the basis of overall CV risk factors, not by BP alone. Age, gender, and ethnicity are important nonmodifiable risk factors, whereas cholesterol, high-density lipoprotein (HDL) cholesterol, smoking, control of diabetes, obesity, and left ventricular hypertrophy (LVH) are potentially modifiable[32] (Fig. 33-6). The cluster of risk factors that increase CV risk and are often associated with hypertension is termed the metabolic syndrome (Table 33-5). Decreased renal function and proteinuria are recognized as independent CV risk factors, including even microalbuminuria.[33] JNC 7 recommendations include follow-up of BP findings in a given individual (Table 33-6).

Special Definitions

Prehypertension (High-normal or Borderline Hypertension) Prehypertension is defined as SBP of 130 to 139 and DBP of 85 to 89 mm Hg. An earlier definition of "borderline hypertension" defined individuals whose BP was sometimes above 140/90 mm Hg but would decrease to levels below this with rest. Estimates of prehypertension or borderline hypertension have ranged between 12% and 30% of the adult population. Individuals with prehypertension have a threefold greater likelihood for development of sustained hypertension. Borderline hypertension may represent an

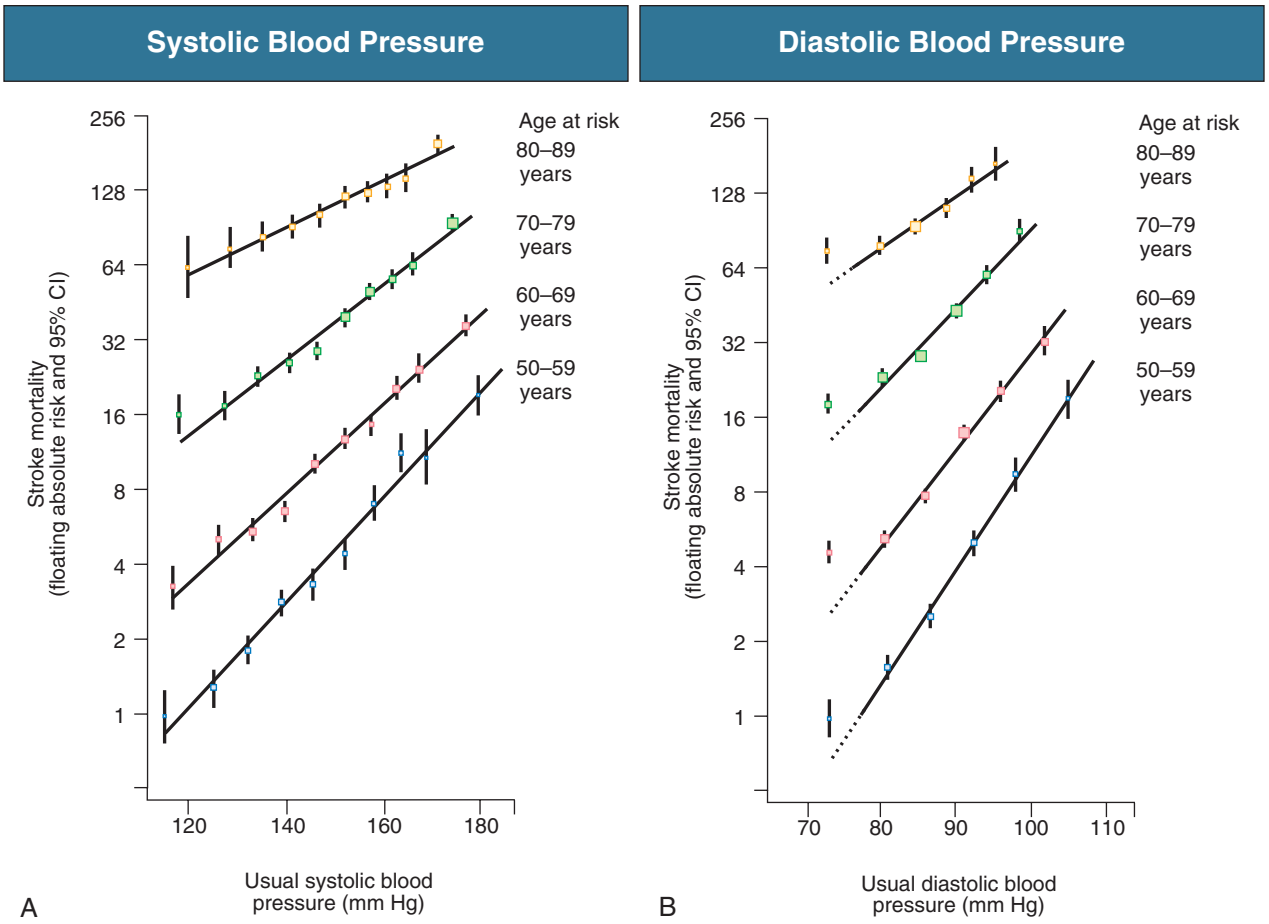

Figure 33-5 Stroke mortality rate in each decade of age versus usual blood pressure at start of that decade. A, Systolic blood pressure. **B,** Diastolic blood pressure. Floating absolute risk is a relative risk score that corrects for a baseline group, in this case the absolute death rate within a particular community. The size of the squares correlates inversely with the variance of the data collected for that data point. *CI,* Confidence interval. *(From reference 24.)*

European Society of Hypertension Consensus Classification

		Ambulatory and Self-Recorded BP Measurement†			
Category	***Office BP****	***Measurement***	***P95‡***	***Normotension***	***Hypertension***
Normotension		**Ambulatory**			
Optimum	<120/<80	24-hour	132/82	<130/<80	>135/85
Normal	120-129/80-84	Daytime	138/87	>135/<85	>140/90
High-normal	130-139/85-89	Nighttime	123/74	<120/<70	>125/75
Hypertension		**Self-Recorded**			
Grade I (mild)	140-159/90-99	Morning	136/85	<135/85	>140/90
Subgroup borderline	140-149/90-94	Evening	138/86	<135/85	>140/90
Grade II (moderate)	160-179/100-109	Both	137/85	<135/85	>140/90
Grade III (severe)	>180/>110				
Isolated systolic hypertension	>140/<90				
Subgroup borderline	140-149/<90				

Table 33-3 European Society of Hypertension consensus classification. Blood pressure readings are in millimeters of mercury (mm Hg). *Consensus classification proposed by the European Society of Hypertension/European Society of Cardiology guidelines (see reference 32). †Classification proposed at the Eighth International Consensus Conference on Ambulatory Blood Pressure Measurement (Sendai, Japan, October 2001). ‡Mean of 95th percentiles in patients who on conventional BP measurement were normotensive in large-scale studies.

JNC 7 Classification of Blood Pressure for Adults

BP Classification	SBP (mm Hg)	DBP (mm Hg)
Normal	<120	and <80
Prehypertension	120-139	or 80-89
Stage 1 hypertension	140-159	or 90-99
Stage 2 hypertension	≥160	or ≥100

Table 33-4 JNC 7 classification of blood pressure for adults (2003). *SBP,* Systolic blood pressure; *DBP,* diastolic blood pressure.

Common Definitions for Metabolic Syndrome

Criterion	NCEP ATP III (≥3 criteria)
Abdominal obesity Men Women	Waist circumference >40 inches (>102 cm) >35 inches (>88 cm)
Hypertriglyceridemia	>150 mg/dl (≥1.7 mmol/l)
Low HDL Men Women	 <40 mg/dl (<1.03 mmol/l) <50 mg/dl (<1.30 mmol/l)
Hypertension	≥130/85 mm Hg or taking antihypertensive
Impaired fasting glucose or diabetes	100 mg/dl (5.6 mmol/l) or taking insulin or hypoglycemic medication

Table 33-5 Common definitions for the metabolic syndrome. *NCEP ATP III,* National Cholesterol Education Program–Adult Treatment Panel III. *(From reference 25.)*

Follow-up Based on Initial BP Measurement for Adults

Initial Blood Pressure (mm Hg)*		
Systolic	***Diastolic***	**Follow-up Recommendation**
<130	<85	Recheck in 1 year.
130-139	85-89	Recheck in 1 year; provide information about lifestyle modification.
140-159	90-99	Confirm within 2 months.
160-179	100-109	Evaluate or refer to source of care within 1 month.
≥180	≥110	Evaluate or refer to source of care immediately or within 1 week, depending on clinical situation.

Table 33-6 Recommendations for follow-up based on initial blood pressure (BP) measurements for adults. *If systolic and diastolic categories are different, follow recommendations for the shorter time for follow-up. The schedule for follow-up should be modified according to reliable information about past BP measurements, other cardiovascular risk factors, or target organ disease.

Absolute Risk of Cardiovascular Disease by Systolic Blood Pressure

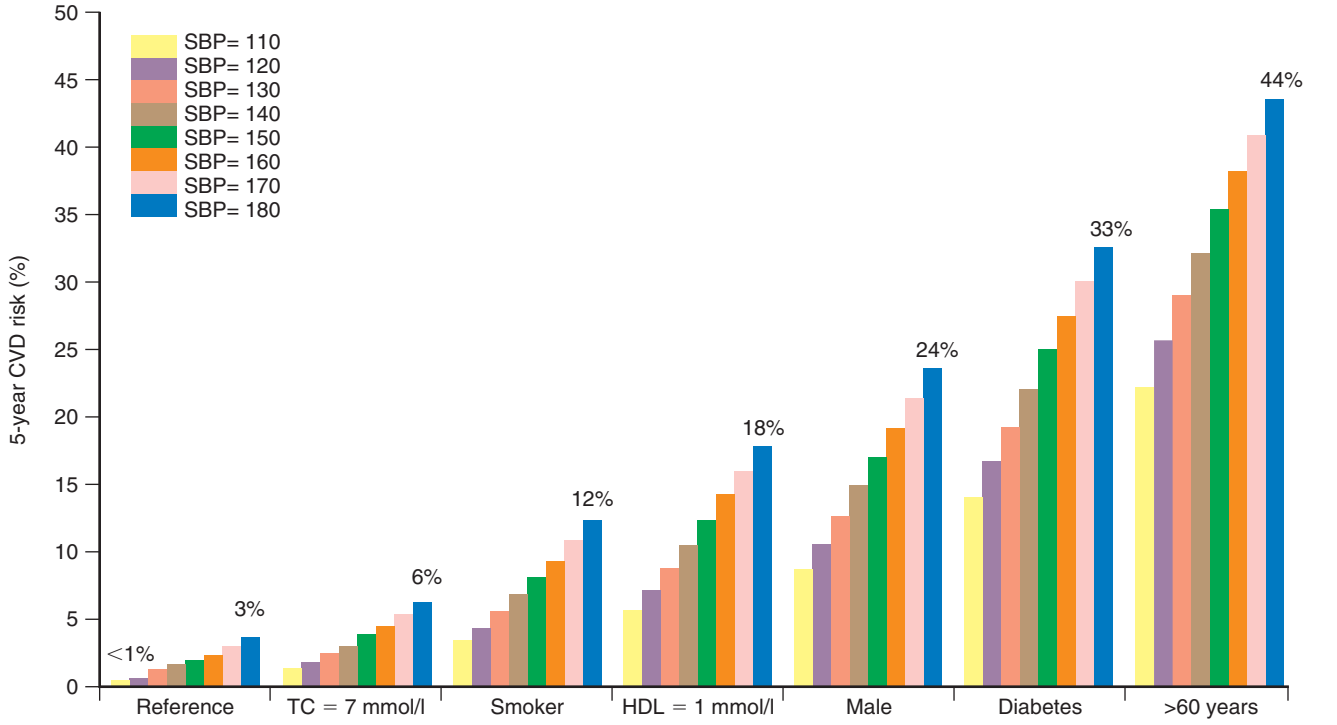

Figure 33-6 Absolute risk of cardiovascular disease during 5 years in patients by systolic blood pressure at specified levels of other risk factors. Reference category is a nondiabetic, nonsmoking woman age 50 with total cholesterol *(TC)* level of 4 mmol/l (155 mg/dl) and high-density lipoprotein *(HDL)* level of 1.6 mmol/l (62 mg/dl). Risks are given for systolic blood pressure *(SBP)* levels of 110, 120, 130, 140, 150, 160, 170, and 180 mm Hg. In the other categories, additional risk factors are added consecutively; for example, the diabetes category is a diabetic 50-year-old male cigarette smoker with TC level of 7 mmol/l (270 mg/dl) and HDL level of 1 mmol/l (39 mg/dl). *CVD,* Cardiovascular disease. *(From reference 32.)*

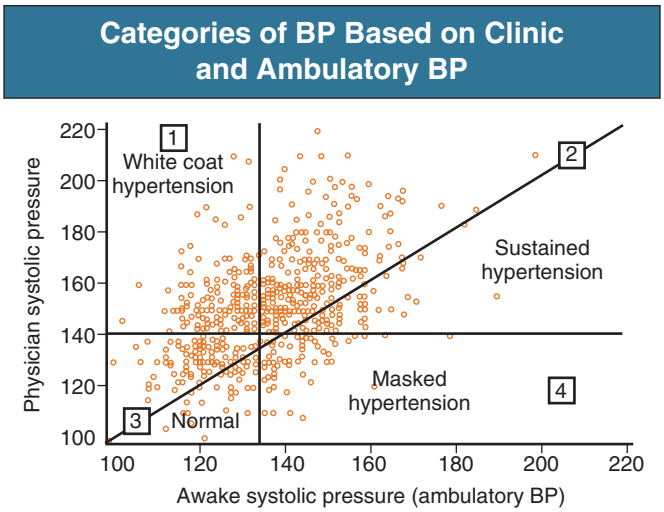

Figure 33-7 Plot of clinic systolic and daytime ambulatory blood pressure. BP plot defines four groups: normal, white coat hypertension, sustained hypertension, and masked hypertension. *(From reference 37.)*

exaggeration of normal physiologic responses to stress. Individuals with prehypertension may have a greater frequency of obesity, abnormal lipids, and other CV risk factors, with twice the CV events compared with those with BP below 120/80 mm Hg.[34] Because all BP is "labile" (variable) and generally varies on a diurnal cycle, the term "labile hypertension" is not helpful and should not be used.

White Coat Hypertension "White coat" hypertension is defined as BP that is normal during usual daily activities but is hypertensive in a clinical setting (Fig. 33-7). Normal pressures outside the physician's office are determined by measurement with standard techniques or by ambulatory BP recordings. White coat hypertension can be seen at all ages, including elderly persons. The white coat phenomenon is seen less frequently when a nurse or technician takes the BP rather than a physician. White coat hypertension is present in approximately 20% of hypertensive persons. Guidelines are available to assist in assessing patients with isolated clinic hypertension or isolated ambulatory hypertension.[35]

Although some studies suggest this hypertension is benign, in the long term, others suggest that white coat hypertension is characterized by increases in left ventricular mass index at levels intermediate between normotensive and persistently hypertensive persons.[36] White coat hypertensive patients have impaired diastolic function and higher levels of catecholamines, plasma renin activity, aldosterone, and low-density lipoprotein (LDL) cholesterol. Patients with white coat hypertension may also be at increased risk for development of persistent hypertension.[36] Thus each patient with white coat hypertension needs evaluation for CV risk factors and continued follow-up.

Masked Hypertension Masked hypertension is defined as BP that is lower in the office or clinic compared with ambulatory BP (see Fig. 33-7). In one study, the 10-year risk of stroke and CV mortality in patients with masked hypertension was similar to that of those with sustained hypertension.[36]

Sustained Hypertension Sustained hypertension, also called *persistent hypertension,* defines individuals whose BP level is elevated both inside and outside the clinic setting, including at home and during usual daily activities. Office BP readings are frequently higher in sustained hypertensive patients compared with their ambulatory BP.[37]

Pseudohypertension Pseudohypertension is defined as "a condition in which the cuff pressure is inappropriately higher when compared to the intra-arterial pressure because of excessive atheromatosis and/or medial hypertrophy in the arterial tree."[38] Pseudohypertension can be suspected by the "Osler maneuver," in which the BP cuff is inflated above the SBP (detected by auscultation). If either the brachial or the radial artery remains palpable, when pulseless, the patient is considered to be Osler maneuver positive. In general, patients with pseudohypertension have intra-arterial DBP measurements 10 to 15 mm Hg below indirect BP cuff diastolic measurements. None of the definitions specifically addresses the SBP. If a patient is suspected of having pseudohypertension, confirmation by intra-arterial pressure measurement may be considered, with therapeutic goals based on the intra-arterial findings.

Isolated Systolic Hypertension Arteriosclerosis, characterized by remodeling and stiffening of large elastic arteries, is the most significant manifestation of vascular aging.[39] The increased stiffening is believed to originate from a gradual mechanical senescence of the elastic network, alterations in cross-linking of extracellular matrix components, fibrosis, and calcification of elastic fibers. Stiffening of large arteries reduces their capacitance and accelerates pulse wave velocity, thus contributing to a widening of pulse pressure and increased prevalence of isolated systolic hypertension with age. Perhaps as a consequence, the increase in SBP continues throughout life, in contrast to DBP, which increases until age 50 and decreases later in life (Fig. 33-8). Diastolic hypertension is more common before 50 years, either alone or in combination with elevated SBP. After age 50, SBP is more important than DBP.

Isolated systolic hypertension (ISH) is defined as SBP of 140 mm Hg or higher and DBP of 90 mm Hg or lower. The prevalence of ISH increases with age and affects most individuals older than 60. In the Framingham study, elevations in SBP determined a greater risk of both "heart attacks" and strokes compared with elevations of DBP. Indeed, JNC 7 assigned SBP a higher level of importance than DBP.[25] Several clinical trials have clearly demonstrated that treatment of ISH reduces the CV event rate.[40] Nevertheless, controversy exists as to the choice of antihypertensive agent. Elderly hypertensive patients should be treated aggressively to the same target BP identified for younger patients. However, treatment should be initiated with lower antihypertensive doses to bring the pressure down more slowly in elderly patients, with monitoring for orthostatic hypotension, impaired cognition, and electrolyte abnormalities.

Resistant Hypertension Resistant hypertension is defined as BP that is not at treatment goal despite optimal doses of three antihypertensive drugs, including a diuretic. Some clinical trials suggest that resistant hypertension may occur in 30% of hypertensive patients. Older age and obesity are strong risk factors. Secondary hypertension is more common in resistant hypertension, with primary aldosteronism present in 18% to 23% of patients, and renal artery stenosis in 24%.[21,41]

Hypertensive Urgencies and Emergencies Accelerated hypertension is severe diastolic hypertension (usually >120 mm Hg) in the presence of grade III retinopathy (arteriolosclerotic changes of arteriolar narrowing and nicking plus hypertensive changes of flame-shaped hemorrhages and soft exudates).[42] In the past, "malignant" hypertension referred to severe diastolic hypertension and grade IV retinopathy (grade III plus papilledema). Because the prognosis for untreated severe hypertension in patients with grade III or IV retinopathy is so poor, there is little clinical rationale for using the two terms separately. More recently, accelerated hypertension with hypertensive retinopathy is defined as a *hypertensive urgency* if treatment is required to decrease BP within hours, whereas *hypertensive emergency* refers to clinical conditions in which severe hypertension must be lowered within minutes. Emergencies include acute

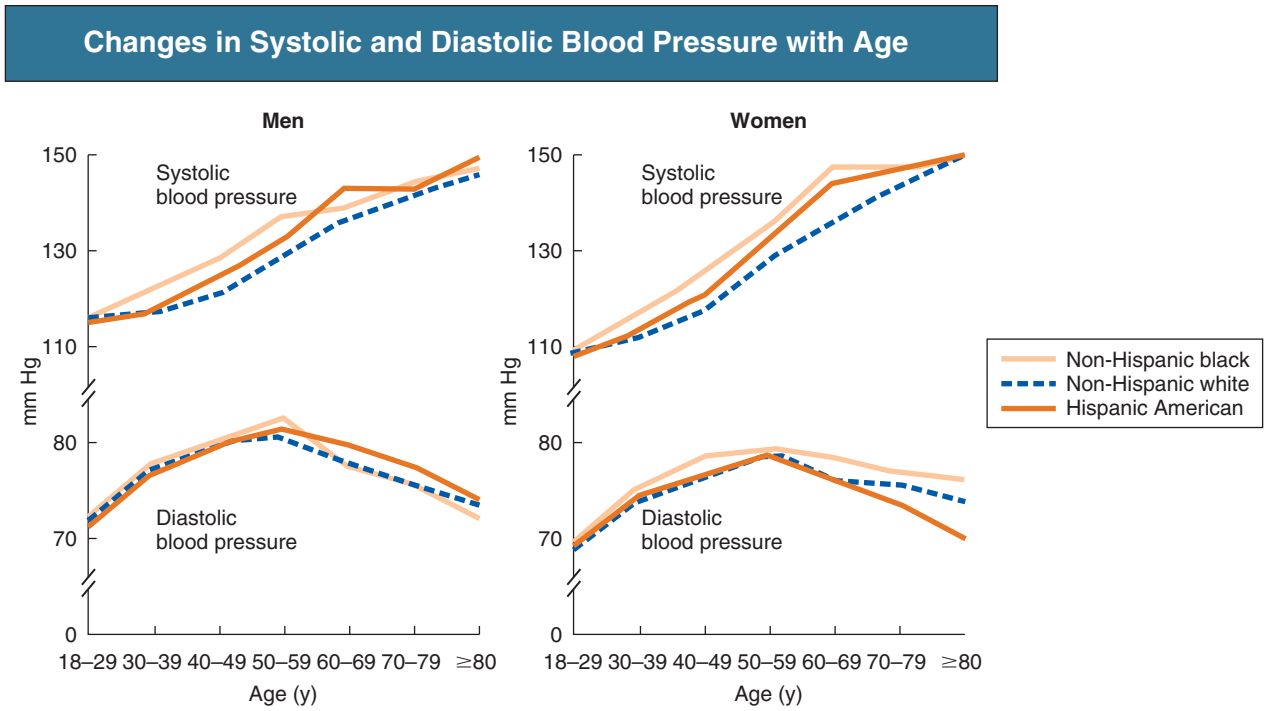

Figure 33-8 Changes in systolic and diastolic blood pressure with age. Systolic blood pressure and diastolic blood pressure by age and race or ethnicity for men and women older than 18 years in the U.S. population (NHANES III, 1988-1991). *(From reference 50.)*

dissection of the aorta, acute left ventricular failure, intracerebral hemorrhage, and crises caused by pheochromocytoma, drug abuse, and eclampsia (see Chapter 37).

Hypertension in Children and Adolescents Pediatric hypertension is defined by average SBP or DBP at or above the 95th percentile for gender and age, measured on at least three occasions. The reported causes of hypertension in children vary. Most preadolescent hypertension is thought to have renal causes, although some children may have BP levels above the 95th percentile because of an earlier growth spurt and large size. In adolescent children, mild hypertension is likely to be primary hypertension, with risk factors including a family history of hypertension and obesity, the latter now an evolving epidemic.[43] More severe hypertension in adolescents is usually of renal cause. Primary aldosteronism and thyroid disease seem to be rare.

Hypertension in Pregnancy Hypertension may occur in more than 5% of all pregnancies and in approximately 5% of women taking oral contraceptives. Definitions and implications of hypertension in pregnancy are discussed in Chapters 44 and 45.

Classification by Cause of Hypertension

In 90% to 95% of patients with hypertension, the etiology is unknown and labeled as "primary" (or essential) hypertension (see Chapter 34). Table 33-7 shows the more common causes of secondary hypertension. Acquired causes include renal parenchymal disease (2% to 6% of all hypertensive patients), renovascular hypertension (1% to 4%), and all endocrine hypertension (traditionally thought to be 1%, including primary aldosteronism, pheochromocytoma, and Cushing syndrome). More recent studies have shown an increasing prevalence of primary aldosteronism, ranging from 2% to 13% in stage 1 to stage 3 hypertension. Other causes include coarctation of the aorta (0.1% to 1.0%) and obstructive sleep apnea and obesity. An often overlooked cause of hypertension is drug induced (1%), including oral contraceptives, decongestants or sympathomimetic agents, nonsteroidal anti-inflammatory drugs (NSAIDs), and illicit drugs. There are also a number of rare monogenic causes of hypertension (see Chapter 49).

EVALUATION OF HYPERTENSION

Blood Pressure Measurement

Arterial BP is usually measured in the brachial artery by the cuff-based sphygmomanometer, in which the arterial pressure is recorded by detecting sounds that are generated (auscultatory method) or by recording vascular pulsations (oscillometric method) after decompression of a compressed artery. Box 33-1 lists guidelines for BP measurement. Unfortunately, if it is not properly used, the method can be inaccurate. The most common reason for inaccuracy is an inappropriate cuff size, because the accuracy of these measurements is influenced by the size of the inflatable bladder relative to the girth of the compressed limb. To provide uniform compression of the underlying artery, the length of the bladder should be at least 80% of the upper arm circumference, and the width of the bladder should be at least 40% of the upper arm circumference. A simple bedside maneuver to check the appropriateness of the cuff size consists of aligning the cuff so that its long axis is parallel to the long axis of the arm. The bladder width should then be sufficient to encircle half of the upper arm circumference. No change in cuff size is necessary if the cuff width encircles more than half the upper arm, because large cuffs on thin limbs do not produce considerable errors in the BP measurement. Table 33-8 provides accepted bladder dimensions for varying arm sizes.

Another potential error in BP measurement relates to the auscultatory method, which relies on the ability to hear the Korotkoff sounds. The human ear has a sound threshold of about 16 Hz. The Korotkoff sounds occur at slightly above this level (25 to 50 Hz). Thus the human ear is almost deaf to the sounds it must hear to

Acquired Causes of Secondary Hypertension	
Condition/Disorder	**Diseases: Comments**
Renal disorders	Renal parenchymal disease, including acute and chronic glomerular diseases, chronic tubulointerstitial disease, PKD, diabetic nephropathy, and obstructive uropathy Renovascular disease: renal artery stenosis caused by atherosclerosis or fibromuscular dysplasia; arteritis; extrinsic compression of renal artery Other renal causes: renin-producing tumors, renal sodium retention (Liddle syndrome)
Endocrine disorders	Adrenocortical disorders: primary aldosteronism, congenital adrenal hyperplasia, Cushing syndrome Adrenomedullary tumors: pheochromocytoma (also extra-adrenal chromaffin tumor) Thyroid disease: hyperthyroidism, hypothyroidism Hyperparathyroidism with hypercalcemia Acromegaly Carcinoid tumors
Exogenous medications and drugs	Oral contraceptives, sympathomimetics, glucocorticoids, mineralocorticoids, NSAIDs, calcineurin inhibitors, tyramine-containing foods and monoamine oxidase inhibitors, EPO, ergot alkaloids, amphetamines, herbal remedies, licorice (mimics primary aldosteronism), ethanol, cocaine and other illicit drugs, abrupt withdrawal of clonidine
Pregnancy	Preeclampsia and eclampsia
Coarctation of the aorta	
Neurologic disorders	Sleep apnea Increased intracranial pressure: brain tumors Affective disorders Spinal cord injury: quadriplegia, paraplegia, Guillain-Barré syndrome Baroreflex dysregulation
Psychosocial factors	Hostility, time-urgency/impatience, depression, anxiety, occupational stress
Intravascular volume overload	
Systolic hypertension	Loss of elasticity of aorta and great vessels Hyperdynamic cardiac output: hyperthyroidism, aortic insufficiency, anemia, arteriovenous fistula, beriberi, Paget disease of the bone
Obesity	White adipose tissue has endocrine function: leptins; adiponectin; cytokines; chemokines; Ang II; other adipokines

Table 33-7 Secondary hypertension: acquired causes. *Ang II,* Angiotensin II; *EPO,* erythropoietin; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *PKD,* polycystic kidney disease.

Accepted Bladder Dimensions for Varying Arm Sizes			
Patient	**Arm Circumference Range at Midpoint (cm)**	**Bladder Width (cm)**	**Bladder Length (cm)**
Newborn	6	3	6
Infant*	6-15	5	15
Child*	16-21	8	21
Small adult	22-26	10	24
Adult	27-34	13	30
Large adult	35-44	16	38
Adult thigh	45-52	20	42

Table 33-8 Accepted bladder dimensions for varying arm sizes. *To approximate a bladder width to arm circumference ratio of 0.4 more closely in children, additional cuffs are available. There is some overlap in the recommended ranges for arm circumference to limit the number of cuffs. It is suggested that the larger cuff be used if it is available. *(From reference 51.)*

measure BP. The bell-shaped stethoscope head should be used to measure BP.

The oscillometric method is based on the principle of plethysmography to detect pulsatile pressure changes in a nearby artery. When an arm cuff is inflated, pulsatile pressure changes in an underlying artery produce periodic pressure changes in the inflated cuff. The oscillometric method thus measures periodic pressure changes, oscillations, in an inflated cuff as an indirect measure of pulsatile pressure in an underlying artery.

There are three types of sphygmomanometers. Because of environmental concerns, the standard mercury manometer has been abandoned in many countries, with recent goals to have mercury-free health care throughout the world in 2020.[44] The second type is the aneroid manometer. There are also numerous semiautomatic oscillometric electronic recording manometers. The manufacturers must ensure accuracy, and in many countries, the local hypertension societies have arranged for certification of these devices. The technical capabilities of the devices have increased greatly. Physicians must be aware that many patients purchase devices and measure their own BP. These devices should be inspected and checked for accuracy by the physician.

Ambulatory BP monitoring uses a noninvasive system. The BP is determined by auscultation with use of either oscillometry, which measures variations in pressure within the cuff, or a microphone placed under the cuff and over the brachial artery. The ambulatory BP device can be programmed to record at frequent intervals during the daytime (e.g., every 10 minutes) and less frequently at night during sleep (e.g., every 30 minutes). The ambulatory BP equipment might not provide accurate readings in patients with large upper arms caused by obesity or increased musculature, and the equipment may be inaccurate during vigorous activity. The equipment generally records BP during a 24-hour period. Although most patients adjust to the repetitive measurements throughout the day, some patients may have a startle response with each BP recording. Most patients

Guidelines for Measurement of Blood Pressure

Patient Factors

Caffeine should not be taken for up to 1 hour before the BP measurement.

Cigarettes should not be smoked for at least 15 minutes before the BP reading.

The standard BP measurement should be made with the patient not talking and seated comfortably, back and arm supported, and legs uncrossed. The cuff must be at the level of the heart, and the arm should be bared.

The urinary bladder should be empty.

On an initial examination, BP should also be checked in the supine position after 5 minutes of rest, in the standing position after 2 minutes, and initially in both arms, especially in patients who are diabetic, older than 65 years, or receiving antihypertensive therapy. Use the higher value if the arms have differing BP readings.

If sequential BP readings are taken in the same position, at least 30 seconds must elapse between BP readings. In patients younger than 30 years, check BP in one leg.

To establish a diagnosis of hypertension, obtain BP readings on three different occasions, at least 1 week apart.

Equipment

The length of the bladder with the cuff should encircle at least 80% of the arm.

The width of the cuff should be equal to two thirds of the distance from the antecubital space to the axilla and should be 40% of the arm circumference. The best cuff for most adults is the 15-cm-wide cuff with a bladder of 33 to 35 cm in length. The distal edge of the cuff should be 2.5 cm (1 inch) above the antecubital fossa. For leg BP, thigh cuff length should encircle 80% of the thigh, and width should be 40% of the thigh circumference. For leg BP, the patient should be prone and popliteal artery sounds measured by auscultation. For automated equipment, the sensor should be over the brachial (or radial or popliteal) artery.

In extremely obese patients, BP may be more accurate when measured in the forearm, palpating and auscultating the radial artery.

For infants, ultrasound equipment may need to be used. The bell of the stethoscope is preferred.

Technique

The initial systolic BP should be checked by palpating the disappearance of the radial or brachial pulse before auscultation, and the cuff then deflated.

The second BP check requires cuff inflation 20 to 30 mm Hg above the palpable systolic level.

Deflate the cuff at a rate of 2 to 4 mm Hg per second.

Record the Korotkoff sound I (appearance of sound) as the systolic BP and record the Korotkoff sound V (silence, 2 mm Hg below the last sound) as the more reproducible diastolic BP. If the sounds do not disappear, record the muffled sound (phase IV) as the diastolic BP.

The sounds may be augmented by the patient raising the arm and opening and closing the hand 10 times before inflating the BP cuff.

Do not stop between systolic and diastolic BP readings; deflate the cuff, wait at least 30 seconds, and then reinflate. On each occasion, record at least two BP readings. If the BP readings vary by more than 5 mm Hg, take additional BP readings until two are within 5 mm Hg.

In children, the same standards apply for cuff size; Korotkoff sound V should be used. If the child is uncooperative, the systolic BP may be determined by palpation.

Box 33-1 Guidelines for measurement of blood pressure (BP): patient factors, equipment, and technique.

are able to sleep, although some have their sleep disturbed by the BP recording, and therefore determination of nocturnal fall in BP is inaccurate.

There are disadvantages to use of the ambulatory BP equipment. Trained personnel must place the monitoring equipment. Calibration of ambulatory BP equipment must be recorded at the beginning and end of the ambulatory BP session. For calibration, three to six readings must be taken at each time, and the SBP and DBP measurements must both agree within 5 mm Hg. The end calibration is critical to ensure proper functioning of the ambulatory BP monitor throughout the 24-hour period. The cuff inflation may interfere with activities, work, or sleep. The cuff may cause discomfort or skin irritation, or it may malfunction and fail to deflate, causing pain and interruption of recording. The data correlating ambulatory BP with target organ disease are limited. Standards for assessment of data and their use in therapeutic decision making are limited. In addition, equipment is expensive, and its use is limited by lack of, or unpredictable, reimbursement by health insurance systems in a number of countries.

Variability of Blood Pressure

Wake-Sleep Cycle and Office Versus Home Blood Pressure

Blood pressure varies considerably among individuals and may vary significantly throughout the day. This variation causes considerable difficulty in identifying individuals who are hypertensive, especially in terms of the preceding classification schemes. The differing BP values are caused by both biologic variation (variations of pressures within a given individual) and variation in the measurement itself. Errors in measurement can be minimized by attention to the proper technique for recording BP, as noted previously. Biologic variation is addressed by repeated BP measurement at a given visit (at least two pressures taken at least 30 seconds apart, or additional BP measurements if there is a difference of 5 mm Hg between repeated measures). In most patients with milder forms of hypertension, repeated measurements during different clinic visits over time are recommended to find the true BP.

Readings of BP at home, and outside the clinic or office setting, are recommended to assess the severity and frequency of hypertension and BP control during treatment. The instruments used at home must be checked against a standard on a regular basis, and the techniques for correct BP measurement must be taught to the patient. This includes having the brachial artery at the level of the heart when BP is measured. Levels measured at home are generally lower than those measured in the clinic or office. Patients should be discouraged from very frequent home BP measurement and from frequent adjustment of medications, which may result in unnecessary emergency department visits and hospital admissions for symptomatic hypotension or uncontrolled hypertension. It is worthwhile to ask the patient to keep a daily calendar and to measure BP under controlled conditions two or three times daily, such as while sitting

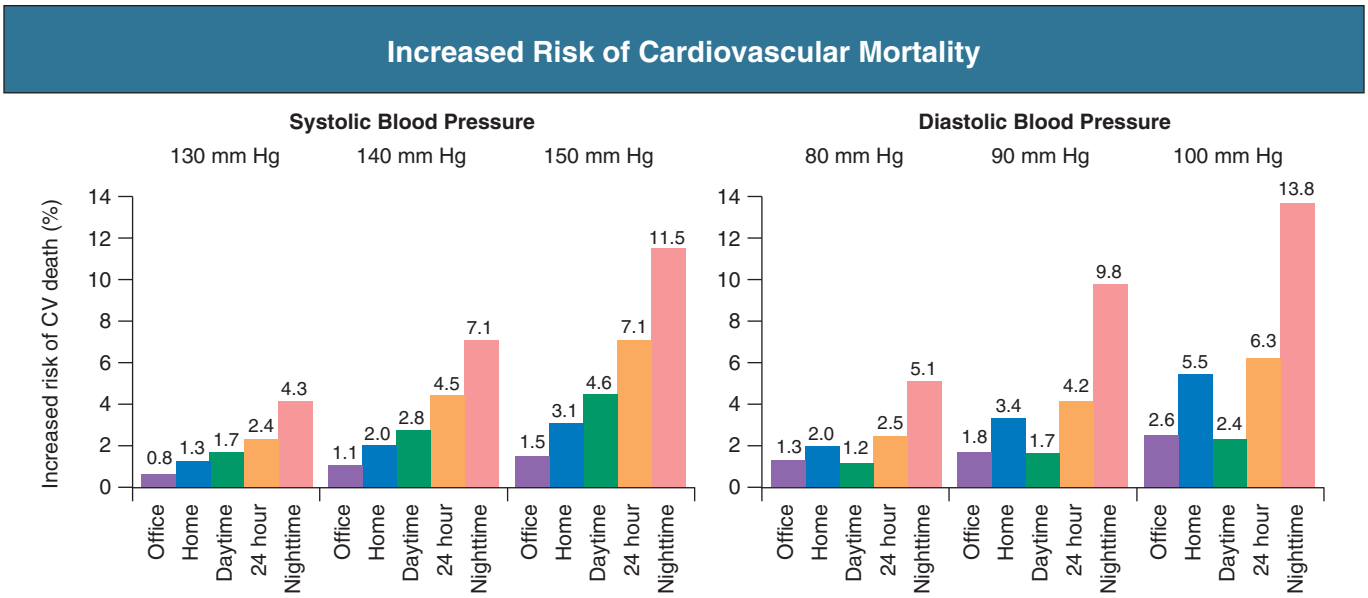

Figure 33-9 Increased risk of cardiovascular mortality. Risk of CV death (%) for 10 mm Hg increase in office, home, and ambulatory blood pressure readings at various initial BP values at 11 years. *(From reference 46.)*

quietly in the morning, afternoon, and evening. If three fourths of the measurements achieve goal value or better, office control is generally also achieved.

Biologic variation during the day is related to physical and mental activity and emotional factors. There is also diurnal variation, with a decrease in BP during sleep (averaging 20%) secondary to a decrease in sympathetic activity; similar reductions in BP occur after hospital admission and bed rest. The normal diurnal pattern includes an increase in BP before awakening that has been associated with increased incidence of myocardial infarction, stroke, and sudden death in the first few hours after awakening.[45] Those with the usual pattern of BP decrease during sleep are known as nocturnal "dippers." Individuals whose BP does not fall during sleep are called "nondippers." The failure to decrease BP during sleep has been associated with increased incidence of LVH and suggests secondary hypertension.

Home and Ambulatory Blood Pressure

Because of the variability in BP that occurs throughout the day, home BP and ambulatory BP monitoring are used to define BP more clearly. Home BP monitoring is advised for all patients to help identify white coat hypertension and borderline hypertension and help monitor response to therapy, including identification of hypotension as well as hypertension. This is particularly important in patients with CKD, who are more likely to have white coat hypertension and masked hypertension. The instructions to each patient must be individualized, but home BP monitoring may be advised two or three times daily while the patient is awake. These BP values must be self-recorded and reviewed. The prognostic value of ambulatory and home BP was compared with office BP in several population studies, and the risk of death increased more with a given increase in home or ambulatory BP than in office BP.[46] The overall ability to predict death, however, was not greater for home and ambulatory than for office BP, although it was somewhat increased by the combination of office and outside-of-office values. SBP was almost invariably superior to DBP, and night BP was superior to day BP in CV mortality risk (Fig. 33-9). Ambulatory BP monitoring is recommended over home BP recording in a few settings[47] (Fig. 33-10 and Box 33-2).

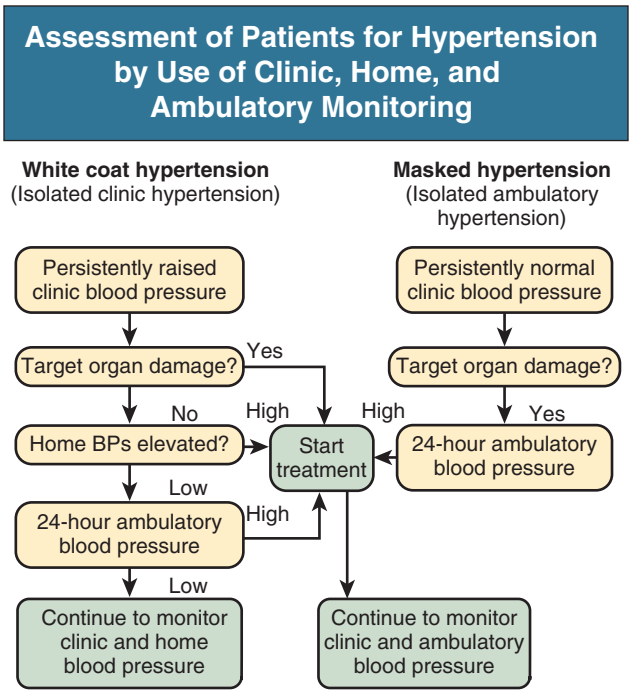

Figure 33-10 Guidelines for patient assessment: clinic, home, and ambulatory monitoring of blood pressure.

Risk Factors for Hypertension

A number of factors are known to be associated with an increased risk of primary hypertension.[48] These are discussed in detail in Chapter 34.

Evaluation for Primary Versus Secondary Hypertension

The medical history, the physical examination, and a limited number of laboratory tests provide critical information in deciding which individuals require further evaluation for secondary hypertension and target organ disease (Tables 33-9 and 33-10). All hypertensive

Indications for Ambulatory Blood Pressure Measurement
White coat hypertension
Evaluation of apparent drug resistance
Hypotensive symptoms
Autonomic dysfunction
Episodic hypertension
Evaluation of nocturnal decreases in BP as a prognostic factor for target organ disease (e.g., left ventricular hypertrophy, ischemic optic neuropathy)
Evaluation of BP changes in patients with paroxysmal nocturnal dyspnea and nocturnal angina
Carotid sinus syncope
Pacemaker syndromes
Safety of withdrawing antihypertensive medication
Assessment of 24-hour BP control in patient receiving once-daily medication
Borderline hypertension with target organ damage
Evaluation of antihypertensive drug therapy in clinical trials

Box 33-2 Indications for ambulatory blood pressure (BP) measurement.

persons should be assessed for CV risk factors, including total cholesterol, HDL and LDL cholesterol, fasting triglycerides, renal function, and proteinuria, and for the presence of diabetes mellitus or the metabolic syndrome.

If the history, physical examination, or screening laboratory studies suggest secondary hypertension, additional studies are warranted. If renal parenchymal disease is suspected, quantitative studies to assess GFR and urinary protein excretion should be performed. Renal ultrasound is useful to evaluate renal size and echogenicity (to help assess chronicity) and to evaluate for obstructive uropathy. Renal artery stenosis should be suspected in the patient with severe hypertension and abnormal renal function or with asymmetric renal size or a renal ultrasound with abnormal Doppler flow studies. If primary aldosteronism is suspected because of hypokalemia, the ratio of plasma aldosterone to plasma renin activity may be useful. If the ratio is above 25 to 30, and plasma aldosterone concentration is greater than 20 ng/dl, the diagnosis should be pursued further.

In the extended results of patients undergoing surgery,[49] resolution of hypertension after adrenalectomy for primary aldosteronism was independently associated with a lack of family history of hypertension and with preoperative use of two or fewer antihypertensive agents. Further evaluation for other forms of secondary hypertension is listed in Table 33-10.

Evaluation for Primary Versus Secondary Hypertension			
Classification	**Medical History**	**Physical Examination**	**Laboratory Studies**
General information and evaluation of target organs	Duration and course of hypertension Prior workup and treatment Diet/lifestyle: salt intake, tobacco, caffeine	Evaluation of volume status, optic fundi, heart, lungs, peripheral vessels, and nervous system	Complete blood count, fasting glucose, lipid profile (includes HDL, LDL, cholesterol, triglyceride), uric acid Consider echocardiogram
Primary (essential or idiopathic) or secondary?	Family history: hypertension, cardiovascular and renal diseases Symptoms of target organ disease (related to eyes, central nervous system, cardiorespiratory, and peripheral vascular)	See Table 33-10 for signs suggestive of secondary hypertension	See Table 33-10 for additional laboratory studies to rule out secondary hypertension

Table 33-9 Evaluation for primary versus secondary hypertension. *HDL,* High-density lipoprotein; *LDL,* low-density lipoprotein.

Evaluation for Secondary Hypertension			
Target Organ/System	**Medical History**	**Physical Examination**	**Laboratory Studies**
Kidney			
Renal parenchymal	History of renal disease (including glomerulonephritis, nephrotic syndrome, calculi, urinary tract infection) Symptoms include nocturia, frequency, dysuria, hesitancy, urgency, incomplete emptying, dribbling, hematuria, pyuria, flank pain	Tenderness in costovertebral angles; palpable kidneys, edema	BUN, serum creatinine; urinalysis, urine culture if indicated; 24-hr urine for protein and creatinine clearance if indicated; consider microalbuminuria measurement, or random urine protein-creatinine ratio
Renovascular hypertension		Epigastric bruit; other vascular bruits	Renal ultrasound with duplex Doppler flow study; consider angiography or magnetic resonance angiography
Endocrine			
Primary aldosteronism	Muscle weakness, cramps		Serum potassium: consider serum aldosterone/plasma renin activity ratio; 24-hr urine aldosterone, Na^+, K^+, creatinine

Table 33-10 History, physical examination, and initial laboratory evaluation for secondary hypertension. A more detailed discussion is provided in other relevant chapters. Pregnancy-associated hypertension is discussed in Chapters 44 and 45. *BUN,* Blood urea nitrogen; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *VMA,* vanillylmandelic acid. *Medical history, physical examination, and laboratory tests are either obvious or beyond the scope of the discussion.

Evaluation for Secondary Hypertension			
Target Organ/System	**Medical History**	**Physical Examination**	**Laboratory Studies**
Cushing syndrome	Weight gain, cosmetic changes	Body habitus: body fat, striae	Morning serum cortisol after dexamethasone suppression
Pheochromocytoma	Headaches; vasomotor symptoms, (inappropriate sweating, pallor); cardiac symptoms (awareness, tachycardia, palpitations)	Paroxysmal or intermittent hypertension (50% of patients)	Single-voided urine for metanephrine and creatinine; consider 24-hr urine for VMA, metanephrines, and catecholamines; if positive, proceed with magnetic resonance imaging or thin-section computed tomography of the adrenals
Carcinoid	Flushing		24-hr urine 5-hydroxyindoleacetic acid excretion
Hyperthyroidism	Weight loss, tachycardia, palpitations, sweating, heat intolerance	Palpable thyroid	Total and free thyroxine
Hypothyroidism	Weight gain, dry skin, cold intolerance, hair loss	Palpable thyroid	Total and free thyroxine
Hyperparathyroidism	Nausea, vomiting, bone pain, nephrolithiasis		Serum calcium, intact parathyroid hormone
Acromegaly	Change in size of head, hands, or feet (adult)	Appearance	Growth hormone (GH) level
Medication			
	Review of prescribed and over-the-counter medications (especially oral contraceptives, NSAIDs, sympathomimetic agents [cold and allergy drugs], illicit or recreational drugs, including alcohol, herbal remedies)		
Coarctation of the Aorta			
	Onset or detection of hypertension in childhood or adolescence	Simultaneous palpation of radial and femoral arteries to detect pulse lag in femorals; leg blood pressure	Chest radiograph for heart size, configuration of aorta, rib notching; consider aortography
Neurologic Disorders			
Sleep apnea	Obesity; weight gain; daytime somnolence; snoring, poor sleep habits (frequent awakening, not rested on arising); early-morning headache	Obesity; narrowed airway in hypopharynx; redundant pharyngeal tissue	Formal sleep study (polysomnography)
Increased intracranial pressure	Headache; neurologic symptoms	Papilledema	↑Cerebrospinal fluid pressure
Affective disorders*			
Spinal cord injury*			
Psychosocial Factors			
	Family and support structure, occupation, education, stressors		
Volume Overload			
	Excess salt and water intake (may be iatrogenic with excess parenteral fluid)	Increased jugular venous distention, pulmonary rales, presacral and peripheral edema, hepatomegaly	Chest radiograph
Isolated Systolic Hypertension			
		Pseudohypertension (positive Osler maneuver); cardiac and vascular examination (evaluate for aortic insufficiency, arteriovenous fistula)	

Table 33-10 History, physical examination, and initial laboratory evaluation for secondary hypertension—cont'd.

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CHAPTER 34

Primary Hypertension

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DEFINITION

Primary (essential) hypertension is defined as blood pressure (BP) greater than 140/90 mm Hg without an identifiable cause. Several readings at different times, following the American Heart Association (AHA) and other guidelines, are necessary to document the diagnosis of primary hypertension. Variability in BP results from several factors, but under normal circumstances, a natural circadian rhythm generates the most significant increase in BP in the morning (6 to 10 AM). BP falls during sleep, secondary to a decrease in sympathetic nervous system (SNS) tone and reduced activity of other neuroendocrine systems. There are also minute-to-minute variations in BP (Fig. 34-1). Transient elevations in BP, reaching 150 mm Hg systolic, occur in the majority of normotensive individuals in any given day, especially during exercise.[1] However, BP that is 140/90 mm Hg or greater for more than 50% of the day is considered *hypertensive.* Chapter 33 describes the method and interpretation of BP measurements, including the use of ambulatory BP monitoring.

Primary hypertension is classified according to severity (Table 34-1). Stages in hypertension have been adapted by both the Joint National Committee (JNC 7)[2] and European Society of Hypertension and European Society of Cardiology (ESH/ESC) guidelines to allow a prognosis to be associated with different levels of BP elevation. The prognosis has been adapted from epidemiologic studies that demonstrate a linear relationship between the risk of cardiovascular events and sustained elevations of arterial pressure.

When only the systolic BP is elevated (systolic BP >140 and diastolic BP <90 mm Hg), the term used is *isolated systolic hypertension.* The former terms "borderline" or "high-normal" hypertension (defined as BP of 130 to 139/85 to 89 mm Hg) are now classified as *prehypertension* (defined as BP ≥120 to 139/80 to 89 mm Hg). *White coat hypertension* is an increase of more than 20 mm Hg in systolic BP noted only in the physician's office above that seen at home or another setting. In contrast, *masked hypertension* is BP that is normal in the office but elevated by more than 20 mm Hg when measured by ambulatory BP measurement.

Other terms used to describe specific clinical presentations include *hypertensive emergencies,* associated with acute end-organ damage requiring immediate treatment, usually in a critical care setting, and *hypertensive urgencies,* when BP needs correction in hours or a few days (see Chapter 37). In hypertensive emergencies, the reduction of BP will halt, prevent, or reverse decreasing glomerular filtration rate (GFR). These terms have replaced "malignant hypertension" and "accelerated hypertension." *Resistant hypertension* is defined as hypertension that remains above 140/90 mm Hg despite use of three maximally dosed antihypertensive medications of different classes, including a diuretic.

ETIOLOGY AND PATHOGENESIS

The kidney has a key role in the pathogenesis of hypertension. Guyton and colleagues[3] proposed that the kidney in patients with hypertension has a physiologic defect in sodium excretion. Whereas in most individuals an increase in sodium intake is related to an increase in pressure associated with prompt excretion of the salt load, this "pressure-natriuresis" relationship is abnormal in the hypertensive patient (Fig. 34-2). In some hypertensive patients, especially those under age 40, the response to a salt load is similar to that in normal individuals but is shifted rightward, such that higher pressures are required for a specific salt load, called *salt-resistant hypertension.* In contrast, most hypertensive patients, especially older and African American individuals, have both a rightward shift and a change in the slope, such that BP increases more for the same sodium load, called *salt-sensitive hypertension.* Additional evidence of a renal defect in sodium handling is the observation that kidney transplantation transfers the susceptibility for hypertension in response to salt in various rat strains. Dietary sodium content also correlates with the prevalence of hypertension in various populations, and intervention studies with salt restriction or loading have shown that the BP response in many hypertensive patients is salt sensitive. The basis for this renal defect in hypertension remains controversial, but three major hypotheses have been proposed.

Genetic (Polygene) Hypothesis

Pickering proposed that hypertension results from the expression of multiple genetic polymorphisms (polygene hypothesis), and Lifton later extended this hypothesis by stating that the cumulative effects of these polymorphisms act to favor sodium retention by the kidney, which would be accentuated in a Westernized society in which there is excessive salt intake (>10 g/day). The observation that numerous monogenic forms of both hypertension and hypotension are mediated by specific mutations involving renal sodium transport, especially involving the epithelial sodium channel (see Chapter 49), supports this hypothesis (Table 34-2). Currently, more than 20 genes have been identified in which mutations or polymorphisms influence blood pressure.[4] Many of these involve sodium transport in the distal tubule or the collecting duct. Some heterozygous mutations, such as the Na-K-2Cl cotransporter *SLC12A1,* the inward rectifier K^+ channel *KCNJ1* (carrier state for Bartter syndrome), and the heterozygous mutation of the Na-Cl cotransporter *SLC12A3* (carrier state for Gitelman syndrome), confer protection from hypertension.[5] Whereas genetic polymorphisms influence BP, most studies suggest that genetic mechanisms account for only 20% to 30% of primary hypertension, indicating that other mechanisms are more important in driving the hypertensive response.

Congenital (Low Nephron Number) Hypothesis

In 1989, Barker and associates[6] reported an increased risk for hypertension in individuals with low birth weight (LBW), and LBW was also found to increase the risk later for diabetes and obesity. Mothers of LBW infants frequently have hypertension, obesity, preeclampsia, or malnutrition, and these maternal factors also carry an increased risk for hypertension in the infant. This has led to interest in the role of "fetal programming" (e.g., from epigenetic changes) in the causation of hypertension. Brenner and colleagues[7] have postulated that LBW might lead to hypertension because of impaired renal development, leading to lower nephron number. Maternal malnutrition in laboratory rats predisposes to small babies, low nephron number, and the future predisposition for hypertension. A study of Caucasians with primary hypertension found almost 50% fewer nephrons than in age- and gender-matched controls.[8] Studies in African

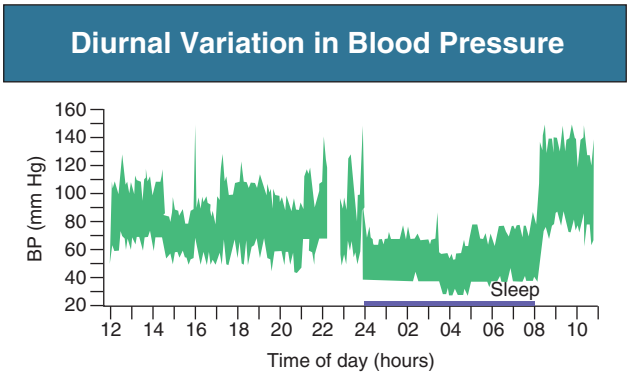

Figure 34-1 Blood pressure variability in normotensive individual. In most normal individuals, systolic blood pressure *(BP)* reaches 150 mm Hg at least once daily. *(From reference 1.)*

Classification of Blood Pressure

BP Classification	Systolic BP (mm Hg)		Diastolic BP (mm Hg)
Normal	<120	and	<80
Prehypertension	120-139	or	80-89
Stage 1 hypertension	140-159	or	90-99
Stage 2 hypertension	≥160	or	≥100

Table 34-1 Classification of blood pressure (JNC 7). *(From reference 2.)*

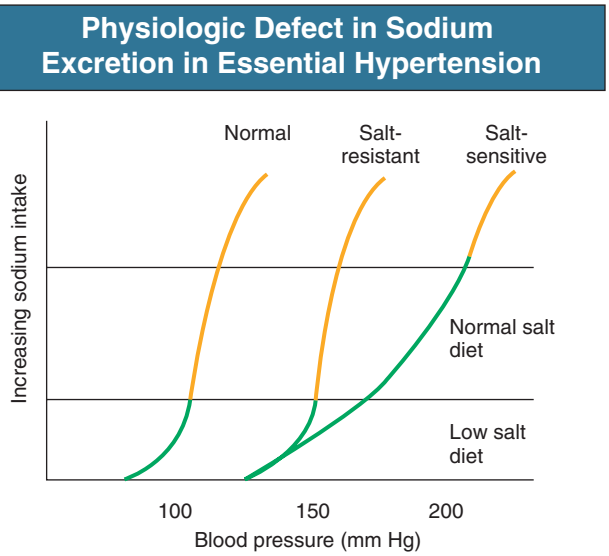

Figure 34-2 Physiologic defect in sodium excretion in primary hypertension. Evidence suggests that in patients with primary hypertension, a higher blood pressure is required to excrete an individual sodium load. In salt-resistant hypertension, the pressure-natriuresis curve has a rightward but parallel shift; with salt-sensitive hypertension, it is both a shift to the right and a change in slope. *(Modified from reference 4.)*

Monogenic Diseases Associated with Alterations in Blood Pressure

Condition	Gene	Inheritance	Site	Manifestations
Glucocorticoid-remediable aldosteronism (GRA)	Chimeric ACTH-responsive promoter with aldosterone synthase	AD	Collecting duct	Hypertension, metabolic alkalosis
Mendelian hypertension exacerbated by pregnancy	MR gain of function	AD	Collecting duct	Hypertension, worsened by pregnancy (progesterone)
Liddle syndrome	Gain-of-function of β or γ subunit of ENaC	AD	Collecting duct	Hypertension, metabolic alkalosis
Pseudohypoaldosteronism type 1 (PHA1)	ENaC loss of function MR loss of function	AR AD	Collecting duct	Neonatal hypotension, acidosis, salt wasting
Gitelman syndrome	Na-Cl cotransporter loss of function	AR	DCT	Low BP, salt wasting, metabolic alkalosis
Bartter syndrome	4 gene mutations: Na-K-2Cl, K channel, C1 channel, Barttin	AD or AR	Thick ascending limb	Low BP, salt wasting, metabolic alkalosis
Metabolic syndrome	Mitochondrial transfer RNA	Maternal	?	Hypertension, hypercholesterolemia, hypomagnesemia
Pseudohypoaldosteronism type 2 (PHA2) or Gordon syndrome	WNK1 and WNK4 serine-threonine kinases	AD	DCT and collecting duct	Hypertension, ↑K, metabolic acidosis

Table 34-2 Monogenic diseases associated with alterations in blood pressure. *ACTH,* Adrenocorticotropic hormone; *AD,* autosomal dominant; *AR,* autosomal recessive; *BP,* blood pressure; *DCT,* distal convoluted tubule; *ENaC,* epithelial sodium channel; *MR,* mineralocorticoid receptor; *WNK,* "with no lysine" kinase.

Americans, however, could not confirm the relationship between low nephron number and hypertension.

Individuals with LBW also have endothelial dysfunction early in life that likely predisposes to development of hypertension. Some studies suggest this may be caused by uric acid, which is also elevated in LBW infants and children before the development of hypertension. Regardless, LBW cannot be the primary risk factor. For example, one study found that although LBW infants have a 25% risk for developing hypertension as an adult, high-birth-weight infants have a 20% risk.[9] Thus, low birth weight and low nephron number likely reflect risk factors for development of hypertension rather than the underlying mechanism.

Acquired Renal Injury Hypothesis

Primary hypertension is frequently associated with renal arteriolosclerosis and hyalinosis with variable degrees of glomerulosclerosis and ischemic tubular injury. Renal function is usually normal or only slightly depressed, whereas renal vascular resistance is high and renal blood flow is low because of intense vasoconstriction of the afferent arteriole. Whereas the microvascular and inflammatory changes may reflect hypertension-associated injury, evidence suggests that these changes may also have a role in the development and maintenance of salt-sensitive hypertension.

Salt-sensitive hypertension can be induced by other means that usually involve renal vasoconstriction (Box 34-1). Ischemia stimulates the influx of macrophages and T cells, resulting in oxidative stress, activation of the intrarenal renin-angiotensin system (RAS), and a decrease in local nitric oxide (NO). It is highly likely that the inflammation also activates renal sympathetic nerves. A recent study suggests that rather than responding nonspecifically, the infiltrating T cells may be reacting with specific antigens induced by the local vasoconstriction, particularly heat shock protein 70 (HSP-70).[10] Blocking the intrarenal T cell infiltration or infusing T cells that have been tolerized to HSP-70 can block experimental salt-sensitive hypertension in different models.[11] Rats born with low nephron number also develop renal microvascular disease and intrarenal T cell accumulation, and administering mycophenolate mofetil (MMF) also reduces BP in these animals. MMF has also been reported to lower blood pressure in hypertensive patients with psoriasis.

Triggers of Salt-Sensitive Hypertension in Experimental Animals

- Angiotensin II infusion
- Inhibition of nitric oxide synthesis (treatment with L-NAME)
- Catecholamine infusion
- Diet-induced hypokalemia
- Hyperuricemia induced by uricase inhibition
- Reduced nephron number through maternal malnutrition
- Induction of nephrotic syndrome with use of bovine serum albumin
- Page kidney
- Lead-induced hypertension
- Cyclosporine nephropathy
- Genetic models of hypertension (Dahl salt-sensitive rat, spontaneously hypertensive rat)

Box 34-1 Mechanisms that can trigger salt-sensitive hypertension in experimental animals through the induction of microvascular injury and/or interstitial inflammation.

Role of Renal Injury in Sodium Retention

Renal T cell infiltration is associated with local oxidative stress and angiotensin II (Ang II) generation that results in renal vasoconstriction and an impaired pressure-natriuresis response. This may be augmented by afferent arteriolar remodeling and peritubular capillary loss, which also maintain renal ischemia. Activation of renal afferent sympathetic nerves, likely secondary to the local inflammation, also impairs sodium excretion. The consequence of this condition is a right shift of the pressure-natriuresis curve with a change of the slope, characteristic of salt-sensitive hypertension[12] (Fig. 34-3).

Although T cells in the kidney play a role in impairing pressure natriuresis, there are also countering mechanisms to reduce the hemodynamic impact of sodium excretion. In particular, the skin can act as a subcutaneous reservoir for sodium as a result of hypertonic accumulation of sodium proteoglycans that activates local macrophages to release vascular endothelial growth factor C (VEGF-C), which stimulates lymphangiogenesis.[13] The increase of lymph capillaries attenuates the hemodynamic effects of sodium retention. Depletion of the mononuclear phagocyte system blocks lymphangiogenesis and induces salt-sensitive hypertension.

How Does Salt Retention Lead to Hypertension?

An acute infusion of saline administered to animals with experimentally induced hypertension initially raises blood volume and cardiac output, but the increase in cardiac output is transient and is replaced by a rise in the systemic vascular resistance (SVR). Guyton and colleagues[3] called this process "autoregulation," postulating that the vasoconstriction was an adaptive response resulting from the need to reduce unnecessary increments in tissue perfusion.

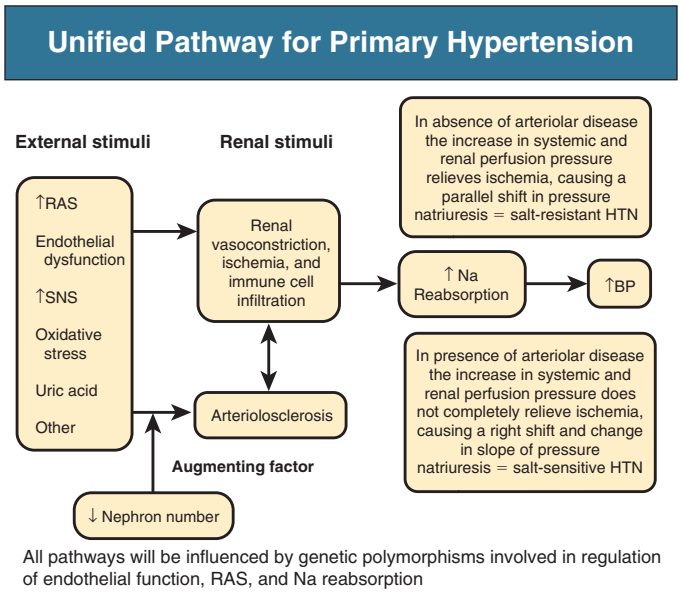

Figure 34-3 Unified pathway for primary hypertension. Hypertension *(HTN)* may be hypothesized as occurring in two phases. The first phase is mediated by renal vasoconstriction caused by stimuli such as a hyperactive sympathetic nervous system *(SNS),* hyperuricemia, endothelial dysfunction, or an activated renin-angiotensin system *(RAS).* This results in a salt-resistant form of hypertension. While hypertension may remain salt-resistant, we hypothesize that in many patients, progressive renal microvascular disease and tubulointerstitial inflammation will develop, with a switch to a salt-sensitive phenotype and an increased risk for microalbuminuria. *BP,* Blood pressure.

Several mechanisms may account for the rise in SVR. First, volume expansion increases circulating endogenous cardiotonic steroids, which function as Na^+,K^+-ATPase inhibitors. For example, ouabain is a digitalis-like factor that is released from the hypothalamus, hippocampus, and pituitary and stimulates the SNS, and marinobufagenin is a digitalis-like factor released from the adrenal cortex. These factors block Na^+,K^+-ATPase in the kidney, thereby facilitating the excretion of sodium, but at the expense of also blocking Na^+,K^+-ATPase in the vascular smooth muscle, resulting in increased intracellular calcium with vascular smooth muscle contraction and systemic vasoconstriction.[14] Circulating nitric oxide synthase (NOS) inhibitors are also present in some patients with primary hypertension. A small increase in serum sodium concentration from salt ingestion may also stimulate release of vasoconstrictive substances such as vasopressin, which may have a role particularly in African Americans.[15] Activation of the SNS also occurs in salt-sensitive hypertension in response to a salt load.[16] A possible explanation is that, in the setting of tubulointerstitial injury and intrarenal ischemia, the salt load triggers an intense renal afferent SNS activity that stimulates central nervous system (CNS) sympathetic output.[16] The importance of the renal sympathetic nerves in activating the CNS/SNS has become more evident after the introduction of renal artery denervation as a means for treating resistant hypertension (see Chapter 38).

Other mechanisms that could contribute to increased SVR are loss of vasodilatory substances from the kidney (e.g., kallikrein, medullipin) or simply the loss of systemic capillaries (microvascular rarefaction).

Pathogenic Mechanisms Driving the Current Epidemic of Hypertension

As discussed under Epidemiology, there has been a marked rise in the prevalence of hypertension in the last century. The rise in hypertension corresponds with the introduction of Western diet and lifestyle and with the dramatic increase in obesity. Obesity may cause hypertension through multiple mechanisms, including subtle renal injury, effects of hyperleptinemia or hyperinsulinemia, hyperuricemia, coexistence of endothelial dysfunction, and activation of the SNS.[17] Chronically elevated leptin levels, which are common in obese persons, can activate the SNS in the CNS through pro-opiomelanocortin neurons that activate melanocortin-4 receptors.[18]

Another proposed mechanism is an elevated uric acid level, possibly driven by intake of fructose-containing sugars. Experimental studies have reported that elevated uric acid can mediate hypertension in association with the development of subtle renal injury, and small clinical trials have reported a benefit on BP of reducing uric acid in adolescents with either prehypertension or primary hypertension.[19] Some studies also have implicated a hyperactive SNS in early hypertension, particularly in young or borderline hypertensive patients.[20] Postulated mechanisms include a defect in baroreceptor sensitivity and an increase in SNS response to emotional or work-related stress. Activation of either the systemic or the local RAS is also common in hypertension. Whereas plasma renin activity is elevated in 20% of patients, renin activity is either normal (50%) or low (30%) in the majority. However, normal renin activity may be inappropriately high in relation to the total body sodium.

In addition, some hypertensive patients have elevated plasma aldosterone, especially if the RAS is inhibited with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), known as *aldosterone breakthrough*.[21,22] Typically, such patients are obese and have hyperinsulinemia or some degree of endothelial dysfunction. Their aldosteronism is driven by a mechanism other than Ang II or hyperkalemia.

EPIDEMIOLOGY

Primary hypertension is epidemic. In the United States, the prevalence has increased from 5% to 11% of the population in the early 1900s to 31% (72 million people) in 2010[23] (Fig. 34-4). Although some of the increase in hypertension reflects an increasingly aging population, there is also an increase in primary hypertension in the pediatric population. By 2025, an estimated 1.56 billion people worldwide will have primary hypertension. The increase in hypertension correlates with increasing frequency of obesity, type 2 diabetes, and chronic kidney disease (CKD), suggesting a strong interrelationship.

Among the several major risk factors for hypertension, family history is the most important (Table 34-3). First, the risk for primary hypertension increases with age, and a normotensive person at age 55 has a 90% chance of being hypertensive at age 80.[2,24] This age-related increase in prevalence of hypertension has been observed in most Western countries but has not been uniformly observed in all populations. Second, hypertension is more common in men,

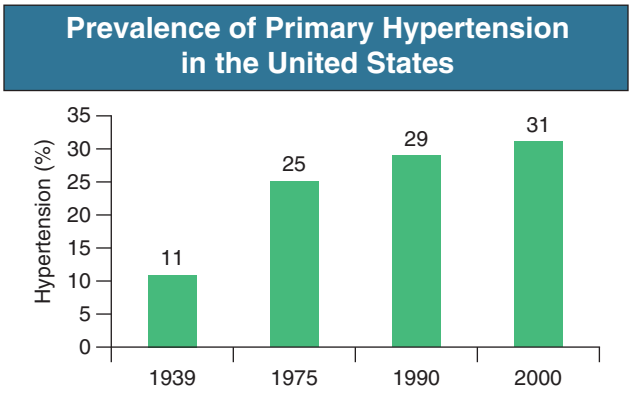

Figure 34-4 Epidemic of hypertension. The prevalence of primary hypertension (defined as BP >140/90 mm Hg) in the United States increased from 11% in 1939 to 31% of the population in 2000.

Risk Factors for Primary Hypertension

Genetic	Family history Polymorphisms (adducin, endothelial nitric oxide synthase, angiotensinogen, β2-adrenoceptor, human G protein β3 subunit)
Congenital	Low birth weight, low nephron number, maternal hypertension, maternal preeclampsia, maternal malnutrition
Physical	Obesity, older age, African American, African Caribbean, some Bantu-speaking peoples in Africa, increased heart rate (>83 beats/min), increased emotional stress
Diet/toxin	Increased sodium intake, low potassium intake, low dairy products intake, heavy alcohol intake, low level lead or cadmium intoxication
Metabolic*	Elevated uric acid, insulin resistance, elevated hematocrit
Other	Low socioeconomic status, urban versus rural

Table 34-3 Major risk factors for primary hypertension. *Laboratory-based parameters.

although the prevalence in women is similar to and slightly exceeds that of men after age 55. Certain racial groups are at increased risk of developing hypertension much earlier in life, particularly African Americans and Filipino Americans in the United States and various minority populations throughout the world (e.g., Pima Indians, Australian aborigines, Maoris). Risk factors for hypertension include strong family history, obesity, insulin resistance, hyperuricemia and/or gout, sleep disorders including sleep apnea, and persistent high-stress living environments either at work or home. Certain physical features, such as elevated heart rate or an increased BP response to exercise, are also predictive, as is elevated hematocrit.

Genetic factors also contribute, as discussed earlier. Although the inheritance patterns do not follow mendelian genetics for a single gene locus, evidence suggests that 20% to 30% of hypertension may have a genetic basis, because of the cumulative effect of multiple susceptibility genes (the polygene hypothesis). A recent genome-wide association screen found 29 polymorphisms that could account for approximately 13% of primary hypertension, with several of the polymorphisms linked with natriuretic peptide and NO signaling.[25] Others have noted polymorphisms involving immune system and oxidative stress mechanisms (HSP-70 variants, xanthine oxidase, and extracellular superoxide dismutase), vasoactive mediators (angiotensinogen, endothelial NOS, prostacyclin synthase, β_2-adrenoceptor, 20-HETE synthase [*CYP4F2* gene], G protein β3), mediators of vascular smooth muscle tone (calcium-dependent potassium channel, *KCNMA*), or mediators controlling renal sodium transport (α-adducin and 11β-hydroxysteroid dehydrogenase type 2, aldosterone synthase, WNK kinases).[19]

Hypertension is more likely to occur if the mother has a history of hypertension, obesity, preeclampsia, or malnutrition. These risk factors are all associated with intrauterine growth retardation and low birth weight, both of which predispose to future hypertension, as well as diabetes and obesity.

Dietary and other environmental factors may contribute to the risk for hypertension. Obesity, with or without features of insulin resistance and the metabolic syndrome, is a major risk factor for hypertension and parallels the rise in hypertension in these countries. Epidemiologic and interventional studies have linked salt intake and low potassium intake with persistent BP elevation, leading to earlier development of hypertension, and although the relationship is best demonstrated in older patients and in African Americans, it is true across the world. Increasing potassium intake lowers BP in both experimental and human studies. More recently, intake of added sugars (e.g., sucrose, high-fructose corn syrup) has been found to predict higher BP. Certain toxins, most notably low-level lead and cadmium intoxication, are also associated with increased frequency of hypertension.

CLINICAL MANIFESTATIONS

Evaluation of a patient with hypertension requires a careful history and physical examination, an evaluation of risk factors for hypertension, a search for potential secondary causes, and an evaluation for end-organ damage.

Blood pressure should be measured on at least three occasions to confirm persistent hypertension using the techniques described in Chapter 33. Home BP monitoring or 24-hour ambulatory BP monitoring is recommended to determine if the hypertension occurs only in the physician's office (white coat hypertension) and rarely to identify masked hypertension, in which BP elevations occur only outside the physician's office. White coat and masked hypertension can be associated with end-organ disease, including left ventricular hypertrophy (LVH) and microalbuminuria; diagnosis should be followed by assessment of cardiovascular (CV) risk factors and frequent reevaluation of BP.

The history should investigate the onset and duration of hypertension and the presence of a family history of hypertension or cardiorenal disease. The history should identify risk factors for hypertension (obesity, diabetes, physical activity, gout, alcohol, smoking, diet, emotional or work-related stress, over-the-counter and prescribed medications) and any hypertension-related morbidity. Hypertension is often asymptomatic, but studies have found that even childhood-associated hypertension can be associated with impaired memory and mental performance, and hypertension remains a major risk factor for vascular dementia. Good BP control improves mental performance and decreases the risk of developing dementia.[26,27] Hypertension, especially stage 2 (see Table 34-1), may also be associated with headache, classically occipital and pulsatile. In hypertensive emergency, encephalopathy may rarely occur, with an acute decline in mental status and seizures. Also rarely, patients may lose vision from papilledema. Stage 2 hypertension also places individuals at acute risk for myocardial infarction (MI), congestive heart failure (CHF) with pulmonary edema, aortic dissection, cerebrovascular accident (stroke), and renal failure.

Physical examination includes BP measurement in both arms and a careful cardiac examination. Attention should be focused on both the large vessels (by both palpation and listening for bruits) and the retina to grade the severity of disease in the microvasculature (Fig. 34-5). Laboratory tests should include hematocrit, electrolytes,

Figure 34-5 Different grades of hypertensive retinopathy. A, Mild hypertensive retinopathy, with arteriolar narrowing and arteriovenous nicking. **B,** Moderate hypertensive retinopathy, with cotton-wool spots (nerve fiber layer infarcts) and arteriovenous nicking. **C,** Papilledema, cotton-wool spots, macular yellow exudates (star formation pattern), and retinal hemorrhages in a subject with hypertensive emergency. *(Gift courtesy J. Kinyoun, University of Washington.)*

creatinine (and estimated GFR), calcium and phosphate (to look for primary hyperparathyroidism), fasting lipid profile (cholesterol and triglycerides), uric acid, and urinalysis. A chest x-ray film and electrocardiogram should be performed to assess cardiac size and to look for aortic dilation.

Additional tests include assessment of 24-hour urine sodium and potassium excretion. Urinary Na^+ and K^+ excretion correlates with intake if the patient is in steady state (desirable values are <100 mmol/l Na^+ and >100 mmol/l K^+ in 24 hours). A spot urine albumin-creatinine and an echocardiogram may uncover additional evidence of end-organ damage (Fig. 34-6). Note that a spot urine albumin-creatinine is recommended only for those with diabetes or stage 2 or higher CKD. Echocardiography is not recommended for routine use in patients with hypertension because of its cost, although appropriate for those with cardiac problems.

PATHOLOGY

Primary hypertension is characterized by disease of the preglomerular arterial vessels, primarily the afferent arteriole and interlobular artery. The classic lesion, seen in 90% of patients, is arteriolosclerosis, in which smooth muscle cells of the media in the afferent arteriole are replaced by connective tissue[28] (Fig. 34-7). Often, hyaline material (plasma proteins) accumulates in the subintima (hyalinosis). In addition to the arteriolar disease, there is often evidence of glomerular and tubulointerstitial ischemia with shrinkage of the glomerular tuft, tubular atrophy, and interstitial fibrosis. Occasionally, glomerulosclerosis and severe tubulointerstitial injury are seen. In cases of hypertensive emergency, a proliferative arteriolopathy occurs, occasionally with fibrinoid necrosis. Concentric layers of connective tissue and cells may give an onion-skin appearance to the intima, which may progress to a total obliteration of the lumen.

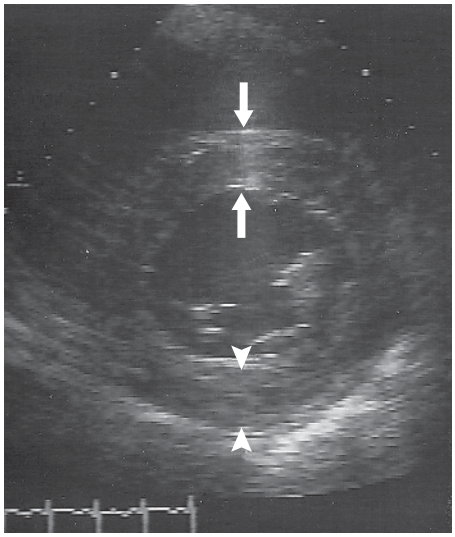

Figure 34-6 Echocardiogram showing concentric left ventricular hypertrophy. Septal thickness *(between large arrows)* and posterior wall thickness *(between arrowheads)* are increased (to 16 mm) in a patient with primary hypertension (normal is 11 mm or less). *(Gift courtesy A. Pearlman, University of Washington.)*

DIAGNOSIS

The diagnosis of primary hypertension requires the elimination of secondary etiologies, of which the more common include medications (nonsteroidal anti-inflammatory drugs, corticosteroids, sympathomimetics, oral contraceptives), recreational drugs (excessive alcohol intake, cocaine), intrinsic renal parenchymal disease, renovascular disease, and primary aldosteronism from adrenal hyperplasia or tumors. Table 33-10 provides a more complete list along with the recommended evaluation for secondary causes.

NATURAL HISTORY

The major long-term risk of hypertension is cardiovascular disease (CVD), which can be separated into pressure-related (stroke, CHF), atherosclerotic (MI), and renal (CKD) etiologies. Hypertension is the most common cause of stroke and CHF, and the risk increases linearly with BP[29] (Fig. 34-8). Other rarer pressure-related morbidities include aortic dissection and cerebral and aortic aneurysms. Increased systolic, diastolic, and pulse pressure all confer risk, although the systolic BP and the pulse pressure (in particular when associated with low diastolic BP) are the more important determinants of risk for the pressure-related morbidities. This increased risk depends on age (increases with age), gender (greater in males), ethnic origin (greater in African Americans), and other conditions (especially diabetes).

Cardiac consequences of poor hypertension control begin with concentric LVH associated with supernormal systolic function. Over time, impaired diastolic dysfunction may occur, as manifested by slow diastolic filling, which reflects decreased diastolic relaxation.

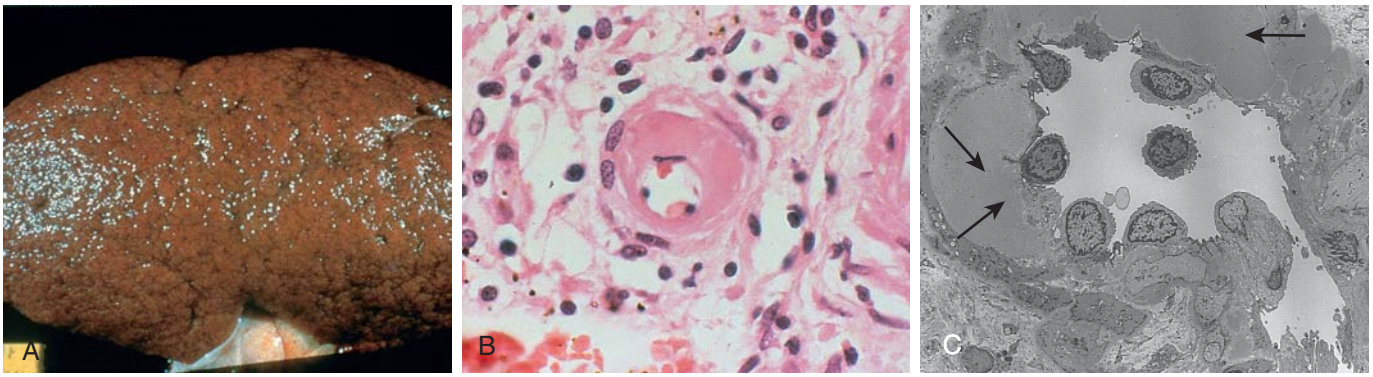

Figure 34-7 Renal pathology in primary hypertension. A, A granular pitted kidney in a subject with chronic primary hypertension. **B,** Arteriolosclerosis with subintimal hyalinosis. **C,** Electron micrograph showing hyalinosis with the accumulation of insudative plasma proteins in the subendothelium of an arteriole. *(**A,** gift courtesy Harvard Medical School; **B** and **C,** courtesy C. E. Alpers, University of Washington.)*

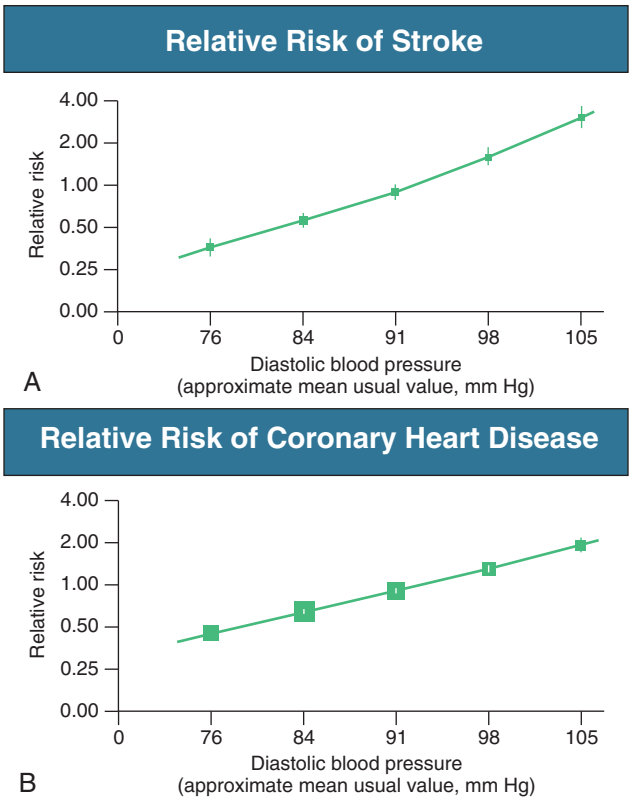

Figure 34-8 Relative risk for stroke and for coronary heart disease increases with increased diastolic blood pressure. A, Cerebrovascular accident (stroke) data are from seven prospective observational studies and 843 events. **B,** Coronary heart disease data are from nine studies and 4856 events. Size of *squares* is proportional to the number of events in each category; *vertical lines* indicate 95% confidence intervals. *(Modified from reference 29.)*

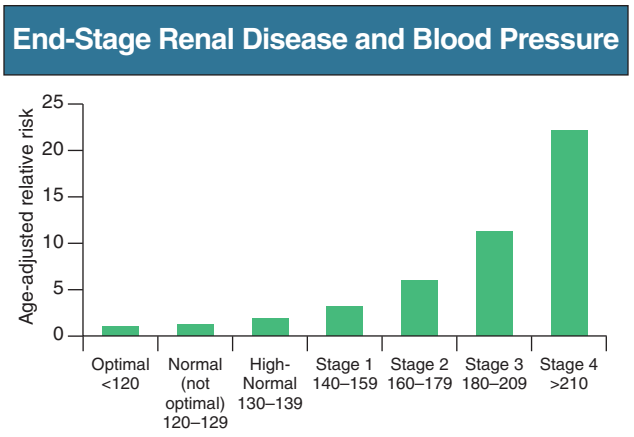

Figure 34-9 End-stage renal disease and blood pressure. Incidence of end-stage renal disease related to baseline blood pressure in the MRFIT study. Mean follow-up was 16 years. *(From reference 32.)*

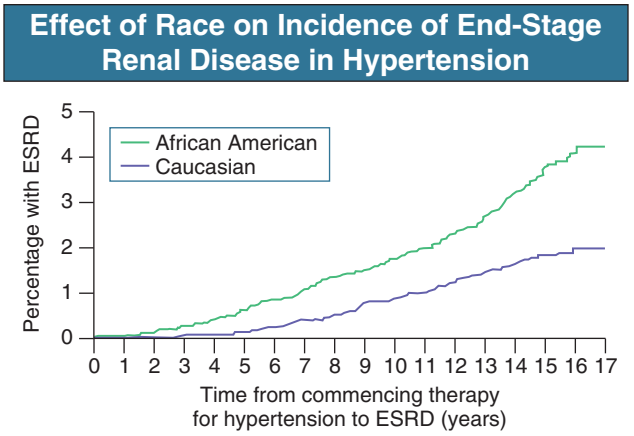

Figure 34-10 Effect of race on incidence of end-stage renal disease in hypertensive patients. The rate of end-stage renal disease *(ESRD)* in African American and Caucasian hypertensive veterans (Kaplan-Meier estimates). *(From reference 33.)*

This may progress to CHF. Almost 90% of patients with CHF have a history of hypertension.

Hypertension also confers risk for atherosclerotic-associated morbidities, including coronary heart disease,[29] peripheral vascular disease, and carotid atherosclerosis with or without cerebral emboli. In addition to an increased prevalence of hypertension, African Americans also have a 50% greater risk for heart disease.

Kidney Disease

Most patients with newly diagnosed primary hypertension have normal renal function or stage 1 (GFR >90 ml/min/1.73 m^2 with microalbuminuria) or stage 2 CKD (GFR 60 to 90 mL/min/1.73 m^2) with elevated renal vascular resistance.[30] Despite relatively normal renal function, renal biopsy, if done, usually shows arteriolosclerosis and hyalinosis (see Fig. 34-7).

Prior to use of effective antihypertensive agents, proteinuria developed in up to 40% of hypertensive patients, and as many as 18% developed renal impairment over time. Microalbuminuria, which is a marker of vascular disease and CV risk, occurs in 15-30% of patients, whereas non-nephrotic proteinuria is uncommon and nephrotic-range proteinuria is rare.[31] Microalbuminuria is associated with salt-sensitive hypertension, the loss of nocturnal dipping in BP, and increased target organ damage, especially LVH. Elevations in serum creatinine develop in 10% to 20% of patients with poorly controlled BP, and the risk is greater in African Americans, elderly persons, patients with hyperuricemia, and those with higher systolic BP (>160 mm Hg).[32,33] In 2% to 5% of those with poorly controlled systolic BP (>160), progression to renal failure will occur over the subsequent 10 to 15 years (Figs. 34-9 and 34-10). Despite the relative infrequency for hypertension to progress to end-stage renal disease (ESRD), hypertension is recorded as the second most common cause of ESRD after diabetes in the United States and Europe. Furthermore, almost all patients with diabetes have hypertension when they start dialysis.

The incidence of ESRD in African Americans with hypertension is fourfold to sixfold greater than in Caucasians.[34] Renal biopsies of African Americans with hypertension show more severe hypertensive injury, with more prominent vascular changes and increased frequency of segmental and global glomerulosclerosis. Although some of these vascular changes may relate to the presence of certain transforming growth factor β (TGF-β) polymorphisms or the higher uric acid levels that are common in this population, recent studies suggest that the increased frequency of glomerulosclerosis may be caused by a polymorphism in apolipoprotein L1 *(APOL1),* the product of which is expressed in the podocyte.[35] The mechanism by which *APOL1* polymorphisms increase the risk for progression of renal disease is unclear but may relate to effects on the podocyte.

Effect of Antihypertensive Therapy on Natural History of Hypertensive Cardiovascular Disease and Kidney Disease Progression

The specific pharmacologic approach to treatment of hypertension is discussed in Chapter 35, whereas the effect of antihypertensive therapy on CV and renal outcomes is discussed here. According to a recent report, only 71% of patients with hypertension in the United States are receiving treatment, and only 48% have their BP under adequate (<140/90 mm Hg) control.[36] Although age-adjusted mortality for stroke and coronary artery disease has been significantly reduced since the early 1980s as a result of better BP control (and better treatment of other risk factors such as hyperlipidemia), heart disease and stroke remain the first and third leading causes of death in Western countries. This emphasizes the importance of identifying and treating patients with hypertension.

Antihypertensive therapy reduces CV complications in patients with stage 2 hypertension, although there are less data to support this for stage 1 hypertension (Table 34-4).[37] The reduced risk is most significant for stroke and CHF, but also occurs for MI. In all trials to date, the group with the best overall BP control has the best outcome.[38] One exception comes from the recent ACCOMPLISH trial, where both groups had similar BP control, but the group initially randomized to an ACE inhibitor with a calcium antagonist had a 20% CV risk reduction compared to the ACE inhibitor plus diuretic group.[39] Note that almost all people with some level of kidney disease will require two or more medications. Diuretics (e.g., chlorthalidone) provide greater initial reductions in BP than most antihypertensive agents and are required in those with stage 3 CKD but are not considered agents of first choice for treatment of primary hypertension by any except U.S. guidelines.

The effect of antihypertensive therapy on the progression of renal disease secondary to hypertension is more controversial. In the Multiple Risk Factor Intervention Trial (MRFIT), in which diuretics and β-blockers were primarily used to control BP, slowing or stabilization of renal function was not seen in African American men, but was seen in all other racial groups studied.[40] In the African American Study of Kidney Disease, use of an ACE inhibitor (ramipril) was more effective at slowing CKD progression than either the dihydropyridine calcium channel blocker amlodipine (Fig. 34-11) or metoprolol.[41,42] However, both studies and others failed to show superior protection with tight BP control compared to conventional BP targets in patients with renal disease secondary to hypertension.[42,43] Masked hypertension may be a confounder to these results; a subanalysis of ambulatory BP showed inadequate 24-hour BP control in more than 70% of the cohort. Masked hypertension and nondipping (i.e., lack of BP decrease with sleep) were the two most common reasons for poor BP control.[44]

Further studies are being performed regarding the dosing and timing of antihypertensive treatment to evaluate changes in overall BP control. In contrast, *post hoc* analyses of trials show that patients with diabetic renal disease, or with proteinuric (>300 mg/day) renal disease, including that caused by hypertension, appear to benefit from lower BP goals in terms of renal protection. Based on current evidence, achieved BP levels should be less than 140 mm Hg systolic for nonproteinuric hypertensive renal disease and less than 130/80 mm Hg in those with diabetes and hypertension.[45] However, because all three of the prospective randomized CKD outcome trials have failed to show a benefit, the updated Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend a BP goal of less than 140/90 mm Hg in those with CKD, as backed with the highest level of evidence. The previous goal of less than 130/80 mm Hg in the presence of very high albuminuria (>300 mg/day) has much lower level of evidence and is not endorsed.[46]

Some studies also suggest that thiazide diuretics are associated with worsening of renal function in patients with hypertension. In the European Working Party on High Blood Pressure in the Elderly trial, a significantly higher incidence of impaired renal function was found in those receiving diuretics than with placebo.[47] In the Systolic Hypertension in the Elderly trial, serum creatinine increased significantly in those treated with thiazide diuretics compared to placebo.[48]

Effect of Antihypertensives on Cardiovascular Outcomes in Hypertension

Outcome	No. of Trials	Effects Model	RR (95% CI)	*P* Value for Heterogeneity
Coronary heart disease	24	Fixed Random	0.86 (0.80-0.93) 0.87 (0.80-0.94)	.55 .55
Stroke	23	Fixed Random	0.69 (0.64-0.74) 0.68 (0.61-0.76)	.004 .004
CHF	7	Fixed Random	0.54 (0.45-0.66) 0.60 (0.49-0.74)	.66 .80
Major CVD events	28	Fixed Random	0.78 (0.74-0.81) 0.73 (0.62-0.87)	<.001 <.001
CVD mortality	23	Fixed Random	0.84 (0.78-0.90) 0.84 (0.78-0.90)	.10 .10
Total mortality	25	Fixed Random	0.90 (0.85-0.95) 0.90 (0.85-0.95)	.58 .59

Table 34-4 Meta-analysis of effect of antihypertensive agents on cardiovascular outcomes in hypertensive patients. The analysis was based on 42 clinical trials that included 192,478 patients randomized to seven major treatment strategies, including placebo. *CHF,* Congestive heart failure; *CVD,* cardiovascular disease; *RR,* relative risk; *CI,* confidence interval. *(From reference 37.)*

Ramipril Is Superior to Amlodipine in Reducing Renal Events in Hypertensive African Americans with Renal Impairment

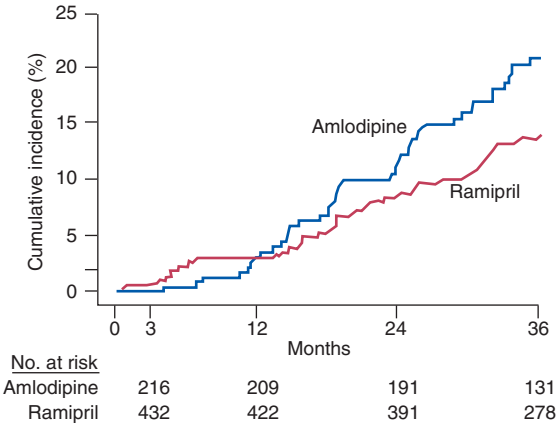

Figure 34-11 Ramipril is superior to amlodipine in reducing renal events in hypertensive African Americans with mild to moderate renal impairment. The angiotensin-converting enzyme (ACE) inhibitor ramipril resulted in fewer renal end points (proteinuria, decline in renal function, ESRD, death) compared with the dihydropyridine calcium channel blocker amlodipine, in the African American Study of Kidney Disease. *(From reference 41.)*

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the chlorthalidone-treated group showed statistically worse renal function than either the amlodipine or the lisinopril group, at both 2- and 4-year end points.[49] This could likely be accounted for by volume depletion in many cases, but diuretics have been shown to induce mild renal injury in various animal models, possibly because of hypokalemia, hyperuricemia, and stimulation of the renin-angiotensin-aldosterone system (RAAS) related to decreased renal perfusion pressure.[50]

Can Primary Hypertension Spontaneously Remit?

In those under age 60, as many as 15% to 20% of patients with prehypertension may become normotensive spontaneously. Furthermore, in patients with established hypertension who have good BP control for 5 years under treatment, as many as 20% to 40% can be withdrawn from therapy successfully, especially if they have stage 1 hypertension and adhere to salt restriction and weight reduction. This suggests that the processes that mediate hypertension are at times reversible.

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CHAPTER 35

Nonpharmacologic Prevention and Treatment of Hypertension

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Lifestyle changes, including a combination of increased fat and refined carbohydrate intake and reduced physical activity, have resulted in an epidemic of obesity, type 2 diabetes mellitus, and hypertension. The epidemic is evident worldwide and often is greatest in underserved and indigenous populations. Adoption of healthy lifestyles is critical for both the prevention of high blood pressure (BP) and its management. According to the Seventh Report of the Joint National Committee on Prevention, Evaluation, and Treatment of High Blood Pressure (JNC 7 Report),[1] lifestyle interventions lower BP, enhance efficacy of antihypertensive medication, and lower overall cardiovascular (CV) risk. The lifestyle changes that are widely agreed to lower BP and CV risk are (1) smoking cessation, (2) weight reduction, (3) moderation of alcohol intake, (4) physical exercise, (5) reduction of salt intake, (6) increase in fruit and vegetable intake, and (7) decrease in saturated and total fat intake.[1] Interventions may have efficacy similar to that of single-drug therapy (Table 35-1). However, lifestyle changes should not delay the initiation of drug therapy in patients at higher CV risk.

PREVENTION

The importance of primary prevention has been underscored by the recognition that (1) the treatment of hypertension is expensive, (2) the control of BP in hypertensive individuals does not restore CV risk to normal, and (3) the majority of hypertensive individuals do not reach goal BP readings. The most important individuals to target are those with *prehypertension* (defined by JNC 7 as 120 to 139/80 to 89 mm Hg; see Chapter 33).[1] Individuals with prehypertension have increased prevalence of early vascular damage, increased risk of incident hypertension, and increased risk of CV events compared with those who have optimal BP levels (<120/80 mm Hg).[2] The JNC 7 Report recommends lifestyle changes in all patients with prehypertension to prevent hypertension and to reduce CV risk.[1]

The contribution of body weight, physical inactivity, and dietary factors to the prevalence of hypertension in Europe and the United States has been quantified in a meta–regression analysis.[3] Being overweight made the largest contribution to hypertension, with population-attributable risk percentage (PAR%) between 11% (Italy) and 25% (United States). PAR% was 5% to 13% for physical inactivity, 9% to 17% for high sodium intake, 4% to 17% for low potassium intake, and 4% to 8% for low magnesium intake. The impact of alcohol was small (2% to 3%) in all populations. PAR% varied among populations for inadequate intake of calcium (2% to 8%) and inadequate intake of fish fatty acids (3% to 16%).

WEIGHT LOSS

Obesity is epidemic throughout the world, and 65% of the adult population in the United States is either *overweight*, with body mass index (BMI) of 25.0 to 29.9, or *obese*, with BMI of 30 or higher.[4] Obese individuals have a threefold increased prevalence of hypertension. Possible mechanisms for obesity-induced hypertension include overactivity of the sympathetic nervous system (SNS), hyperinsulinemia (which may increase renal sodium reabsorption), increased leptin, hyperuricemia, activation of the renin-angiotensin system (RAS), and sleep apnea. Abdominal or visceral obesity is a greater predictor of both hypertension and CV risk than is a predominant lower body fat distribution. *Abdominal obesity* is defined as a waist circumference greater than 88 cm (>35 inches) in women and greater than 102 cm (>40 inches) in men. These reference values were developed in Caucasian populations, and differing criteria may be more appropriate for other ethnic groups.

In obese hypertensive patients or those with high-normal BP, weight loss of as little as 4 to 5 kg (~9 to 11 lb) is often associated with a significant reduction in BP. Weight loss is one of the most effective nonpharmacologic interventions to reduce BP.[5] A meta-analysis has demonstrated that a weight reduction of 5.1 kg reduced systolic BP by 4.4 mm Hg and diastolic BP by 3.6 mm Hg.[6] A rule of thumb is that for every kilogram lost, there is a reduction of 1 mm Hg in both systolic and diastolic BP. To minimize the risk of relapse and to maintain sustainability of the weight loss program, the initial target should be 5% to 10% of current weight, or 1 to 2 BMI units. Marked oscillations in weight should be avoided because this increases the risk for development of hypertension in obese, normotensive persons.[7] A randomized trial of the effectiveness of four popular diets on sustained weight loss and CV disease risk reduction concluded that a variety of diets can similarly reduce weight and BP, but only a minority of individuals can sustain high dietary adherence. High-protein, low-carbohydrate diets, advocated for weight loss by the media and lay public, are associated with an overall increase in CV events in women.[8]

Weight reduction should be accompanied by recommendations to increase physical activity unless it is contraindicated. Bariatric surgery and pharmacologic interventions for weight loss (e.g., orlistat) may be useful to achieve weight loss in some patients, but always as an adjunct rather than a substitute for lifestyle modification.

PHYSICAL ACTIVITY

Physical inactivity is associated with at least a 1.5- to 2-fold higher risk of hypertension and coronary heart disease.[9] Regular physical activity lowers all-cause morbidity and mortality and provides the basis for public health recommendations to exercise at least 30 minutes per day. A recent review reported that patients with high BP who participated in any level of physical activity had a reduced risk (by 16% to 67%) of CV mortality, whereas a greater than twofold increase in CV mortality risk was observed in nonactive individuals.[10] Regular physical activity in childhood was inversely correlated with diastolic BP, even in children as young as 5 years.[11]

Lifestyle Modifications for Prevention and Management of Hypertension

Modification	Recommendation	Average Systolic BP Reduction Range Achieved with Intervention*
Weight reduction	Maintain normal body weight (BMI = 18.5-24.9 kg/m^2)	5-20 mm Hg/ 10 kg
DASH eating plan	Adopt a diet rich in fruits, vegetables, and low-fat dairy products with reduced content of saturated and total fat	8-14 mm Hg
Dietary sodium restriction	Reduce dietary sodium intake to 100 mmol/day (2.4 g sodium or 6 g sodium chloride)	2-8 mm Hg
Aerobic physical activity	Regular aerobic physical activity (e.g., brisk walking) at least 30 min/day, most days of the week	4-9 mm Hg
Moderation of alcohol consumption	Men: limit to 2 drinks† per day; women and lighter-weight persons: limit to 1 drink per day	2-4 mm Hg

Table 35-1 Lifestyle modifications for prevention and management of hypertension (JNC 7). *BMI,* Body mass index; *BP,* blood pressure; *DASH,* Dietary Approaches to Stop Hypertension. *Effects are dose and time dependent. †One drink = ½ oz or 15 ml ethanol (e.g., 12 oz (360 ml) beer, 5 oz (150 ml) wine, 1.5 oz (45 ml) 80-proof whiskey). *(From reference 1.)*

Practical Guidelines for Exercise in Patients with Hypertension

All apparently healthy individuals should undergo pre-exercise screening to determine health risk status. The American College of Sports Medicine (ACSM) recognizes that two or more of the following risk factors increase the risk associated with exercise, and individuals should undergo pre-exercise graded exercise testing. Risk factors include male gender (older than age 45 years) or female gender (older than 55 years); serum cholesterol concentrations greater than 5.2 mmol/l; impaired glucose tolerance or diabetes mellitus; smoking; obesity (body mass index ≥30); inactivity; and family history of cardiovascular disease.

Patients with uncontrolled hypertension should embark on exercise training only after evaluation and initiation of therapy. Furthermore, patients should not participate in an exercise training session if resting systolic blood pressure is above 200 mm Hg or diastolic blood pressure is above 115 mm Hg.

Many patients with hypertension are overweight and should therefore be encouraged to follow a program that combines both exercise training and restricted calorie intake.[18]

Type of exercise: this should be predominantly endurance physical activity, including walking, jogging, cycling, swimming, or dancing. This should be supplemented by resistance exercise that can be prescribed according to the ACSM or American Heart Association guidelines.[19]

Frequency of exercise: most or preferably every day.

Intensity of exercise: moderate intensity at 40% to 60% of maximal oxygen consumption ($\dot{V}O_2$ peak).

Duration of exercise: more than 30 minutes of continuous or accumulated moderate physical activity daily.

Box 35-1 Practical guidelines for exercise in patients with hypertension. *(Modified from references 18 and 19.)*

Exercise Training Dose Response

In a meta-analysis of studies involving more than 1500 patients, exercise training in normotensive individuals has been shown to reduce systolic and diastolic BP by 3.0 ± 1 and 1.7 ± 1 mm Hg, respectively.[12] The rate of progression from prehypertension to hypertension in middle-aged and older male veterans was prevented when exercise capacity exceeded 8.5 peak metabolic equivalents (METs).[13] In hypertensive patients, the effect of exercise training is even more marked: a reduction of 7.8 ± 3.5 and 5.8 ± 2.0 mm Hg for systolic and diastolic BP, respectively. Studies in hypertensive patients have shown that the benefit of exercise on BP is maximal with 90 minutes of exercise per week, after which there was no further improvement.[14] Furthermore, only a modest amount of exercise was needed to reduce BP in patients with hypertension (>30 min/wk). Regular exercise prevents the development of left ventricular hypertrophy (LVH) that is independent of BP in young, stage 1 hypertensive patients.[15]

Fagard[12] found no benefit of increasing exercise intensity on BP reduction with exercise training, as long as intensity ranged between 40% and 70% of maximal, age-predicted heart rate. Exercise of higher intensity (75% maximum) was associated with a more marked and prolonged reduction in BP in the postexercise window compared with lower-intensity exercise (50% maximum).[16]

Mechanisms

In the acute postexercise period, the reduction in BP has been linked to a sympathetic inhibition and increased release of vasodilator substances.[17] The mechanisms by which chronic exercise lowers BP are less well understood but include reductions in systemic vascular resistance (SVR) secondary to neurohumoral and structural adaptations. Chronic exercise is also associated with a loss of weight and a reduction of serum uric acid levels, both of which could reduce BP.

Antihypertensive Medication and Guidelines for Exercise

Box 35-1 provides exercise guidelines for patients with hypertension.[18] β-Blockers decrease exercise tolerance. β-Blockers and diuretics may also alter thermoregulation in hot environments and provoke hypoglycemia. Patients using these medications should be educated about exercising in the heat, clothing, adequate hydration, and methods to prevent hypoglycemia.[19,20] Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers may be better suited for patients who exercise frequently or athletes with hypertension.

For patients undergoing supervised exercise training, the monitoring of postexercise BP may be helpful so that medications may be adjusted appropriately, considering the likelihood of postexercise hypotension. Particular care should be taken with patients planning to exercise in a hot environment.

DIET

Salt Intake

Epidemiologic studies have demonstrated that the prevalence of hypertension is directly related to the dietary salt intake in societies

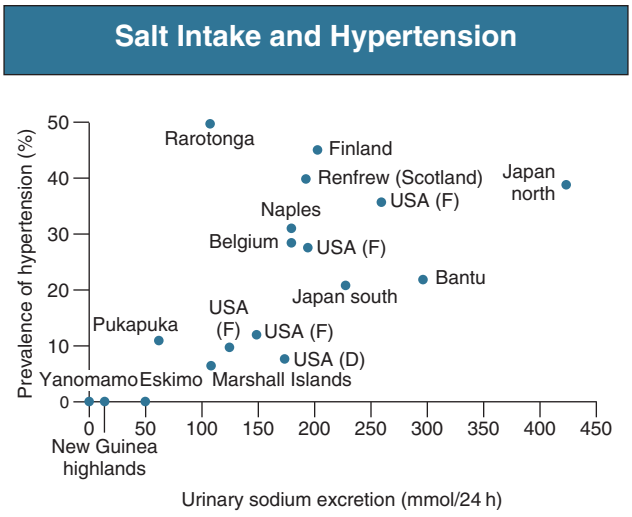

Figure 35-1 Relationship of salt intake with frequency of hypertension in different populations. *(D),* Data from Dahl; *(F),* data from Framingham study from different time periods. *(Modified from reference 21.)*

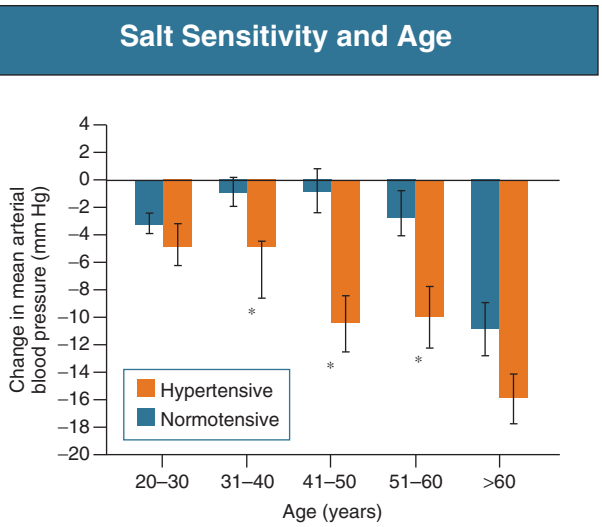

Figure 35-3 Increase in magnitude of salt sensitivity with increasing age. Salt sensitivity (determined by standardized test evaluating change in blood pressure from a volume-expanded to a contracted state) increases proportionately with age in both hypertensive and normotensive individuals (*bars* indicate standard error of the mean; **P* <.05). *(Modified from reference 23.)*

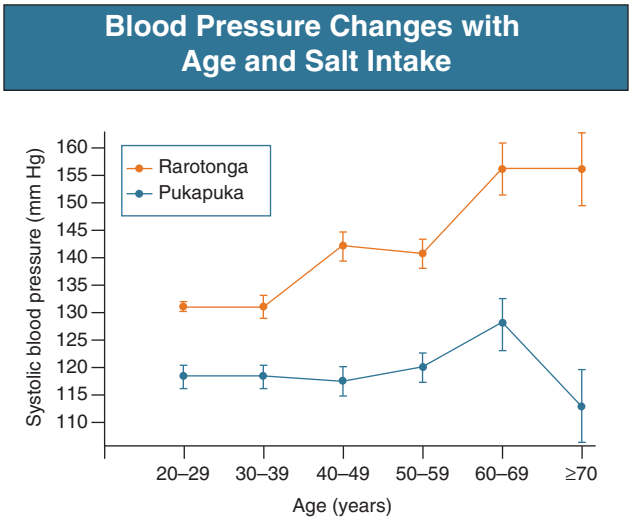

Figure 35-2 Blood pressure changes with age and salt intake. The increase in systolic blood pressure with age correlates with a higher salt intake in two Polynesian populations. In men of Rarotonga Island, where the sodium intake averages 130 mmol/day, systolic blood pressure increases with age. In contrast, it remains constant in men from Pukapuka Island, where the sodium intake averages 50 to 70 mmol/day. *(Modified from reference 22.)*

throughout the world in whom salt intake is above 50 to 100 mmol/day, or 3 to 6 g sodium chloride (NaCl)[21] (Fig. 35-1). Where daily intake is below that range, hypertension is rare. Salt intake also plays an important role in age-related increase in BP[22] (Fig. 35-2). Not all individuals respond similarly to high salt intake. "Salt sensitivity" describes a group of individuals who significantly decrease or increase their BP during periods of salt restriction or loading, respectively. Despite the definition remaining in the research rather than the clinical domain, the following groups of patients tend have increased susceptibility to salt sensitivity (salt-sensitive hypertension):

- People of African descent
- Elderly people
- Obese persons (not in all studies)
- Patients with type 1 or type 2 diabetes
- Patients treated with calcineurin inhibitors
- Patients with chronic kidney disease (CKD)

Salt sensitivity is observed in 75% of hypertensive African Americans compared with about 50% of hypertensive Caucasians[23] and increases with age in both normotensive and hypertensive populations[24] (Fig. 35-3). Response to salt restriction is predicted by polymorphisms in the G protein–coupled receptor kinase 4 (GRK-4) gene, which regulates Na^+ excretion in the proximal convoluted tubule.[25] Putative mechanisms for salt sensitivity are alterations in circulating levels of (or renal responses to) atrial natriuretic factor, kallikrein, prostaglandins, and nitric oxide (NO); increased levels of norepinephrine; abnormal suppression of both renin and aldosterone; genetic mechanisms; congenital reduction in nephron number; and acquired renal microvascular and tubular injury.[23]

The effects of salt restriction on BP have been demonstrated in several well-designed intervention studies.[26] In a randomized controlled trial (RCT) in British people age 60 to 78 who were not receiving antihypertensive medication, modest salt restriction from 10 g to 5 g per day resulted in a reduction in BP of 7.2/3.2 mm Hg during a 4-week period in both normotensive and hypertensive subjects.[27] A meta-analysis in children and adolescents demonstrated that sodium restriction for 4 weeks results in significant BP reductions.[28]

In the follow-up Dietary Approaches to Stop Hypertension (DASH)–Sodium Trial, the additional benefits of salt restriction over and above the DASH diet were investigated (Fig. 35-4).[29] Reduction of sodium intake from a high (150 mmol/day, or 9 g NaCl) to either an intermediate (100 mmol/day, or 6 g NaCl) or a low (65 mmol/day, or 4 g NaCl) intake resulted in a stepwise reduction in BP, which was approximately twice as great in participants receiving the control than receiving the DASH diet (Fig. 35-5). In those following the DASH diet, the addition of salt restriction resulted in a relatively small additional decrease in BP (3.0 and 1.6 mm Hg for systolic and diastolic BP, respectively). Thus, the greatest benefits of salt restriction are seen in those with typical Westernized high-fat, low-nutrient diet. Benefits of short-term salt restriction have been extended to children and adolescents.

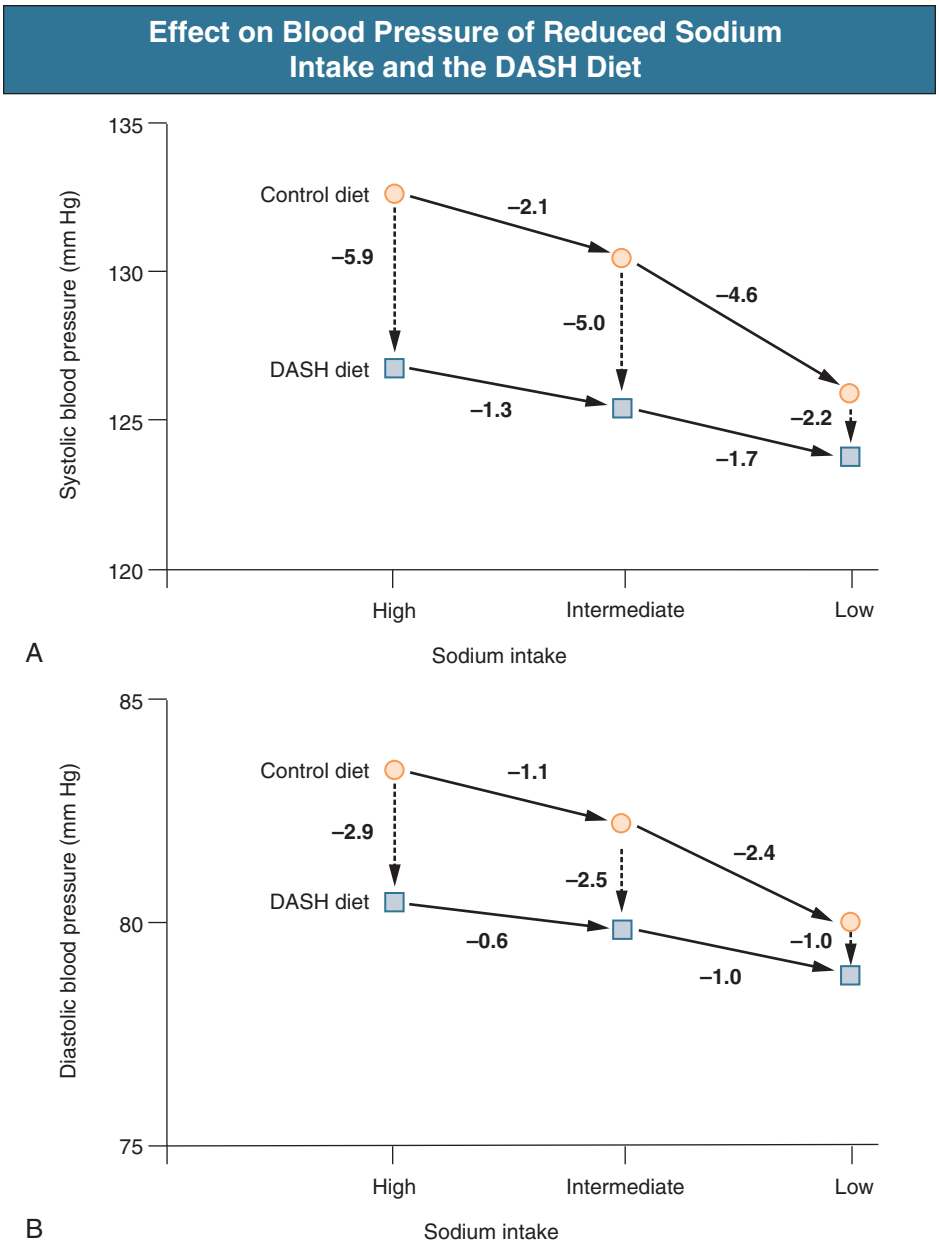

Figure 35-4 Reduced sodium intake and DASH diet. Effect on **A,** systolic blood pressure, and **B,** diastolic blood pressure. (***B*** *redrawn from reference 29.*)

The U.S. Department of Agriculture and U.S. Department of Health and Human Services Joint Dietary Guidelines for Americans calls for no more than 1500 mg/day of sodium (65 mmol/day, or ~4 g NaCl equivalent) in African Americans; people over age 51; and patients with hypertension, diabetes mellitus, or CKD; and no more than 2300 mg/day (100 mmol/day, or ~6 g NaCl) in all others.[30] The JNC 7 guidelines similarly recommend sodium intakes of less than 100 mmol/day.[1] The World Health Organization (WHO) and Food and Agriculture Organization (FAO) of the United Nations recommend less than 5 g NaCl daily (2000 mg, or 90 mmol/day Na) as a population goal, while ensuring that the salt is iodized.[31] The American Heart Association (AHA) Presidential Advisory in 2011 affirmed the recommendation of salt restriction based on evidence that this measure prevents and treats hypertension and reduces adverse cardiovascular disease (CVD) and cerebrovascular accident (stroke).[30]

Avoidance of added salt and salt-rich processed foods can reduce intake from 9 g/day to about 6 g/day. Further reduction in salt requires specialized dietary counseling. Despite these recommendations, long-term studies have reported only small reductions in BP associated with salt restriction (average of only 1.1/0.6 mm Hg).[28] These results undoubtedly reflect limited compliance, but this can be improved by regular contact with the patient, dietetic counseling, and educational sessions. Measurement of 24-hour urinary sodium is useful to check adherence with salt restriction (calculated as urine sodium [mmol/day] × 0.0585 = grams NaCl/day).

Recent reports of select observational studies and a meta-analysis have stirred controversy by suggesting potential harm from sodium restriction and spurred calls for an abandonment of reduction in salt intake. In a recent AHA Presidential Advisory, a detailed review of these studies documents substantial methodologic flaws that limit their usefulness in setting or reversing dietary recommendations. The evidence supporting population reduction in sodium intake remains robust and persuasive.[30] Furthermore, in a meta-analysis of prospective studies, higher salt intake was associated with greater

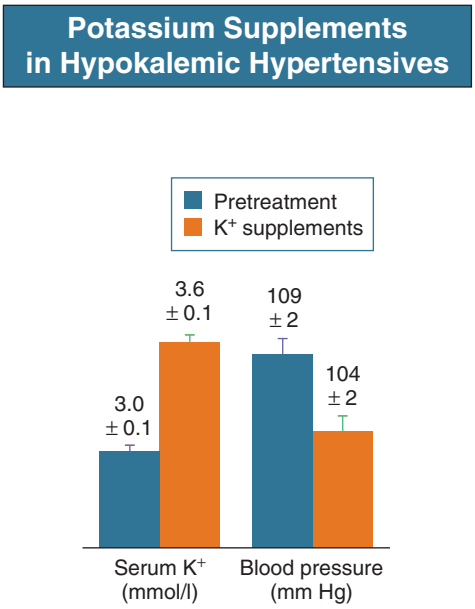

Figure 35-5 Potassium supplementation lowers blood pressure in hypokalemic hypertensive patients. Treatment with potassium chloride (60 mmol/day potassium for 6 weeks) resulted in an increase in serum potassium concentration and a decrease in mean arterial pressure in hypertensive patients taking thiazide diuretics. *(Redrawn from reference 37.)*

risk of stroke (pooled relative risk [RR] 1.23, $P = .007$) and CVD (RR 1.14, $P = .07$), with no significant evidence of publication bias. The associations observed were greater the larger the difference in sodium intake and the longer the follow-up.[32]

One of the most cost-effective ways to lower salt intake in the general population is to reduce salt in processed foods. This approach was effective in lowering the BP in drug-treated hypertensive patients in a low-income community in South Africa through the modification of the salt content of a small number of commonly consumed foods, including bread.[33] In Belgium, the reduction in the salt content of bread between the mid-1960s and the early 1980s was accompanied by marked reductions in 24-hour urinary sodium excretion. In recognition of the need for a concerted global effort to reduce population-wide salt intake, a WHO Forum and Technical meeting in 2006 recommended an integrated approach incorporating a commitment by the food industry to product reformulation, increased consumer awareness, and social marketing around salt and health issues.[34]

The United Kingdom was the first country to set voluntary sodium reduction targets for categories of foods, through its Food Standards Agency (2009), closely followed by Australia, the United States, and Canada. South Africa is the first country to adopt mandatory regulation for maximum sodium levels in food categories that are major contributors to salt intake in that population: bread, margarine and spreads, savory snacks, processed meats, soup powders, and stock cubes.[35] It is estimated that reducing the sodium content of bread by 50%, along with other proposed reductions in margarine, soups, and gravies, would decrease salt intake by 0.85 g/day, resulting in 7000 fewer deaths from CVD and 4000 less nonfatal strokes in the country per year, as well as save about $40 million (U.S.) each year in health care costs associated with nonfatal strokes alone. In the United States, as in most developed nations, a major challenge to sodium intake reduction efforts is the widespread use of sodium in the food supply, with more than 75% of total sodium intake from packaged and restaurant foods.[36]

Potassium Intake

One of the confounding factors of the relationship of salt and BP has been the inverse relationship between the intake of salt and that of potassium. Typically, diets with a high salt content are relatively deficient in potassium (and calcium); but in persons who consume little salt, the potassium (and calcium) intake is high.

In normotensive individuals with an average potassium intake above 1.95 g/day (50 mmol/day), potassium supplementation has no significant effect on BP. However, among hypertensive patients who are potassium deficient because of diuretic treatment or low potassium intake, potassium supplementation lowers BP[37] (see Fig. 35-5). The DASH diet lowers BP and is high in potassium because of the high fruit and vegetable content and inclusion of low-fat dairy products[38] (Table 35-2). However, the synergistic effect of the various food groups in the DASH diet makes it difficult to ascertain the contribution of the individual nutritional components. The mechanisms by which a low-potassium diet may contribute to hypertension are complex and poorly understood but may relate to stimulation of intrarenal angiotensin II (Ang II), oxidants, and endothelin; inhibition of intrarenal NO and prostaglandins; and induction of renal ischemia.

In the Trials of Hypertension Prevention (TOHP) I and II, a higher sodium-potassium excretion ratio (implying a high-salt and low-potassium intake) was more strongly associated with subsequent CV events than either urinary Na^+ or K^+ excretion alone.[39] Overall, it appears to be beneficial to optimize potassium intake in hypertensive patients to minimize hypokalemia, being careful to avoid the risk of hyperkalemia especially in those with renal impairment. If renal function is normal, optimal potassium intake is 80 to 120 mmol/day. For CVD prevention, WHO recommends a potassium intake that will keep the Na-K ratio close to 1 (i.e., 70 to 80 mmol/day if Na guidelines are met).

Calcium and Dairy Food Intake

Cross-sectional population surveys of self-reported nutrient intake suggest an inverse relationship between calcium intake and BP. The relationship is more convincing at low levels of calcium consumption (<300 to 600 mg/day). There may be a threshold of 700 to 800 mg/day, above which any further reduction in BP is attenuated. A meta-analysis of randomized calcium supplementation trials (mostly with 1 or 1.5 g calcium daily) demonstrated reductions in systolic BP (−0.9 to −1.7 mm Hg) that are of little clinical importance.[40] Although calcium in milk may contribute to BP lowering, dairy products may lower BP by other mechanisms. Biologically active peptides formed during the milk fermentation process, such as the casein-derived tripeptides isoleucine-proline-proline and valine-proline-proline, have ACE-inhibiting properties. These milk-derived tripeptides have been shown to reduce BP by 4.8 and 2.2 mm Hg for systolic and diastolic BP, respectively.[41] Vitamin D, which is often added to milk, may also help reduce BP by reducing renin expression. At present, AHA and JNC 7 do not recognize dairy consumption as a dietary approach to the prevention and management of hypertension.[1] Nevertheless, low-fat dairy products are recommended as an integral part of the DASH diet.

Magnesium Intake, Other Micronutrients and Bioactive Food Components

A weak inverse relationship has been reported between dietary intake of magnesium and BP, but in a meta-analysis of 20 RCTs,[42] magnesium supplementation had an insignificant effect on BP.

Dietary Approaches to Stop Hypertension (DASH) Diet*				
Food Group	**Daily Servings**	**Serving Sizes**	**Examples and Notes**	**Significance to the DASH Diet Pattern**
Grains and grain products	7-8	1 slice bread ½ cup dry cereal ½ cup cooked rice, pasta, or cereal	Whole-wheat bread, muffin, pita bread, bagel, cereals, oatmeal	Major sources of calories and fiber
Vegetables	4-5	1 cup raw, leafy vegetables ½ cup cooked vegetables 6 oz vegetable juice	Tomatoes, potatoes, carrots, peas, squash, broccoli, turnip greens, kale, spinach, artichokes, green beans, sweet potatoes	Rich sources of potassium, magnesium, and fiber
Fruits	4-5	1 medium fruit ¼ cup dried fruit 6 oz fruit juice ½ cup fresh, frozen, or canned fruit	Apricots, bananas, dates, oranges, orange juice, grapefruit, grapefruit juice, mangoes, melons, peaches, pineapples, prunes, raisins, strawberries, tangerines	Important sources of potassium, magnesium, and fiber
Low-fat or nonfat dairy foods	2-3	8 oz milk 1 cup yogurt 1.5 oz cheese	Skim or low-fat (2%) milk, skim or low-fat buttermilk, nonfat or low-fat yogurt, nonfat or low-fat cheeses	Major sources of calcium and protein
Meats, poultry, and fish	≤2	3 oz cooked meats, poultry, or fish	Select only lean meats; trim away visible fats; broil, roast, or boil instead of frying; remove skin from poultry.	Rich sources of protein and magnesium
Nuts, seeds, and legumes	4-5/wk	1.5 oz or ⅓ cup nuts ½ oz or 2 tbsp seeds ½ cup cooked legumes	Almonds, mixed nuts, peanuts, walnuts, sunflower seeds, kidney beans, lentils, split peas	Rich sources of calories, magnesium, potassium, protein, and fiber

Table 35-2 Dietary Approaches to Stop Hypertension (DASH) diet. *The DASH eating plan shown is based on 2000 kcal/day. Depending on energy needs, the number of daily servings in a food group may vary from those listed. *(Modified from the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.)*

In contrast, the inverse association between fruit/vegetable intake and BP and other CV risk factors is well established. Epidemiologic evidence suggests that polyphenol compounds found in fruit may explain in part the cardioprotective properties of fruits. Intervention trials have shown that fruits containing relatively high concentrations of flavonols, anthocyanins, and procyanidins, such as pomegranate, purple grapes, and berries, were effective at reducing CVD risk factors. Regular consumption of flavonol-rich foods, cocoa products, tea, and red wine may reduce BP.[43]

Dietary Fats and Sugars

High intake of fructose present in table sugar and high-fructose corn syrup has been correlated with the epidemics of obesity, hypertension, metabolic syndrome, and diabetes. In animals, the intake of fructose but not of glucose or starch can rapidly induce features of the metabolic syndrome. In an experimental study, an intake of 200 g fructose daily in healthy overweight adult men caused a significant increase in systolic and diastolic BP, a rise in plasma triglycerides, a fall in high-density lipoprotein (HDL) cholesterol, and an increase in relative insulin resistance. Other studies have shown that a diet rich in fructose can increase intra-abdominal fat and cause insulin resistance, particularly in those who are already overweight. The pathogenesis of the hypertension may be related to the unique ability of fructose as a sugar to cause intracellular adenosine triphosphate (ATP) depletion and uric acid generation. Allopurinol has been found to block the BP increase with fructose in both humans and rats.[44] These studies suggest that excessive sugar intake could have a role in the metabolic syndrome, and that reduction of sugar intake could be beneficial. Interestingly, whole fruits, which also contain fructose, do not appear to cause metabolic syndrome, probably because of the lower fructose content and the presence of numerous antioxidants (e.g., vitamin C) that block the effect of fructose to induce insulin resistance.

In epidemiologic studies, substantial red meat intake (mean 103 g/day) is associated with a rise in systolic BP of 1.25 mm Hg.[45] Red meat intake has also been associated with an increased risk for diabetes. The mechanisms are unknown but may be related to the production of oxidants, inflammatory cytokines, or uric acid. Supplementation with omega-3 fatty acids reduces the risk of myocardial infarction (MI) and sudden cardiac death,[46] but their effect on BP is small. In a recent meta-analysis, omega-3 supplementation significantly reduced diastolic BP by a mean of 1.8 mm Hg but had no effect on systolic BP, fibrinogen level, or heart rate.[47] About 10 portions of oily fish per week or 9 or 10 fish oil capsules per day are required (equivalent to ~3 g/day long-chain n-3 fatty acids), and this is not tolerated by most because of belching and fishy taste. Concerns about the cholesterol content as well as dioxin and polychlorinated biphenyl (PCB) content (environmental pollutants that have carcinogenic potential and, being fat soluble, can accumulate in the body) of some fish oil supplements also raise questions about the safety of very large doses. As a guideline for overall health, individuals with hypertension should aim to consume about 2 to 3 portions (200 to 400 g) of oily fish (e.g., herring, kippers, mackerel, pilchards, sardines, salmon, trout, fresh tuna, swordfish) per week.

Dietary Approaches to Stop Hypertension (DASH) Diet

The DASH RCT provided unequivocal evidence that nonpharmacologic methods can reduce BP.[38] Participants receiving a diet rich in fruit and vegetables for 8 weeks had a greater reduction in systolic and diastolic BP (2.8 and 1.1 mm Hg, respectively) than did those receiving a typical American control diet. Those randomized to the DASH diet, rich in fruit, vegetables, and low-fat dairy products and with a reduced sugar and saturated and total fat intake, had an even greater reduction in both systolic and diastolic BP (5.5 and 3.0 mm Hg). The effects of the 8-week DASH diet were greatest in hypertensive African Americans, in whom the BP reduction was 13.2/6.1 mm Hg. Increased efficacy of the DASH diet in African Americans may reflect a greater response to the higher potassium,

calcium, and magnesium content of the diet in persons who have habitually low intake of these nutrients.

SMOKING

Cigarette smoking is a well-established major risk factor for CVD, but its role in the development of hypertension is not well elucidated and not routinely included in recommendations for prevention and treatment of hypertension.[1] The relationship with hypertension may be confounded by changes in weight during and after the cessation of smoking. In a large epidemiologic study of middle-aged and older men from the United States, smoking was associated with a modest but important risk for development of hypertension; but in a study of Turkish adults, current smoking carried a borderline protective effect, whereas former smokers with abdominal obesity had a higher risk of incident hypertension.[48,49] Nevertheless, smoking increases overall non-CV and CV morbidity and mortality, and all smokers should be advised to quit.

ALCOHOL

A linear relationship exists among alcohol consumption, BP levels, and prevalence of hypertension in populations.[50] In Japan, alcohol intake above 300 g/wk (about 3 drinks daily) was associated with significantly greater increases of BP during a 7-year period, and baseline BP was higher in drinkers consuming 200 g/wk, with the effects more marked in men.[51,52] Heavy drinking is associated with increased risk of stroke, increase in BP after alcohol withdrawal, and attenuation of antihypertensive efficacy. Paradoxically, alcohol has a J-shaped relationship with coronary heart disease, with moderate consumption (1 to 2 drinks daily) having the lowest risk. In a large epidemiologic study, modest alcohol consumption was protective against first MI.[53] Alcohol may increase BP through activation of the SNS, whereas its protective effects include increasing HDL cholesterol, lowering fibrinogen, and inhibiting platelet activation. The JNC 7 guidelines recommend limiting alcohol consumption to no more than 2 drinks per day (24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) in most men and no more than 1 drink per day in women or lighter-weight men (see Table 35-1).

CAFFEINE

Caffeine is the most widely used psychoactive substance worldwide. Caffeine stimulates the cardiovascular system through the blockade of vascular adenosine receptors.[54] In a meta-analysis of RCTs of coffee ingestion, there was no effect on BP or risk of hypertension, although the quality of the evidence was low.[55] Caffeine tablets may have a greater effect on BP.[56] Coffee may also increase CV risk in smokers,[57] whereas paradoxically, it may reduce the risk for metabolic syndrome and diabetes. The JNC 7 guidelines do not address the issue of caffeine, but it seems reasonable to propose that coffee consumption is safe, at least in nonsmokers, but that pharmacologic ingestion of caffeine and the use of "smart drinks" supplemented with caffeine should be avoided.

PSYCHOLOGICAL STRESS

Chronic psychological stress is an important contributor to the development and maintenance of hypertension. Men exposed to job strain had a 10.7 mm Hg and 15.4 mm Hg higher work and home ambulatory systolic BP than did controls, respectively.[58] The INTERHEART study showed that psychosocial stress was associated with a twofold increase in the risk of the first MI.[53] Nevertheless, stress reduction approaches have shown either negative or heterogeneous effects on BP.[59] As a result, JNC 7 offers no recommendations on stress reduction techniques for the management of hypertension.[1]

ADOPTING LIFESTYLE MODIFICATIONS

Compliance with lifestyle changes has always been a concern. The Prevention of Myocardial Infarction Early Remodeling (PREMIER) trial evaluated the effects of implementing JNC 7 lifestyle recommendations and the DASH diet.[60] Adults with prehypertension or untreated stage 1 hypertension were randomly assigned to one of three groups for 6 months: advice only, JNC recommendations, and JNC recommendations plus DASH diet. At 6 months, the JNC and JNC plus DASH groups had significantly reduced BP compared with the advice-only group, but there was little additional benefit of adding the DASH diet to JNC recommendations. However, participants purchased their own foods in the PREMIER study, instead of being provided with foods as in the DASH[38] and DASH low-salt diet[28] studies. Similarly, in the DASH low-salt diet study, the BP-lowering effect attributable to salt reduction was −6.7/−3.5 mm Hg; whereas in meta-analyses of 40 salt restriction trials in which participants prepared their own low-salt meals, this effect was only −2.54/−1.96 mm Hg.[61] Thus, in the outpatient setting, even highly motivated individuals usually cannot meet DASH dietary goals unless their meals are provided.

The TOHP II study demonstrated the problems of sustainability of dietary intervention and the need for regular counseling.[62] The effect of adding salt restriction to weight loss appeared to offer no further decrease in BP. Assessed by urinary sodium excretion, adherence to lower dietary sodium was poor in the long term. At 36 months of follow-up, mean urinary sodium was 40 mmol/24 hours lower than baseline in the sodium-restricted group, and only 21% achieved the target of less than 80 mmol/24 hours. A higher attendance at counseling sessions was associated with a greater reduction in urinary sodium. At 36 months, a decrease of 84 mmol/day of sodium from baseline levels could be achieved only in those who attended more than 80% of the counseling sessions. In summary, the sustainability of long-term lifestyle interventions remains problematic, but it appears that regular and long-term counseling can improve adherence.

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CHAPTER 36

Pharmacologic Treatment of Hypertension

Bryan Williams

Successful lifestyle interventions can delay the development of hypertension (see Chapter 35), but the majority of patients with confirmed hypertension require lifelong drug treatment, usually with more than one drug. This has resulted in a multibillion-dollar industry, in which numerous pharmacologic agents have been introduced (Table 36-1). In turn, this creates complexity for clinicians in trying to decide which drugs would be the most effective option for specific patient groups. The following sections review who should receive pharmacologic treatment, what target blood pressures to attain, and how to decide on what pharmacologic agent to use.

DEFINING WHO SHOULD RECEIVE PHARMACOLOGIC TREATMENT

Blood pressure (BP) is distributed normally within populations, and thus "hypertension" is an arbitrarily defined, moving target with diagnostic thresholds subject to change as new evidence from clinical trials emerges. From a practical perspective, hypertension is best defined as *that level of blood pressure at which treatment to lower blood pressure results in significant clinical benefit*. This statement highlights the conundrum in defining hypertension because the risk associated with BP is a continuum, and the BP level at which treatment results in "significant clinical benefit" for any individual will depend on the absolute cardiovascular (CV) risk.[1-3] This varies because some people will be more vulnerable than others to end-organ damage at a given level of pressure. Defining that vulnerability case by case remains impractical, and thus differential BP targets and thresholds have emerged that group patients into categories defining their threshold BP for therapeutic intervention and optimal BP goals. In addition, specific drug classes have been given "compelling indications" and "compelling contraindications" for specific groups of patients. This has been useful in tailoring therapy from a wide range of drug classes but has sometimes been misinterpreted as indicating that the specific drug is more important than the achieved BP, which is not the case. The primary objective of therapy must always be to lower BP as effectively as possible.[4-6]

Blood Pressure Thresholds for Intervention (Office Blood Pressure)

There is substantial evidence that treating a seated "office" BP above a systolic pressure of 160 mm Hg and/or a diastolic pressure above 100 mm Hg reduces cerebrovascular accidents (strokes), myocardial infarction (MI), heart failure, and mortality.[4-10] There is also evidence that treating pressures above 140/90 mm Hg, especially in high-risk patients, is beneficial. Consequently, most recent guidelines define hypertension as an office BP of 140/90 mm Hg or higher.[7,8] The exception is the recent United States guideline (JNC VIII), which has adopted a treatment threshold of 140/90 mm Hg for adults aged younger than 60 years but recommends a more relaxed threshold for the diagnosis of hypertension (i.e., 150/90 mm Hg in those aged 60 years and older).[9] Various grades of hypertension have also been specified (Table 36-2). Previous guidelines from the United States (JNC VII) included a category of prehypertension to highlight those with borderline hypertension.[10] This was designed to encourage lifestyle change because the risk of progression from prehypertension to overt hypertension is very high. Furthermore, data from the Framingham heart study have shown that people with a "high normal" BP experience a doubling in risk of CV complications (Fig. 36-1).[11] Thus, prehypertension is not benign, and these people are almost certain to develop more severe hypertension without successful lifestyle intervention or drug therapy.

Clinical Dilemma of End-Organ Damage and "Normal" Blood Pressure

There is debate about treatment for people with prehypertension who already have evidence of end-organ damage, such as left ventricular hypertrophy (LVH), or microalbuminuria. This could be an example of the insensitivity of the defined thresholds for diagnosis of hypertension. Clearly, such a patient who has developed hypertensive LVH or microalbuminuria has a BP that is causing damage, but considered below the usual threshold for intervention. Thus, clinical understanding of the disease process is critical to enable the optimal use of guidelines for treatment decisions. There remains considerable uncertainty in the evidence base, and clinical judgment should not, and indeed cannot, be replaced by guidelines.

Blood Pressure Thresholds for Intervention (Ambulatory and Home Blood Pressure Monitoring)

Diagnostic thresholds for hypertension vary according to the method of measurement. Ambulatory blood pressure monitoring (ABPM) and home BP monitoring are increasingly advocated and used. When used to classify hypertension, the diagnostic thresholds are lower. The recent National Institute for Health and Clinical Excellence (NICE) guideline[8] in the United Kingdom has recommended the routine use of ABPM to confirm the diagnosis of hypertension because of high rates of white coat and masked hypertension (http://guidance.nice.org.uk/CG127). Table 36-3 summarizes the diagnostic thresholds for hypertension according to different methods of measurement (see also Chapter 33).

WHAT ARE THE BLOOD PRESSURE TREATMENT GOALS?

An area of great uncertainty has been the definition of the optimal BP treatment goals. As previously discussed, the ideal BP treatment goal is likely to be patient specific, but guidelines must be generalizable to populations. Thus, guidelines should be conservative and pragmatic, should curb the zeal of specialists to advocate ever lower BP goals, and should confine their recommendations to those supported by solid evidence. Until recently, there was international

consensus that two BP goals were appropriate: less than 140/90 mm Hg for those with "uncomplicated hypertension" and a lower goal of <130/80 mm Hg for those at higher risk, that is, patients with diabetes, established CV or cerebrovascular disease, or chronic kidney disease (CKD). To define such goals, ideally there should be randomized controlled trials (RCTs) with different groups of patients randomized to different BP treatment targets (i.e., "more versus less" BP control) to determine whether the more aggressive BP target is appropriate and safe. Despite the firm consensus on BP targets previously outlined, no large-scale RCTs have targeted more versus less systolic BP lowering, and only a small number have targeted more versus less diastolic BP lowering.[12,13] The guidelines were ahead of the evidence (Fig. 36-2).

In an attempt to obtain more data with regard to systolic BP lowering, the Cardio-Sis study showed that targeting treatment to a systolic BP of less than 130 mm Hg versus less than 140 mm Hg was more effective at preventing the development of electrocardiographically defined LVH and a composite CV outcome.[14] However, this is a single, relatively small study ($n = 1111$), and insufficient to justify a widespread application of a lower BP target of <130/80 mm Hg. An analysis of the baseline and in-treatment BP levels of patients at

Development of Therapeutic Strategies for Hypertension

Year	Nondrug Therapy
1920s	Strict low-sodium diet
1929	Lumbar sympathectomy
1944	Kempner rice diet
Year	**Drug Therapy**
1930s	Veratrum alkaloids
1940s	Thiocyanates
1948	Reserpine, phenoxybenzamine
1950	Ganglion blockers
1951	Monoamine oxidase inhibitors
1958	Thiazide diuretics (chlorothiazide)
1960s	Central α_2-receptor agonists, nondihydropyridine calcium channel blockers, and β-blockers
1970s	Angiotensin-converting enzyme (ACE) inhibitors, α_1-receptor blockers
1980s	Dihydropyridine calcium channel blockers
1990s	Angiotensin receptor blockers (ARBs)
2000s	Renin inhibitors, angiotensin receptor neprilysin inhibitor (ARNI)

Table 36-1 The development of therapeutic strategies for hypertension.

Diagnostic Thresholds for Hypertension

	Blood Pressure (mm Hg)	
Place/Time of Measurement*	***Systolic***	***Diastolic***
Office or clinic	140	90
24-hour	125-130	80
Day	130-135	85
Night	120	70
Home	130-135	85

Table 36-3 Diagnostic thresholds for hypertension according to different methods of measurement. **24-hour, day,* and *night* refer to average blood pressure (BP) measurements in those time periods recorded using ambulatory BP monitoring. *Home* refers to an average of at least 4 days of seated BP monitoring at home, usually twice daily (i.e., average of ~14 readings).

Classification of Hypertension According to Current Hypertension Guidelines

ESH/ESC Classification of Hypertension (2013)

Category	Systolic (mm Hg)		Diastolic (mm Hg)
Optimal	<120	and	<80
Normal	120-129	and/or	80-84
High-normal	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	And	<90

Guideline	BP Threshold (mm Hg)	BP Goal (mm Hg)	Initial Therapy
U.S. JNC VIII Committee 2014	Age < 60 yr = 140/90 Age ≥ 60 yr = 150/90	<140/90 <150/90	Non-Black: Thiazide type diuretic, ACEi, ARB, CCB Black: Thiazide-type diuretic, CCB
ESC/ESH 2013	Age < 80 yr = 140/90 Age ≥ 80 yr = 150/90	<140/90 <150/90	Thiazide-type diuretic, β-blocker, ACEi, ARB, CCB
NICE U.K. 2013	Age < 80 yr = 140/90 Age ≥ 80 yr = 150/90	<140/90 <150/90	Non-Black Age < 55 yr: ACEi/AGB Non-Black ≥ 55 yr: CCB Black any age: CCB

Table 36-2 Blood pressure treatment thresholds, goals, and initial therapy choices according to most recent major international guidelines. Hypertension grades or stages replace the older terminology of mild, moderate, and severe. *ESH/ESC,* European Society of Hypertension/European Society of Cardiology; *ACE,* angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *BB,* β-blocker; *CCB,* calcium channel blocker; *DBP,* diastolic blood pressure; *SBP,* systolic blood pressure. *Treatment determined by highest blood pressure (BP) category. †Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension. ‡Treat patients with chronic kidney disease (CKD) or diabetes to BP goal of less than 130/80 mm Hg.

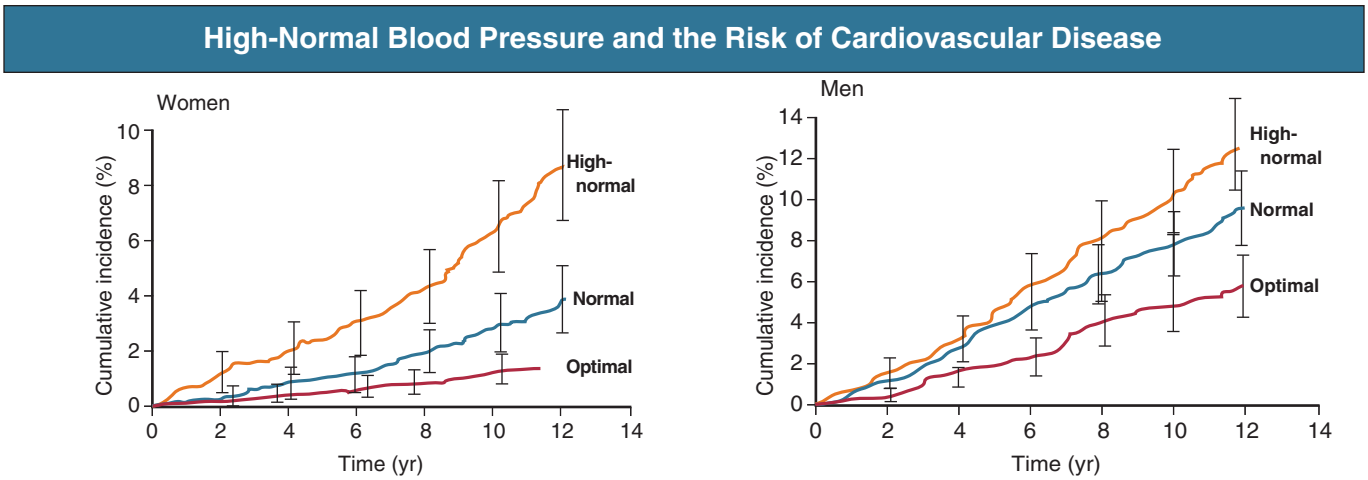

Figure 36-1 "High-normal" blood pressure (BP) and risk of cardiovascular disease. Cumulative incidence of cardiovascular events in women *(left)* and men *(right)* without hypertension, according to BP category at the baseline examination, showing 95% confidence intervals. For this analysis, "optimal" BP was defined as systolic pressure of less than 120 mm Hg and diastolic pressure less than 80 mm Hg; "normal" BP as systolic 120 to 129 or diastolic 80 to 84 mm Hg; and "high-normal" BP as systolic 130 to 139 or diastolic 85 to 89 mm Hg. *(Modified from reference 11.)*

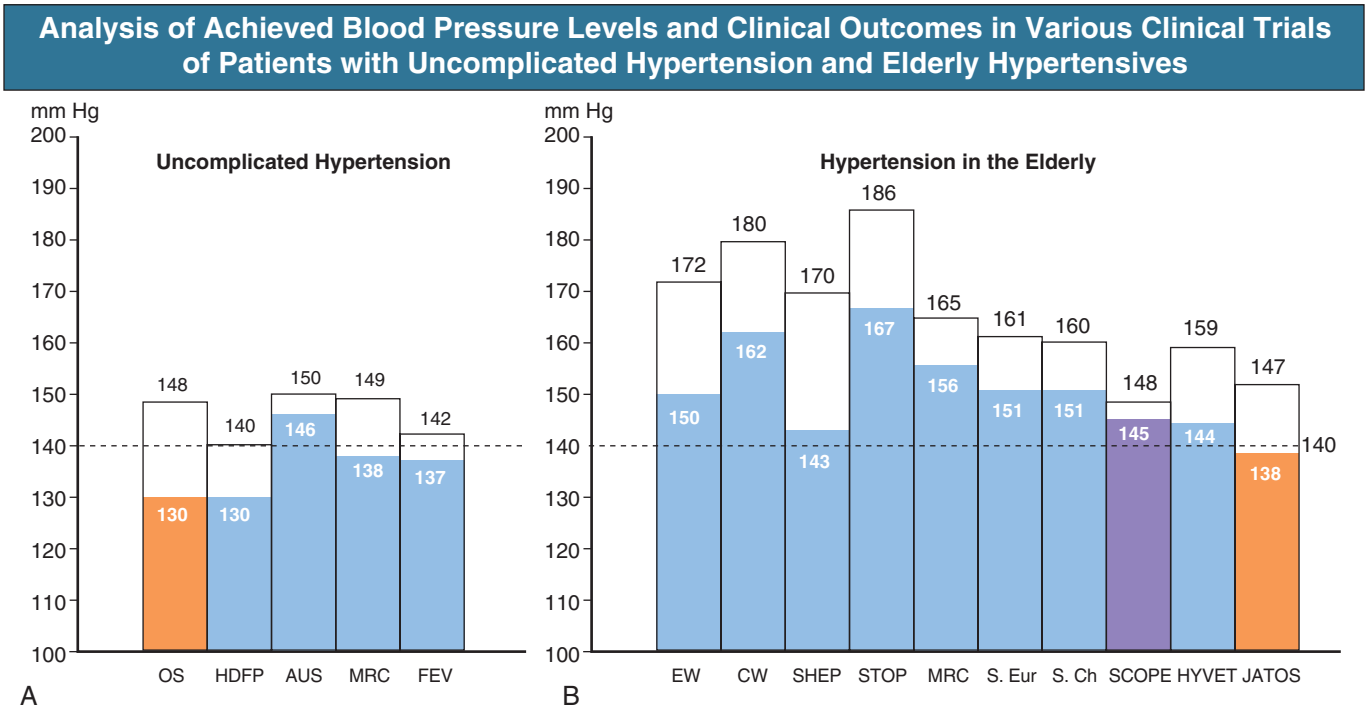

Figure 36-2 Analysis of achieved blood pressure (BP) levels and clinical outcomes in various clinical trials of hypertensive patients. A, Patients with uncomplicated hypertension. **B,** Elderly patients with hypertension. The abbreviations on the base axis refer to the trials for the source data. *Open rectangles* show less active BP lowering; *solid rectangles* show more active BP lowering. The achieved systolic BP values are shown; *orange rectangles*, no significant benefit of more active treatment; *blue*, significant benefit of more active treatment on major cardiovascular outcomes; *purple bar*, significant benefit limited to some secondary outcomes. Numbers refer to achieved mean systolic BP for less active versus more active treatment for each study. The *dotted line* shows the currently recommended systolic BP treatment target. *(Modified from reference 13.)*

high CVD risk in the ONTARGET trial suggests that for people with hypertension at baseline (i.e., systolic BP ≥140 mm Hg), the risk of major CV events and of stroke in particular was reduced with progressive BP lowering.[15] However, for those with a systolic BP of 130 mm Hg or less at baseline, there was much less evidence of benefit with further BP lowering and a signal of possible harm. The ACCORD trial tested the more (<120 mm Hg) versus less (<140 mm Hg) systolic BP lowering hypothesis in a high-risk population with type 2 diabetes.[16] The study failed to provide conclusive evidence that the more intensive BP treatment strategy reduced a composite of major CV events, although stroke rates were significantly reduced. This study appeared underpowered to test this hypothesis definitively.

Thus, although previous guidelines have advocated the more aggressive target of less than 130/80 mm Hg for all higher-risk patients, the evidence has always been weak, and more recent studies and analyses have generated concern about a "lower is better for all" approach. As a consequence, recent guidelines have retreated from

the "lower is always better" philosophy for BP goals. The European and U.K. NICE guidelines have adopted a single BP goal for most people with treated hypertension (uncomplicated or high risk) of less than 140/90 mm Hg, with a more conservative BP goal of less than 150/90 mm Hg for patients aged 80 years and older, based on the data from the HYVET study.[7,8,17] The recent U.S. JNC VIII guideline has adopted a much more conservative approach, consistent with their more conservative aforementioned BP thresholds for intervention. The JNC VIII guideline has recommended a BP goal of <140/90 mm Hg, similar to other guidelines, for those aged younger than 60 years but a BP goal of less than 150/90 mm Hg for those aged 60 years and older, with the caveat being those with diabetes and/or CKD, where a BP goal of <140/90 mm Hg is recommended.[9] Thus, the European and NICE BP goals for those aged 60 to 80 years are lower than those recommended for Americans in the same age group, a notable reversal of usual trends. All guidelines acknowledge that lower BP targets may be appropriate for higher risk patients, on a case-by-case basis, depending on the patient's ability to tolerate lower BP goals, with the caveat that the evidence supporting such a strategy is limited.

GUIDE TO SELECTION OF ANTIHYPERTENSIVE AGENTS

Key Principles from Clinical Trials

Aside from the limitations of the evidence defining optimal BP treatment targets, the pharmacologic treatment of hypertension has the most impressive evidence base in medicine to guide treatment decisions. BP lowering undoubtedly reduces morbidity and mortality, but nephrologists do not know "how low to go." Many large RCTs have compared different classes of active treatments with placebo and different treatment strategies with each other (see references 4 to 6 for overviews). Table 36-4 summarizes a detailed systematic review and analysis conducted for the UK NICE hypertension guideline development group in 2006 (http://www.nice.org.uk/CG034guidance), which compared and ranked the effectiveness of different classes of BP-lowering medication with regard to major CV events. The differences between the various drug classes on clinical outcomes are primarily driven by differences in the quality of BP control. Analysis of these trials has provided some important guiding principles with regard to treatment strategies for hypertension, as follows:

1. Effective BP lowering is overwhelmingly important in reducing the risk of major CV events in people with hypertension. Thus, the first priority in treatment is to control BP.
2. Early studies focused primarily on diastolic BP as the treatment target, but systolic BP is invariably more difficult to control and more closely linked to CV outcomes and should now be the primary but not the sole focus of treatment.
3. Monotherapy is rarely sufficient to control BP, and many patients will require more than one drug as part of their treatment strategy.
4. The response to any class of BP-lowering medication is heterogeneous; that is, some patients will respond better than others.
5. Some trials have indicated that certain comorbidities (e.g., diabetes) and target organ damage (e.g., LVH, CKD) provide compelling indications for inclusion of specific classes of drug therapy in the treatment regimen, but this consideration should not override the importance of BP control.
6. There are inadequate clinical outcome data for treatment studies of younger patients. Most studies, especially the more recent, have been conducted in patients older than 55 and typically with a mean age older than 65.
7. On average, lowering of BP by 20/10 mm Hg in hypertensive patients will reduce the risk of major CV events by half.
8. The reduction in stroke risk appears to follow the predicted reduction in risk based on the epidemiologic association between stroke and BP.
9. There appears to be a shortfall in the reduction in risk of coronary heart disease with BP lowering compared with epidemiologic predictions, which is best addressed by attention to concomitant risk factors.
10. The risk reduction associated with BP lowering appears to be continuous across a wide range of BPs; thus the absolute benefit from treatment is greatest in those with the highest absolute CVD risk. This provides the rationale for advocating the use of complementary strategies to reduce CVD risk (e.g., statins and antiplatelet therapy in those with established vascular disease, with target organ damage, or at high calculated CVD risk, i.e., ≥20% during 10 years).

Selection of Drug Therapy

The major classes of BP-lowering therapies are summarized here. International guidelines recommend certain indications and contraindications for the use of specific classes of BP-lowering therapy in specific clinical situations (Box 36-1 and Table 36-5). These lists are not comprehensive and are subject to change as new evidence emerges. Table 36-6 outlines the more common adverse effects associated with the major classes of BP-lowering drug therapies.

Relative Risk and Benefit of Antihypertensive Drug Classes

Outcome	Thiazide-Type Diuretics (D)	Calcium Channel Blockers (C)	β-Blockers (B)	ACE/ARBs* (A)
Unstable angina	0.89	0.88	0.98	0.97
Myocardial infarction	0.78	0.79	0.85	0.81
Diabetes	0.98	0.80	1.13	0.72
Stroke	0.69	0.65	0.85	0.73
Heart failure	0.53	0.73	0.76	0.64
Death	0.91	0.88	0.93	0.90

Table 36-4 Relative risk and benefit of drugs used to treat hypertension. Table shows effectiveness of drugs where 1.0 = no benefit/harm, <1.0 = benefit, and >1 = potential harmful effect, from a meta-analysis of major blood pressure–lowering trials conducted for the UK National Institute for Health and Clinical Excellence (NICE) Hypertension Guideline Development Group, 2006. *Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) were grouped as a single class for the purposes of this analysis. *(Modified from data in http://www.nice.org.uk/CG034guidance.)*

Clinical Indications Favoring Use of Specific Antihypertensive Medications

ACE Inhibitors
Heart failure
LV dysfunction
Post–myocardial infarction
Diabetic nephropathy
Nondiabetic nephropathy
LV hypertrophy
Carotid atherosclerosis
Proteinuria/microalbuminuria
Atrial fibrillation
Metabolic syndrome

Angiotensin Receptor Blockers
Heart failure
Post–myocardial infarction
Diabetic nephropathy
Proteinuria/microalbuminuria
LV hypertrophy
Atrial fibrillation
Metabolic syndrome
ACE inhibitor–induced cough

β-Blockers
Angina pectoris
Post–myocardial infarction
Heart failure
Tachyarrhythmias
Glaucoma
Pregnancy

Calcium Antagonists (Verapamil, Diltiazem)
Angina pectoris
Carotid atherosclerosis
Supraventricular tachycardia

Calcium Antagonists (Dihydropyridines)
Isolated systolic hypertension (elderly)
Angina pectoris
LV hypertrophy
Carotid/coronary atherosclerosis
Pregnancy
Hypertension in blacks

Thiazide Diuretics
Isolated systolic hypertension (elderly)
Heart failure
Hypertension (blacks)

Diuretics (Antialdosterone)
Heart failure
Post–myocardial infarction

Loop Diuretics
End-stage renal disease
Heart failure

Box 36-1 Clinical indications favoring the use of specific classes of BP-lowering medications in hypertensive patients. *ACE,* Angiotensin-converting enzyme; *LV,* left ventricular.

Contraindications to Specific Blood Pressure–Lowering Therapies

Pharmacologic Therapy	Contraindications	
	Compelling	***Possible***
Thiazide diuretics	Gout	Metabolic syndrome Glucose intolerance Pregnancy
β-Blockers	Asthma A-V block (grade 2 or 3)	Peripheral artery disease Metabolic syndrome Glucose intolerance Athletes, physically active patients COPD Asthma (use cardioselective β-blocker)
Calcium antagonists (dihydropyridines)		Tachyarrhythmias Heart failure
Calcium antagonists (verapamil, diltiazem)	A-V block (grade 2 or 3) Heart failure β-blocker therapy	
Angiotensin-converting enzyme inhibitors	Pregnancy Angioneurotic edema Hyperkalemia Bilateral renal artery stenosis	
Angiotensin receptor blockers	Pregnancy Hyperkalemia Bilateral renal artery stenosis	
Diuretics (antialdosterone)	CKD stages 4 and 5 Hyperkalemia	
Direct renin inhibitors	Pregnancy Hyperkalemia Bilateral renal artery stenosis	

Table 36-5 Compelling and possible contraindications to specific classes of BP-lowering therapies. *A-V,* Atrioventricular; *COPD,* chronic obstructive pulmonary disease.

Figure 36-3 shows the sites of mechanism of action of the various classes of BP-lowering drugs discussed.

Thiazide and Thiazide-like Diuretics

Thiazide diuretics were the first major class of drug used to treat hypertension. The class includes the traditional thiazide diuretics such as hydrochlorothiazide and bendroflumethiazide, as well as thiazide-like diuretics such as chlorthalidone and indapamide. The latter are termed *thiazide-like* because like the thiazide diuretics, these agents act primarily by inhibiting the Na^+-Cl^- cotransporter in the distal tubule of the kidney, promoting sodium excretion, which is integral to their antihypertensive effect. However, the thiazide-like diuretics have different structure to the classic thiazides and differing actions on other aspects of renal tubular function, such as carbonic anhydrase inhibition in the proximal tubule. The importance of the differentiation of the thiazide and thiazide-like diuretics will become apparent in this discussion.

Thiazide and thiazide-like diuretics remain an important therapeutic option for the treatment of hypertension. The early changes in salt and water balance induced by these diuretics are usually accompanied by counteractivation of several vasoconstrictor mechanisms, including the renin-angiotensin-aldosterone system (RAAS), which may transiently raise peripheral vascular resistance (PVR) and attenuate BP lowering. Subsequently, a gradual reduction in PVR and a new steady state of reduced total body sodium and BP are established, usually after about 2 months of treatment.

The sustained actions of thiazide-type diuretics on the kidney make them preferable to loop diuretics for the control of BP. Although loop diuretics are more potent with regard to promoting acute sodium and water loss, their shorter duration of action can result in compensatory sodium retention during the latter part of the dosing interval, thereby reducing their BP-lowering efficacy. Loop diuretics have no place in the routine management of primary hypertension in patients with a well-preserved glomerular filtration rate (GFR). However, thiazide-type diuretics lose efficacy in patients with a GFR below 30 ml/min. In such patients, loop diuretics are often required for effective BP lowering, especially when there is clinical evidence of sodium and water retention.

The main adverse effects of thiazide/thiazide-like diuretics are hypokalemia, hyponatremia (less frequently), impaired glucose tolerance, and small increments in blood levels of low-density lipoprotein (LDL) cholesterol and triglycerides. Thiazide-type diuretics also elevate serum uric acid levels and should be avoided in patients predisposed to gout, as well as in those receiving lithium because of a high risk of lithium toxicity. Lithium is reabsorbed similar to

Common Side Effects Associated with Various Classes of Antihypertensive Drugs

Drug Class	Side Effects
ACE inhibitors	Cough, hyperkalemia
ARBs	Much less frequent hyperkalemia compared to ACE inhibitors
CCBs	
DHP CCBs	Pedal edema, headache
Non-DHP CCBs	Constipation (verapamil), headache (diltiazem)
Diuretics	Frequent urination, hyperglycemia, hyperlipidemia, hyperuricemia, sexual dysfunction
Central α-agonists	Sedation, dry mouth, rebound hypertension, sexual dysfunction
α-Blockers	Pedal edema, orthostatic hypotension, dizziness
β-Blockers	Fatigue, bronchospasm, hyperglycemia, sexual dysfunction
Potassium [K^+] channel openers	Hypertrichosis (minoxidil); lupus-like reactions, pedal edema (hydralazine)

Table 36-6 Common side effects associated with various classes of antihypertensive drugs. *ACE,* Angiotensin-converting enzyme; *ARBs,* angiotensin receptor blockers; *CCBs,* calcium channel blockers; *DHP CCBs,* dihydropyridine calcium channel blockers; *non-DHP CCBs,* nondihydropyridine calcium channel blockers.

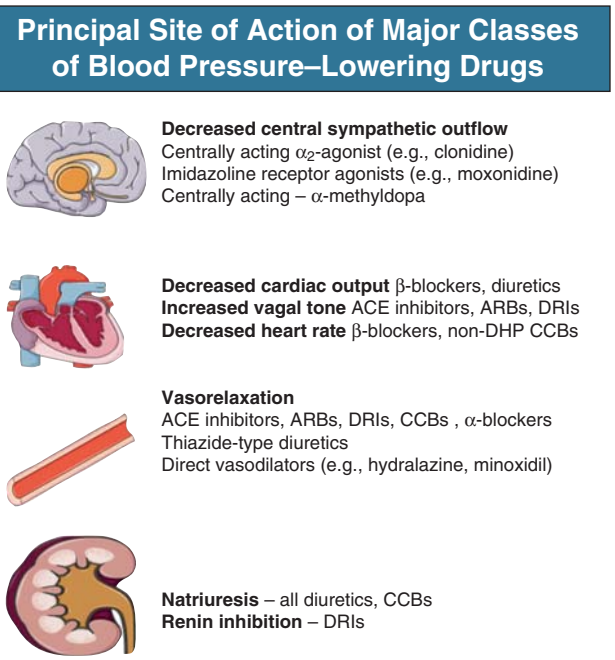

Figure 36-3 Principal site of action of major classes of blood pressure (BP)–lowering drugs. *ACE,* Angiotensin-converting enzyme; *ARBs,* angiotensin receptor blockers; *CCBs,* calcium channel blockers; *DRIs,* direct renin inhibitors; *non-DHP CCBs,* nondihydropyridine calcium channel blockers.

sodium through the proximal tubule, and thus distal sodium loss caused by thiazides can promote proximal reabsorption of sodium and lithium; because lithium has a narrow therapeutic window, this can lead to lithium toxicity. An incidental advantage of thiazide-type diuretics may be reduction in osteoporosis as a result of calcium retention.

There has been a trend during recent years to reduce the recommended dose of thiazide-type diuretics to minimize their adverse metabolic effects. The dose-response to thiazide-type diuretics is flat (unlike the adverse effect profile), and this has been used to justify the low-dose strategy. However, some patients respond well to higher doses of thiazide-type diuretics, which they tolerate. Moreover, when thiazides are combined with drugs that block the renin-angiotensin system (RAS), such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), the dose-response curve is steeper, and higher doses (e.g., hydrochlorothiazide 25 to 50 mg or chlorthalidone 25 mg) may be especially effective in patients with more resistant hypertension. The recent NICE hypertension guideline reviewed the evidence for clinical outcome benefits with low dose thiazide and thiazide-like diuretics and has recommended the preferred use of thiazide-like diuretics such as chlorthalidone and indapamide, rather than traditional thiazides such as hydrochlorothiazide because there is limited outcome data with the latter when used at low dose.[10]

Potassium-Retaining Diuretics (e.g., Spironolactone, Amiloride, Eplerenone) Spironolactone is an aldosterone receptor antagonist that acts in the renal distal tubule and collecting ducts, decreasing the reabsorption of sodium and water and decreasing the excretion of potassium. The main action of spironolactone is to decrease the tubular expression of epithelial sodium channel (ENaC) and renal outer medullary potassium (ROMK) channels, and thus it has a relatively slow onset and offset of action. Because its main site of action is on sodium and water handling in distal tubule and collecting ducts, spironolactone is a relatively weak diuretic. Nevertheless, it is effective as a BP-lowering agent but currently rarely used for the initial routine treatment of hypertension. Spironolactone has the advantage over thiazide-type diuretics that it does not cause hypokalemia or hyperuricemia, and it does not impair glucose tolerance. However, spironolactone has antiandrogen activity by binding to the androgen receptor and preventing it from interacting with dihydrotestosterone. Consequently, it can cause nipple tenderness and gynecomastia in some male patients (~6%), which is dose dependent and can limit its use. Another concern with potassium-sparing diuretics in general is the risk of hyperkalemia in people with substantially reduced GFR (see later discussion).

Eplerenone is more selective for the aldosterone receptor than spironolactone and thus avoids its antiandrogen effects. There is very limited experience with use of eplerenone for the routine management of hypertension. Empirically, milligram per milligram, eplerenone is less potent than spironolactone and less effective at lowering BP.

Amiloride is an antagonist of the ENaC in the distal convoluted tubules and collecting ducts of the kidney, decreasing sodium and water reabsorption and promoting potassium excretion. Previously, amiloride was a popular treatment of primary hypertension, when, like spironolactone, it was often used in combination with thiazide-type diuretics. Amiloride is less used now even though it shares the advantage of spironolactone over thiazide-type diuretics of not causing hypokalemia, hyperuricemia, or impaired glucose tolerance. Amiloride is the treatment of choice in patients with Liddle syndrome who have hypertension caused by a gain-of-function mutation of ENaC.

The reason for the decline in popularity of potassium-sparing diuretics for the initial treatment of primary hypertension is not clear; it may reflect the emergence of ACE inhibitors or ARBs. These RAAS blockers are increasingly used for the routine management of hypertension, and there is an increased risk of hyperkalemia when these are combined with spironolactone or amiloride, especially in patients with renal impairment. Spironolactone and amiloride are,

however, increasingly used as additional diuretic therapy as part of a multidrug strategy for the treatment of patients with resistant hypertension, for whom these drugs can be very effective.[18-20]

β-Adrenoceptor Blocking Drugs

β-Blockers reduce BP and CV events in patients with hypertension. Most β-blockers, with the exception of those with strong intrinsic sympathomimetic activity, reduce cardiac output by their negative chronotropic and inotropic effects. As with diuretics, short-term hemodynamic responses can be offset by counteractivation of vasoconstrictor mechanisms, which may limit initial BP lowering. Longer-term reduction in arterial pressure occurs because of restoration of PVR to pretreatment levels. Partial blockade of renin release from the kidney may contribute to the later hemodynamic response.

The β-blockers differ in their duration of action, selectivity for β_1 receptors, lipophilicity, and partial agonist activity. Side effects include lethargy, aches in the limbs on exercise, impaired concentration and memory, aggravation of depression and psoriasis, erectile dysfunction, vivid dreams, and exacerbation of symptoms of peripheral vascular disease and Raynaud syndrome. Nonselective β-blockers are contraindicated in asthma patients and can cause adverse metabolic effects, including impaired glucose tolerance and worsening of dyslipidemia, notably reduced high-density lipoprotein (HDL) cholesterol and raised triglyceride levels. There is accumulating evidence that β-blockers increase the likelihood of new-onset diabetes, particularly in combination with thiazide-type diuretics.[21,22] Moreover, recent meta-analyses suggest that there is a shortfall in CV protection with β-blocker–based treatment of hypertension (especially in stroke reduction) compared with treatment with other major drug classes[10,23,24] (see Table 36-4). As a consequence, the UK guidelines have suggested since 2006 that β-blockers are no longer preferred as an initial therapy for routine hypertension and should be used only when there is a compelling indication other than BP control (e.g., in patients with hypertension and angina or chronic heart failure).[10]

One caveat is in younger women of childbearing potential, in whom β-blockers are often effective at lowering BP and are safer than ACE inhibitors or ARBs in women anticipating pregnancy. The generally good BP-lowering efficacy in younger people most likely reflects the higher renin levels in younger than in older people, and the BP-lowering action of β-blockers, at least in part, relates to suppression of renin release. Newer β-blockers have associated α-blocking activity, such as carvedilol and nebivolol. However, no clinical outcome trial data exist for the treatment of hypertension with these agents. The recent ESC/ESH guideline did not come out quite so strongly against β-blockers but did not specifically endorse these agents as a preferred initial treatment, or as an ideal drug in combination with other treatments, compared with other options for combination therapy.[8] The U.S. JNC VIII committee guidelines, like the U.K. NICE guidance, no longer cite β-blockers as a preferred initial therapy for hypertension unless there are specific indications for their use, other than the routine lowering of BP.[9]

Calcium Channel Blockers

Calcium channel blockers (CCBs) are effective at reducing BP and have an extensive evidence base supporting their use for the treatment of hypertension.[4,6] In addition to their BP-lowering properties, CCBs are also effective antianginal agents. They appear to be metabolically neutral with regard to glucose tolerance and lipid parameters. More recent data have highlighted that CCBs are especially effective at smoothing BP variability. Increased BP variability is an independent risk factor for stroke, which may explain why systematic reviews have shown CCBs (particularly amlodipine) to be the most cost-effective treatment option for hypertension, mainly because they are the most effective agent at preventing stroke.[10] An interesting aspect of the BP response to CCBs is that it is largely determined by the magnitude of BP elevation, perhaps more so than with other drugs. Thus, patients with higher baseline BP levels experience greater BP lowering with CCBs, whereas those with only modest elevations of BP experience much smaller decreases in BP. This property may also explain the "smoothing" effect of CCBs on BP variability.

There are two main groups of CCBs, the *dihydropyridines* (e.g., amlodipine, nifedipine) and the *nondihydropyridines* (e.g., diltiazem, verapamil). The dihydropyridine (DHP) CCBs act mainly by inducing relaxation of arterial smooth muscle by blocking L-type calcium channels, thereby inducing peripheral vascular relaxation with a fall in PVR and arterial pressure. Nondihydropyridine (non-DHP) CCBs block calcium channels in cardiac muscle and reduce cardiac output. Verapamil has an additional antiarrhythmic action through its effects on the atrioventricular node. Physicians have occasionally combined DHP and non-DHP CCBs, but no robust data are available on the BP-lowering efficacy of this approach or on clinical outcomes, and it is not a recommended combination therapy in international guidelines.

Earlier formulations of some DHP CCBs, such as capsular nifedipine, had a rapid onset and a short duration of action, with unpredictable effects on BP. These responses were often accompanied by reflex sympathetic stimulation and tachycardia. The shorter-acting oral preparations of CCBs have no place in the routine management of hypertension. More modern, longer-acting formulations of DHP CCBs produce more sustained and predictable responses.

Side effects of DHP CCBs include dose-dependent peripheral edema, which is not caused by fluid retention but by transudation of fluid from the vascular compartments into the dependent tissues as a result of precapillary arteriolar dilation. This edema does not respond to diuretic therapy but is alleviated by limb elevation. There is emerging evidence that this edema may also be reduced by coadministration of an ACE inhibitor or ARB because of its effects on venous capacitance. Gum hypertrophy can occur with DHP CCBs but is rarely seen with non-DHP CCBs. Nondihydropyridine CCBs cause less peripheral edema but are negatively inotropic and negatively chronotropic and should therefore be avoided in patients with compromised left ventricular function and in combination with β-blockers. Verapamil use is commonly accompanied by constipation.

Blockade of Renin-Angiotensin System

The RAS has become a popular target for drug development to treat hypertension. Inhibition of RAS is predictably effective at lowering BP by inhibiting the various central and peripheral pressor effects of angiotensin II (Ang II). Blockade of RAS may also lower BP by other mechanisms involving improvements in endothelial function, vagal tone, and baroreceptor function and through inhibition of the renal tubular reabsorption of sodium. In addition, inhibition of RAS has been popularized by clinical trial evidence showing reduced morbidity and mortality in patients with heart failure, delayed progression of renal disease, and reduced CV events in those at high CV risk with treatment strategies that involve inhibition of RAS.[6] Three classes of drugs are now available that directly target the RAS (Fig. 36-4): ACE inhibitors, ARBs, and a new class, the direct renin inhibitors (DRIs).[25]

Angiotensin-Converting Enzyme Inhibitors ACE inhibitors were the first effective strategy to inhibit RAS and have been used to

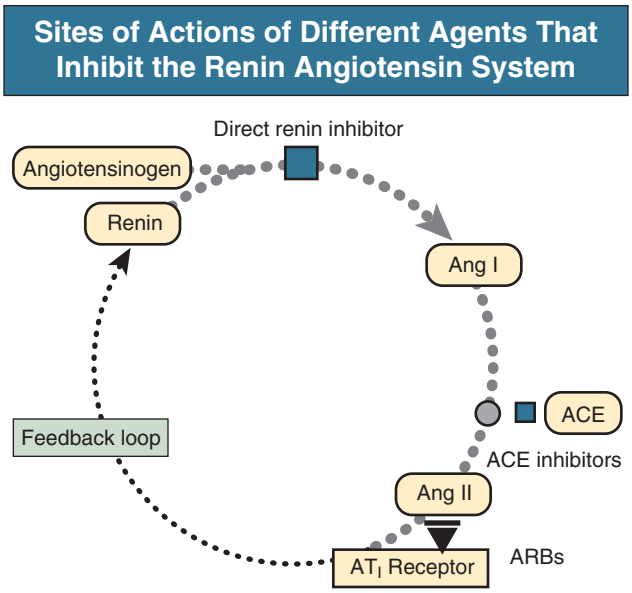

Figure 36-4 Sites of actions of different agents that inhibit the renin-angiotensin system. The resulting neurohumoral profile is also shown. *ACE,* Angiotensin-converting enzyme; *Ang,* angiotensin; *ARB,* angiotensin receptor blocker; *DRI,* direct renin inhibitor.

treat hypertension since the late 1970s. ACE inhibitors block the conversion of Ang I to Ang II by inhibiting ACE. The resulting reduction in levels of Ang II leads to vasodilation and a fall in BP. Ang II has many additional actions that are potentially harmful to the CV system and has been implicated in the pathogenesis of structural changes in the heart, blood vessels, and kidneys in hypertension. Sharp falls in BP after the introduction of ACE inhibitors may occur when the RAS is activated, for example, in patients who are dehydrated, in heart failure, or with accelerated hypertension. This is rarely a problem when therapy is initiated in uncomplicated hypertensive patients.

Side effects of ACE inhibitors include the development of a persistent dry cough in about 20% of users. This is more common in women and in people from the Far East and Pacific Rim. The cough disappears only after discontinuation of the drug. Another rare but important complication is angioedema, which occurs in about 1% and is much more common in the black population (~4%). ACE inhibitors should be avoided in women of childbearing potential because of the danger of fetal malformation, especially from exposure in the first trimester, when women may be unaware they are pregnant. ACE inhibitors should not be used in patients with significant bilateral renal artery disease because they may precipitate deterioration in renal function and renal failure. Careful monitoring of renal function and serum potassium concentration is also required in patients with more advanced renal impairment of any cause, because of the risk of hyperkalemia.

Angiotensin Receptor Blockers In the 1990s, ARBs emerged as an alternative to ACE inhibition. ARBs are highly selective inhibitors of the Ang II type 1 receptor (AT_1). In common with ACE inhibitors, ARBs inhibit the actions of Ang II on the CV system and kidney. ARBs reduce BP as effectively as ACE inhibitors but generally have a longer duration of action than ACE inhibitors. When ACE inhibitors and ARBs have been compared, they appear to be equally effective in reducing albuminuria and preserving GFR,[26] as well as similar in efficacy for preventing major CV events in patients with established CVD.[27] Because of their selectivity and specificity for the AT_1 receptor, the ARBs are well tolerated by patients, with a placebo-like adverse effect profile. Moreover, cough and angioedema are much less likely to occur with ARBs than with ACE inhibitors, and most guidelines recommend switching patients to an ARB when an ACE-induced cough occurs. Cautions and contraindications are similar to those outlined for ACE inhibitors.

Direct Renin Inhibitor A third strategy recently emerged to inhibit RAS for the treatment of hypertension: the first nonpeptide, orally active direct renin inhibitor (DRI), aliskiren.[25] Aliskiren has high specificity for renin and is a potent inhibitor of plasma renin activity with a long half-life (~24 hours). Aliskiren inhibits the rate-limiting step in angiotensin production, notably the renin-dependent conversion of angiotensinogen to Ang I. The DRI appears to have BP-lowering efficacy similar to that of other means of inhibiting the renin system (i.e., ACE inhibitors, ARBs) but with less side effects than ACE inhibitors.[26] The contraindications to use are similar to those for ACE inhibitors and ARBs. The main factor differentiating the DRI from ACE inhibitors or ARBs is that ACE inhibitors or ARBs activate plasma renin activity, whereas the DRI inhibits plasma renin activity. Aliskiren also has a much longer duration of action than the other forms of RAAS blockade. The ALTITUDE trial tested the efficacy of aliskiren at reducing CV and renal events when added to preexisting RAS blockade in patients with type 2 diabetes and high CVD risk.[28] The study was discontinued for futility and a signal of potential increased risk of harm when aliskiren was combined with another RAS blocker in this high-risk group of patients. Thus, aliskiren remains as a strategy for RAS blockade to treat hypertension, but the DRI should not be used in combination with either an ACE inhibitor or ARB in patients with diabetes or renal impairment. Further studies are ongoing.

α-Adrenergic Blocking Drugs

The original members of the α-adrenergic blocking class (e.g., prazosin) were short-acting drugs that blocked the activation of α_1-adrenoceptors in the vasculature, leading to vasodilation. Initially, the recommended dosage was too high, and postural hypotension and syncope proved serious problems that hindered the acceptance of this class of drugs, although the use of lower doses and the development of longer-acting agents (e.g., doxazosin) have largely overcome this problem. Blockade of sphincteric receptors improves symptoms in patients with benign prostatic hypertrophy. On occasion, these same sphincteric effects can worsen symptoms of stress incontinence in women. Uniquely among antihypertensive drugs, the α_1-antagonists produce modest favorable changes in plasma lipids, with a reduction in total and LDL cholesterol and triglyceride levels and an increase in HDL cholesterol.

Centrally Acting Sympatholytic Drugs

Some of the earliest drugs developed to treat hypertension targeted the activation of the sympathetic nervous system (SNS) at various levels, including the CV regulatory nuclei in the brainstem, the peripheral autonomic ganglia, and the postganglionic sympathetic neuron. Few of these agents have any residual role to play in the modern treatment of hypertension because side effects are common, and their use has been superseded by classes of drugs with a more tailored mechanism of action.

Methyldopa reduces sympathetic outflow from the brainstem. Originally developed in the late 1950s, methyldopa was a mainstay of antihypertensive therapy for many years. However, it frequently causes sedation, impaired psychomotor performance, dry mouth, and erectile dysfunction. Its unfavorable impact on quality of life resulted in methyldopa being gradually replaced by more effective drugs, although it is still extensively used in the management of hypertension of pregnancy, which is now its main indication.

Clonidine is now rarely used because of its short duration of action and risks of a withdrawal syndrome, which occurs when sudden discontinuation results in a rebound rise in catecholamines with features that may resemble pheochromocytoma, such as severe hypertension, tachycardia, and sweating. This is exacerbated when patients are also receiving nonselective β-blockers such as propranolol. The syndrome is treated by readministration of the drug and then gradual discontinuation or the intravenous infusion of labetalol in an emergency. Clonidine is still used and can be effective in some patients with drug-resistant hypertension. Longer-acting preparations of clonidine are being developed and may find a place in the management of resistant hypertension.

A newer centrally acting agent, *moxonidine* is an imidazoline receptor agonist that reduces sympathetic outflow and BP. It has a lower incidence of side effects and is better tolerated than other centrally acting agents. Moxonidine has no clinical trial evidence to support its use as a preferred first-line agent but is used in patients with more resistant hypertension.

Direct Vasodilators

Hydralazine was previously extensively used as part of the original "stepped care" treatment regimens for hypertension. The main disadvantages were sympathetic activation and the development of a lupus-like syndrome, particularly in patients with the slow acetylator genotype. Also, multiple daily dosage was required. Hydralazine is no longer recommended as a first-line agent for hypertension management. It is still occasionally used in severe hypertension and hypertension associated with pregnancy.

Minoxidil is a potent vasodilator, and its use is largely confined to specialist centers for the treatment of severe and resistant hypertension. This is because of its side effect profile, which includes stimulation of body hair growth; tachycardia and severe fluid retention reflect its potent vasodilator action and concomitant reflex SNS activation. For this reason, minoxidil is usually combined with a potent loop diuretic and a β-blocker as part of a triple-therapy approach to severe hypertension. Long-term use can be associated with insidious development of peritoneal and pericardial effusions (especially in patients with impaired renal function). These necessitate and respond to treatment withdrawal.

Treatment Strategies

Given the multiple drug classes for the treatment of hypertension, there is a need for a treatment strategy that identifies the preferred drugs for initial therapy and preferred combinations for patients requiring more than monotherapy to control their BP. The use of drug therapy to lower BP should usually follow a period of observation and repeated measures of BP to ensure that there is a sustained elevation of BP that merits treatment. The duration of the observation period is inversely related to the severity of hypertension. This ranges from immediate treatment to repeated measurement over days or months.

Lifestyle interventions should be initiated during this period of observation and continued even if treatment with drug therapy is initiated (see Chapter 35). This is important because the actions of drug therapy can often be potentiated by concomitant lifestyle changes, especially body weight reduction and reduction in dietary sodium intake.[29] Furthermore, lifestyle changes are also important to improve the overall health and CV risk profile of the patient, beyond the impact on BP. Another key aspect of the initial assessment of patients is to identify concomitant risk factors, comorbidities, and target organ damage, all of which might influence the selection of drug therapies to improve BP control.

Initial Drug Therapy

Current practice is to initiate treatment with a single drug. Depending on the BP level at baseline, monotherapy will on average reduce systolic pressure by 7 to 13 mm Hg and diastolic pressure by 4 to 8 mm Hg; the greater reductions will generally be observed in those with the highest baseline BP.[30] It is emphasized that these are "average BP responses," and there can be marked heterogeneity in response among individual patients and with different classes of drugs in individual patients. Treatment should normally commence with a low dose of the drug selected. If this is inadequate, there is the following range of options:

1. If BP responds to low-dose monotherapy and is not yet controlled but is likely to be controlled with monotherapy (i.e., BP within ~10/5 mm Hg of BP goal), the dose of the initial drug should be titrated upward.
2. If the BP response to the initial low dose is inadequate and the patient's BP remains well short of the target BP, a more appropriate action is to add a second drug, either separately or as a combination tablet, because the majority of patients will require two or more drugs to control their BP.
3. If the initial drug produced a weak response or no response at all and the patient could conceivably achieve the BP goal with monotherapy, the first drug could be discontinued and replaced with another class of antihypertensive agent.

Choice of Initial Therapy There was previously wide variation in international guidelines with regard to the preferred initial therapy for primary hypertension. The previous U.S. JNC VII report recommended low-dose thiazide diuretic therapy as initial therapy for all, unless contraindicated. The recent report from the U.S. JNC VIII committee has changed that stance and has recommended initial therapy with an ACE-inhibitor, ARB, a low-dose thiazide-type diuretic, or a CCB for non-black patients. The recommendation for initial therapy for black patients is either a thiazide-type diuretic or CCB.[9]

The most recent European guideline recommends that five major classes of BP lowering drugs—ACE-inhibitor, ARB, low-dose thiazide-type diuretics, CCBs, or β-blockers—are suitable as initial therapy, guided by the specific indications shown in Box 36-1 and Table 36-5.[7] The U.K. NICE guideline adopts a different approach and suggests that both age and ethnicity are important determinants of the BP response to initial therapy,[8] the latter now also adopted by the U.S. JNC VIII guideline. The rational for this approach is that the renin-angiotensin system is usually more active in younger people and less so in older people and black people at any age. Thus, the U.K. NICE guideline recommends initial therapy with and ACE-inhibitor or ARB in non-black patients aged younger than 55 years and a CCB as the preferred initial therapy for most patients aged 55 years and older. For black patients at any age, the U.K. NICE guidence recommends a CCB as the preferred initial therapy. The caveats to these recommendations are (1) that a thiazide-type diuretic may be preferred to a CCB where a CCB is not tolerated or in those with signs of heart failure or at high risk of heart failure (e.g., the very elderly) and (2) that an ACE-inhibitor or ARB should not be used in women of child-bearing potential, when instead a β-blocker may be preferred. Thus, the U.S. JNC VIII has moved much closer to the U.K. (see Fig. 36-7). NICE and European guidelines with regards to initial therapy choices. Moreover, like the U.K. NICE guidelines, the U.S. JNC VIII committee have recommended against the preferred use of β-blockers as initial therapy for hypertension, unless there is a specific indication for their use (e.g., in patients with chronic heart failure, symptomatic angina, or post-myocardial infarction). The reason for this is that the JNC VIII committee agreed with the assessment of the U.K. NICE conclusions

that β-blockers (1) appear less effective than alternative drugs at reducing the risk of stroke, (2) were no more effective than other drugs at preventing incident ischemic heart disease, (3) were more likely to increase the risk of developing type 2 diabetes, especially when combined with diuretic therapy, and (4) were as a consequence, the least cost-effective option for the initial treatment of primary hypertension.[8,24]

Combination Therapy for Controlling Blood Pressure

The U.S. JNC VIII committee has recommended ACE-inhibitor or ARB with CCB and/or thiazide-type diuretic, for the preferred dual and triple therapy combinations. This is now very similar to the prior U.K. NICE recommendations, with the caveat that U.K. NICE guidance was the first to give explicit guidance for the use of ACE-inhibitor or ARB with a CCB (A+C) as the preferred two-drug combination for most people, while accepting that an ACE-inhibitor or ARB with a low-dose thiazide-type diuretic is a suitable alternative when a diuretic has been used as initial therapy (see Fig. 36-5). The recommendation for the preferred use of A+C by the U.K. NICE guideline was supported by the ACCOMPLISH trial, which specifically evaluated whether the type of two-drug combination was important in influencing clinical outcomes by comparing two different single pill combinations, an ACE-inhibitor with a CCB versus the same ACE-inhibitor combined with a low-thiazide diuretic, in a high-risk group of patients.[31] There was a significant (~20%) reduction in the primary end point in favor of the ACE-inhibitor-CCB combination, and all components of the primary composite en-point showed this trend. Moreover this outcome was not determined by any obvious difference in BP control between the two treatment groups. These data from ACCOMPLISH, alongside the wealth of data from ACE-inhibitor or ARBs in combination with low-dose thiazide diuretic therapy, provide two excellent evidence-based options to combine with either an ACE-inhibitor or ARB as a two-drug combination therapy (i.e., A+C or A+D, with the use of A+C+D when a three-drug combination is required in more resistant hypertension). Thus, there is strong alignment between the U.K. NICE and JNC VIII committee guidance on preferred combination therapy for most patients at steps 2 and 3 of the treatment algorithm. In fact, distilling the down European guideline to only the solid green lines (see Fig. 36-6) (i.e., the preferred combinations), the preferred combinations are also similar to the U.S and U.K. guidance (i.e., A+C or A+D, and A+C+D when required). The only difference is that the European guideline also endorses another step 2 combination, that is, a CCB + thiazide-type diuretic, which has been effective in some trials but is rarely used because it eliminates RAS blockade, which many would consider complementary to either a CCB or thiazide-type diuretic to both lower BP and prevent reflex activation of the RAS system, which would otherwise occur with a C+D combination. What is clear is that all guidelines have converged and are closer than they have ever been with regard to preferred initial and combination therapies.

Initial Therapy with a Two-Drug Combination "Low-dose" two-drug combination therapy has been recommended in the European and American hypertension guidelines for the treatment of patients whose BP is more than 20/10 mm Hg above their goal BP

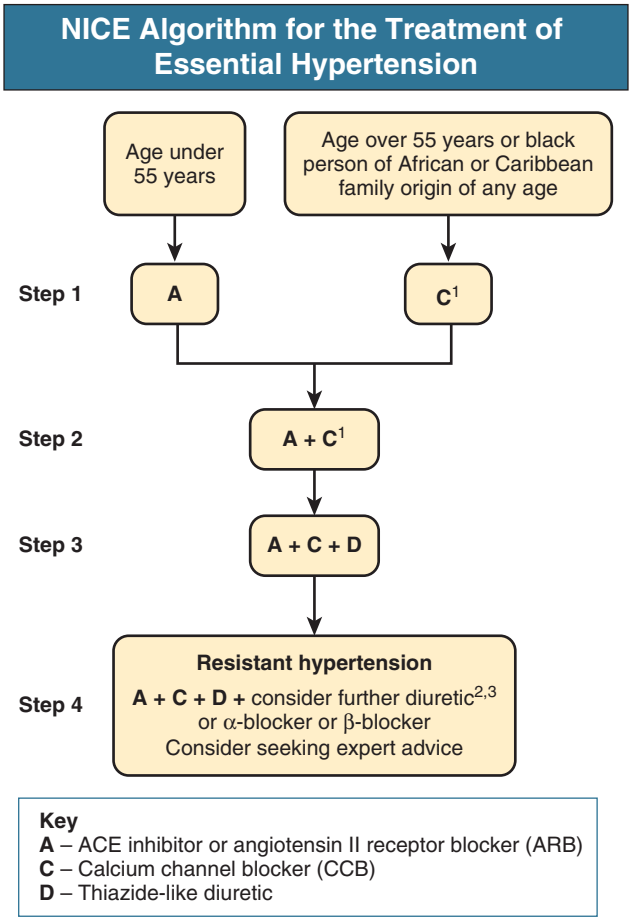

Figure 36-5 Algorithm for treatment of essential hypertension. UK National Institute for Health and Clinical Excellence (NICE) guidelines: [1]CCB is preferred, but consider a thiazide-like diuretic (chlorthalidone or indapamide) if a CCB is not tolerated or the patient has edema, heart failure or is at high risk of developing heart failure; [2]consider low-dose spironolactone; [3]higher doses of the thiazide-like diuretic. *(Modified from reference 8.)*

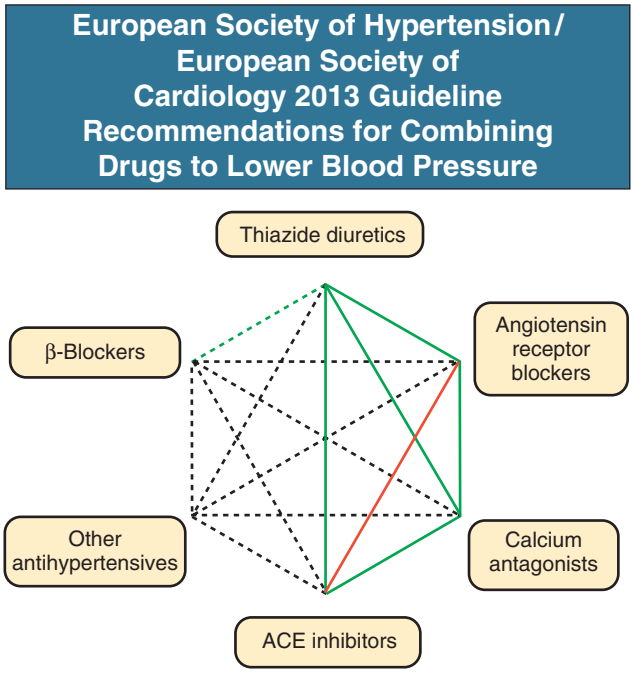

Figure 36-6 ESH/ESC recommendations for combining drugs to lower blood pressure. *Green continuous lines* are the preferred combinations, *green dashed line* is considered a useful combination but with some limitations, *black dashed line* are possible but less well tested combinations; and the *red line* is not recommended as a combination treatment for hypertension; *ACE,* angiotensin-converting enzyme. *(From reference 7.)*

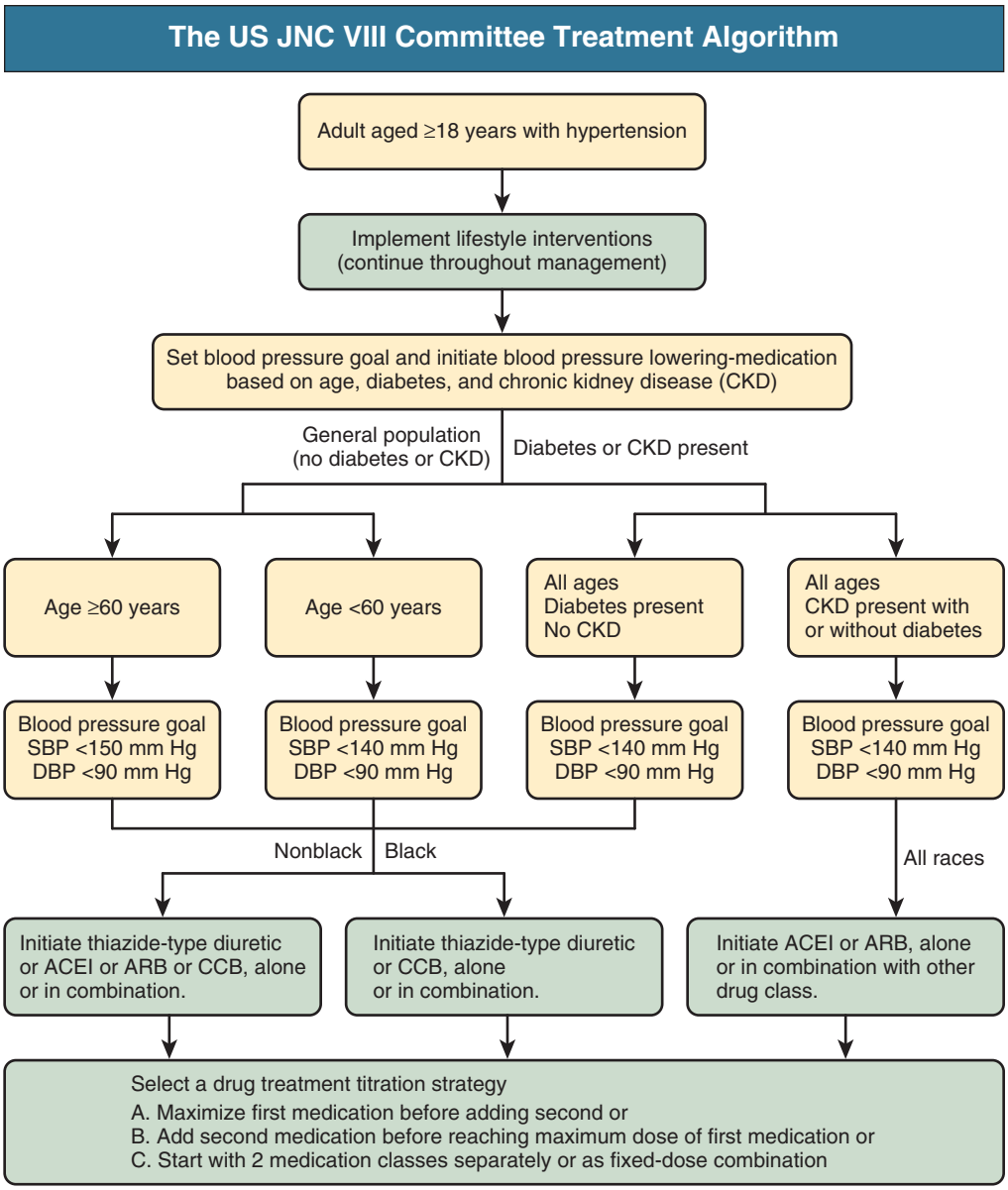

Figure 36-7 **The U.S. JNC VIII Committee treatment algorithm.**

and therefore unlikely to be controlled with monotherapy. The concept of initial therapy with a two-drug combination has in part been driven by concern that the upward titration of treatment in people at high risk may be too slow and leave them at risk for too long. A two-drug combination is also logical because the response to a single drug is often limited by counteractivation of pressor systems that limit the effectiveness of monotherapy. This also explains why many BP-lowering drugs in monotherapy have a relatively flat dose-response curve. For example, sodium and water loss caused by diuretics or vasodilation with CCBs will activate RAAS, which limits the BP lowering. Thus, low-dose two-drug combination therapy is likely (1) to produce much greater BP lowering, (2) to reduce heterogeneity in the BP-lowering response, and (3) to have a more effective dose-response to upward titration of either component. The main concern has been safety and tolerability with regard to potentially large initial BP falls in treatment-naive patients. It seems inevitable that low-dose combinations will become more popular as an initial therapy option for a greater proportion of patients, with the preferred combinations likely to be RAAS blockade plus diuretic and RAAS blockade plus CCB.

Combining Renin-Angiotensin-Aldosterone System Blockade?

The popular view that RAAS blockade is an important way of preventing or regressing hypertension-mediated structural and functional damage led to suggestions that different strategies to block RAAS should be combined to deliver more effective RAAS blockade. Data from the ONTARGET and ALTITUDE trials demonstrated that dual RAAS blockade in high-risk patients with an ACE inhibitor plus ARB combination in ONTARGET,[27] or an ACE inhibitor or ARB plus a DRI in ALTITUDE,[28] was no more effective than RAAS monotherapy alone at preventing major CV events in a high-risk population of patients, including those with diabetes.[28] Moreover, in both studies, the risk of adverse events, especially renal impairment, was greater with the dual RAAS blockade strategy. These findings suggest that dual RAAS blockade should not be routinely used for the management of patients with primary hypertension and especially those with diabetes or renal impairment. All guidelines now concur specifically that two different classes of RAAS blockers, ACE-inhibitors, or ARBs or Direct Renin Inhibitors, should not be combined for the treatment of hypertension.

Considerations in the Patient with Resistant Hypertension

Patient Factors	Secondary Causes of Resistant Hypertension	Concomitant Medications that May Raise BP	Causes of "Pseudoresistant Hypertension"
Demographics	***Common Causes***	***Prescription***	***Poor Patient Adherence to Medications***
Older age, especially over 75 Obesity Women > men More common in blacks Excess dietary sodium High baseline BP and chronicity of uncontrolled hypertension	Primary hyperaldosteronism (Conn adenoma) Atherosclerotic renovascular disease Sleep apnea CKD	Oral contraceptives NSAIDs Sympathomimetics (e.g., decongestants in cold remedies) Cyclosporine Erythropoietin Corticosteroids (e.g., prednisone, hydrocortisone)	Check BP response to directly observed medication.
Concomitant Disease	***Uncommon Causes***	***Nonprescription***	***Errors in BP Measurement***
Target organ damage: LVH or CKD Diabetes Atherosclerotic vascular disease Aortic stiffening	Pheochromocytoma Aortic coarctation Cushing disease Hyperparathyroidism	Drug abuse (e.g., cocaine, amphetamines) Excess licorice ingestion Herbal remedies (e.g., ephedra, also known as ma huang)	Including BP cuff too small for arm circumference
			White Coat Hypertension
			Check BP with ABPM or home BP measurements.

Table 36-7 Considerations in diagnosis and treatment of patient with resistant hypertension. *BP,* Blood pressure; *ABPM,* ambulatory blood pressure monitoring; *CKD,* chronic kidney disease; *LVH,* left ventricular hypertrophy; *NSAIDs,* nonsteroidal anti-inflammatory drugs. *(Modified from reference 18.)*

Resistant Hypertension

Resistant hypertension has been defined as BP that remains above goal despite the concurrent use of three antihypertensive agents of different classes, which would usually include a thiazide-like diuretic. Indeed, the U.S., European, and UK guidance all suggest that one of the three agents should be a thiazide-like diuretic and that all agents should be prescribed at optimal doses.[8,10,19] The definition could have been even more prescriptive, as in the NICE guidelines,[10] by suggesting that the three drugs would usually comprise A + C + D in best tolerated doses. Most of these people will be older, often obese, and invariably with evidence of target organ damage. In the absence of evidence of target organ damage, white coat hypertension should be excluded by 24-hour ambulatory monitoring. Other causes of resistant hypertension should also be considered (Table 36-7).[18]

The evidence base from which to define the optimal treatment of resistant hypertension is limited. Most patients with drug-resistant hypertension are likely to be retaining sodium and will respond to further diuretic therapy. This can be achieved by further increasing the dose of the thiazide/thiazide-like diuretic or using low-dose spironolactone (e.g., 25 mg/day) or amiloride (10 to 20 mg/day), with careful monitoring of electrolytes.[18] For some patients with severe drug-resistant hypertension, it may be necessary to use a combination of minoxidil, loop diuretic, and β-blocker to improve BP control.

Medication to Reduce Cardiovascular Risk

Blood pressure should not be treated in isolation, and treatment should be considered part of a more comprehensive strategy to reduce CVD risk. Patients at high risk, that is, those with established CVD, target organ damage, or diabetes, and those with a calculated CVD risk that is elevated (e.g., ≥20% over 10 years) should be considered for additional interventions to reduce risk.[34] These include reinforcement of lifestyle advice, especially smoking cessation, and treatment with statin therapy to further reduce the risk of stroke and coronary disease. In studies, routine use of statins to reduce total cholesterol values by 40 mg/dl (~1 mmol/l) has been associated with a reduction in the risk of ischemic heart disease events by about one third and of stroke by about one fifth, over and above the benefit already accrued from BP lowering.[34,35] Moreover, the relative risk reduction associated with statin therapy in higher-risk hypertensive patients was not dependent on a high baseline cholesterol value. Higher-risk hypertensive patients should also be considered for treatment with antiplatelet drugs once BP has been controlled.

Follow-up

In the early stages of treatment, the frequency of monitoring will be determined by the patient's response to therapy, the comorbidities, and the complexity of the treatment regimen required to control the BP. Once BP is controlled, patients should be reevaluated at least annually for a formal review, and most will be reevaluated every 6 months. Patients are increasingly monitoring their own BP in the intervening periods, and this trend is likely to increase.

Withdrawal of Therapy

Most patients with hypertension require lifelong therapy. Some with grade 1 hypertension who make major adjustments to their lifestyle may obtain sufficient fall in their BP to warrant safe withdrawal of monotherapy. However, patients with target organ damage or those at high CVD risk should not usually have their therapy withdrawn unless there is a compelling clinical reason to do so.[7-9] In patients with previously severe hypertension that has subsequently been well controlled, treatment withdrawal may not always result in an immediate increase in BP. After treatment withdrawal, BP can sometimes take many months to rise progressively back to dangerously high pretreatment values. Any patient who discontinues therapy must remain under review with regular BP monitoring. All but a very few will require treatment again.

Indications for Specialist Referral

Referral to a specialist center is sometimes indicated for the patient in management of hypertension. Indications include uncertainty about the decision to treat, investigations to exclude secondary hypertension, severe and complicated hypertension, and resistant hypertension (Box 36-2).

Hypertension in People of Black African Origin

Hypertension is more prevalent in blacks, is associated with more target organ damage, and consequently carries a worse prognosis,

Indications for Specialist Referral for Patients with Hypertension

Urgent Treatment Needed

Accelerated hypertension (severe hypertension with grade III or IV retinopathy)

Particularly severe hypertension (>220/120 mm Hg)

Impending complications (e.g., transient ischemic attack, left ventricular failure)

Possible Underlying Cause

Any clue in history or examination of a secondary cause (e.g., hypokalemia with increased or high-normal plasma sodium [Conn syndrome])

Elevated serum creatinine

Proteinuria or hematuria

Sudden onset or worsening of hypertension

Resistance to multidrug regimen (i.e., ≥3 drugs)

Young age (any hypertension <20 years; needing treatment <30 years)

Therapeutic Problems

Multiple drug intolerance

Multiple drug contraindications

Persistent nonadherence or noncompliance

Special Situations

Unusual blood pressure variability

Possible white coat hypertension

Hypertension in pregnancy

Box 36-2 Indications for specialist referral for patients with hypertension.

with a particularly high risk of stroke.[37] Black patients as a group tend to respond better to diuretics, CCBs, and dietary salt restriction than Caucasian patients. ACE inhibitors, ARBs, and β-blockers are generally less effective as initial therapy in black patients but become more effective in combination with diuretics or CCBs.

Hypertension in Older People

If a BP of 140/90 mm Hg or higher is used to define hypertension, more than 70% of people older than 60 years will be hypertensive, the majority of these patients having isolated systolic hypertension.[38] Surveys suggest that physicians consistently underestimate the risks and undertreat hypertension in older people. However, important considerations in treating older people include the following.

1. The arterial wall stiffening that gives rise to systolic hypertension and increased pulse pressure (isolated systolic hypertension) is also associated with impaired baroreflex sensitivity with increased risk of orthostatic hypotension. Thus, it is important to record lying and standing BP readings in elderly patients.
2. Estimated GFR declines with age, with impaired renal conservation of sodium and fluid in the face of depletion. Elderly patients are therefore more subject to volume depletion as a result of diuretic therapy.
3. Clearance of drugs and their active metabolites is decreased as a result of declining hepatic and renal function.
4. Cardiac function and reserve are often reduced, and patients are therefore much more likely to develop cardiac failure. This explains why end point trials of hypertension treatment have consistently shown reductions in morbidity and mortality from cardiac failure.
5. Comorbidity is much more common in elderly patients.
6. Communication and adherence with therapy may be more difficult with decline in cognitive function. Some evidence from clinical trials suggests that this decline may be slowed by antihypertensive treatment.

Despite these considerations, elderly patients tolerate BP-lowering medications well, and the benefits of BP reduction are impressive with regard to reductions in morbidity and mortality from stroke, ischemic heart disease, and heart failure. As a general rule, drug regimens should be as simple as possible and dosages increased more gradually. The greatest danger results from lowering of blood pressure too rapidly. Until recently, there was uncertainty about the risks and benefits of treating hypertension in the very elderly population, that is, those older than 80 years. The HYVET study in this age group confirmed that treatment is well tolerated and associated with impressive reductions in the risk of stroke, heart failure, and mortality.[17] Thus, there is no reason to manage very elderly patients any differently from those who are not as old. Biologic rather than chronologic age should be the deciding factor in initiating antihypertensive treatment.

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CHAPTER 37

Evaluation and Treatment of Hypertensive Urgencies and Emergencies

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The term *malignant hypertension* first appeared in 1928 and described patients with extremely high blood pressure (BP) values, to emphasize that because of rapid target organ damage, their average prognosis was similar to that of most cancer patients.[1] Subsequently, malignant (or accelerated) hypertension was used to describe patients with greatly elevated BP and vascular damage that could manifest as retinal hemorrhage/exudate and papilledema, usually associated with encephalopathy, acute kidney injury, and microangiopathic hemolytic anemia.[2,3] However, dramatic advances in both in-hospital and outpatient treatment of hypertensive emergencies have led to an improved prognosis, that is, a decrease in 1-year mortality from 80% in 1928 to 50% in 1955 and to less than 10% after 1990.[4,5] Thus, terms such as malignant and accelerated hypertension have been replaced by hypertensive emergency and hypertensive urgency.

Marked elevations in systolic and diastolic BP, usually above 180/120 mm Hg, can be classified as either emergencies or urgencies. A *hypertensive emergency* is defined as a marked elevation in BP complicated by evidence of acute target organ damage, such as coronary ischemia, dissecting aortic aneurysm, pulmonary edema, hypertensive encephalopathy, cerebral hemorrhage, and eclampsia. In hypertensive emergency, BP should be reduced by at least 20 to 40 mm Hg within 10 to 30 minutes using parenteral drug therapy in an intensive care unit (ICU) to limit end-organ damage. *Hypertensive urgency* is a clinical setting of significant BP elevation without acute target organ dysfunction. The approach to hypertensive urgency is a gradual BP reduction within hours, usually with oral medications.[4,6-8]

ETIOLOGY AND PATHOGENESIS

Hypertensive emergencies and urgencies can develop *de novo* in normotensive individuals or can complicate underlying primary or secondary hypertension.[4,8] Box 37-1 shows the most common etiologies of hypertensive crises. In some hypertensive emergencies, an underlying condition is the clear cause of acute BP elevation. In acute glomerulonephritis, renal crisis (in patients with scleroderma), or renal artery stenosis, severe BP elevations are evoked through increased activity of the renin-angiotensin system (RAS). In pheochromocytoma, cocaine intoxication, or spinal cord injury, acutely elevated BP is the result of excess catecholamine release. In other patients, acute sustained elevations in BP itself are the etiologic factor resulting in conditions such as hypertensive encephalopathy or acute left ventricular failure and pulmonary edema. In some cases, however, it may be difficult to differentiate whether BP elevation is the cause or the result of a hypertensive emergency. Thus, a careful diagnostic evaluation of hypertensive emergencies and urgencies is essential to guide proper treatment.

A hypertensive emergency can occur in various clinical settings, but the most common is chronic, often untreated or poorly controlled hypertension in a patient whose usual BP is above 180/120 mm Hg. In many of these patients, chronically elevated BP does not affect target organ perfusion because of autoregulation. *Autoregulation* is the ability of blood vessels to dilate or to constrict in response to changes in perfusion pressure and thereby maintain normal organ perfusion. This mechanism is present in the brain and kidneys and involves L-type calcium channels.[9] Arteries from normotensive individuals can maintain flow over a wide range of mean arterial pressures, 80 to 150 mm Hg, associated with systolic BP of around 90 to 180 mm Hg. Chronic BP elevations cause compensatory functional and structural changes in the arteriolar circulation and shift the autoregulatory curve to the right, which allows hypertensive patients to maintain normal perfusion and avoid excessive blood flow at higher BP levels.[3,10] Over time, the structural and functional changes in cerebral and renal arterioles may lead to a progressive inability of the arterioles to autoregulate properly[8,9] (Fig. 37-1).

Target organ damage associated with hypertensive emergency results from the inability of autoregulatory mechanisms to maintain normal perfusion pressures in certain vascular beds (especially of brain and kidney) when BP rises above the autoregulatory range.[10] The resultant endothelial injury causes a loss of endothelial antithrombotic properties, with activation of platelets and the coagulation cascade, increased vascular wall permeability, and vascular smooth muscle cell proliferation culminating in an increase of tissue ischemia and ultimately fibrinoid necrosis. This is coupled with activation of hormonal systems and release of vasoactive substances (RAS, catecholamines, endothelin, vasopressin) that maintain a vicious cycle of elevated BP and vascular injury.[3,8]

The typical structural changes associated with hypertensive emergencies are fibrinoid necrosis of small arteries and arterioles in the brain and kidney (Fig. 37-2). Other findings may show injury of the affected organs (e.g., cerebral edema).[3,10] Hypertensive emergency may rarely present as a thrombotic microangiopathy, in particular if associated with scleroderma (see Chapter 29).

In normotensive or minimally hypertensive individuals, such as children or pregnant women, the symptoms and signs of a hypertensive emergency occur at lower BP levels than in hypertensive patients because adaptive chronic vascular changes are absent. In most patients, however, the development of a hypertensive emergency occurs in the presence of chronic hypertension. This may relate to other mechanisms contributing to impaired autoregulation, such as progressive arteriolar disease (both cerebral and renal circulation) and

Common Hypertensive Emergencies and Urgencies

Non-compliance with Medication

Pain or Emotional Stress

Acceleration of Chronic Hypertension

With features of thrombotic microangiopathy (thrombocytopenia, hemolytic anemia, renal failure, ± papilledema, ± encephalopathy)

With papilledema ± encephalopathy

Cardiovascular Conditions

Acute myocardial ischemia/infarction caused by coronary artery disease

Acute left ventricular failure/pulmonary edema

Acute aortic dissection

Severe hypertension after coronary bypass or other vascular surgery

Epistaxis unresponsive to anterior/posterior packing

Renal Conditions

Acute or rapidly progressive glomerulonephritis

Renovascular hypertension

Renal crises from scleroderma or collagen vascular disease

Severe hypertension after kidney transplantation

Neurologic Conditions

Hypertensive encephalopathy

Intracerebral hemorrhage

Subarachnoid hemorrhage

Cerebral embolism or atherothrombotic cerebral infarction

Severe hypertension after thrombolysis for atherothrombotic stroke

Acute head trauma

Guillain-Barré syndrome

Excess Circulating Catecholamine Conditions

Pheochromocytoma crisis

Interactions of tyramine-containing foods with monoamine oxidase inhibitors

Rebound hypertension after sudden withdrawal of centrally-acting α_2-agonists (clonidine, methyldopa, or other)

Use of sympathomimetic drugs (phencyclidine, phenylpropanolamine, cocaine, or other)

Automatic hyperreflexia after spinal cord injury

Pregnancy-Related Condition

Eclampsia

Surgical Conditions

Severe hypertension in patients requiring immediate surgery

Perioperative hypertension

Postoperative bleeding from vascular suture lines

Hypertension after organ transplantation

Hypertension Associated with Severe Burns

Box 37-1 Common hypertensive emergencies and urgencies.

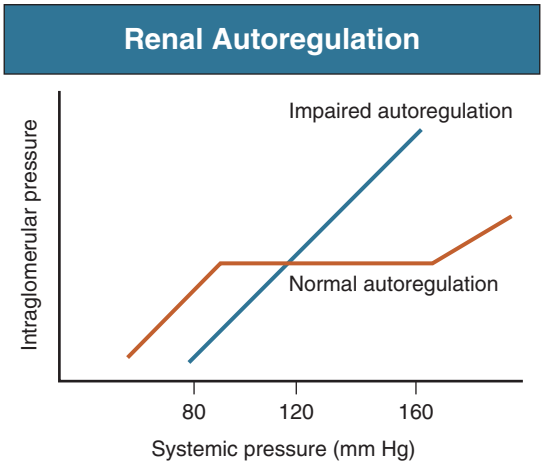

Figure 37-1 Renal autoregulation. Relationship of systemic to glomerular pressure in the setting of normal or abnormal renal autoregulation.

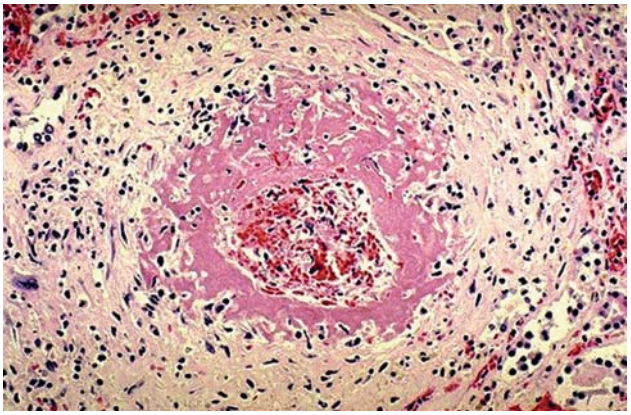

Figure 37-2 Fibrinoid necrosis. Micrograph shows a pink, homogeneous material in the renal interlobar artery of a patient with severe hypertensive emergency.

pharmacologically impaired autoregulation (e.g., use of dihydropyridine calcium channel blockers, or furosemide).

EPIDEMIOLOGY

The exact incidence of hypertensive emergencies and urgencies or the demographic distribution is not known, but an estimated 1% to 2% of individuals with hypertension develop hypertensive crises.[11] One study with more than 14,000 emergency department (ED) visits showed that hypertensive urgencies accounted for 76% and emergencies for 24% of hypertension-related visits.[12] In this study, the most common presentations of hypertensive emergency were associated with cerebral infarction (24.5%), acute pulmonary edema (22%), hypertensive encephalopathy (16%), and acute heart failure (14%), followed by myocardial infarction (12%), cerebral hemorrhage (5%), eclampsia (5%), and aortic dissection (2%). In a different series of 435 hypertensive ED visits, 40% were hypertensive urgencies, almost all with some degree of preexisting kidney disease, and 60% were emergencies.[13] Hospitalization for hypertensive emergency occurs at a rate of 1 to 2 cases per 1 million population per year in the United States.[10]

In developed countries, widespread use of antihypertensive agents has reduced the incidence of hypertensive emergencies, as supported by indirect observations.[10] Use of any antihypertensive drug reduces the risk of hypertensive emergency because poor treatment compliance and outpatient BP control are predictors of subsequent hypertensive crises.[14] Further, hospitalization for hypertensive emergency is more common in developing countries, ethnic minorities of developed countries,[5] and individuals of low socioeconomic status who often have poor BP control.

DIAGNOSTIC EVALUATION

The primary goal of the diagnostic process is differentiation of a true hypertensive emergency from a hypertensive urgency, because of the different therapeutic approaches. The second goal is rapid assessment of the type and severity of ongoing target organ damage. In some hypertensive emergencies, the history (e.g., acute head trauma, preeclampsia, scleroderma) or overt symptoms and signs (e.g., chest/back pain, dyspnea, throbbing abdominal mass) may guide the diagnosis; whereas in other cases (e.g., severe hypertension with altered mental status), the evaluation is more comprehensive.

The diagnostic approach begins with the patient's history, with attention to duration, severity, and treatment of preexisting hypertension and associated conditions[6,8] (Box 37-2). BP measurements should be performed in both arms (if possible, in both sitting and standing positions) and a leg[2] (see Chapter 33). A careful examination and assessment of cardiac, pulmonary, peripheral vascular, and neurologic systems with assessment of mental status should follow, along with a thorough funduscopic (ophthalmoscopic) examination for hemorrhages, exudates, and papilledema.

Signs of secondary hypertension should not be missed in this initial examination. For example, an abdominal bruit may indicate renovascular hypertension; a palpable abdominal mass suggests abdominal aneurysm or polycystic kidneys; a radial-femoral pulse delay suggests aortic coarctation; abdominal striae and central obesity are observed with Cushing syndrome; and exophthalmos may indicate hyperthyroidism. Patients with features of hemolytic anemia and thrombocytopenia should be evaluated for causes of thrombotic microangiopathy.

The initial laboratory studies in a hypertensive emergency include a complete blood count with peripheral smear, urinalysis, creatinine and urea concentration, and electrolyte values.[6,8] Comparison of kidney function with a patient's recent measurement is important. Severe hypertension accompanied by acute deterioration in kidney function, microscopic hematuria with red blood cell casts, or nephritic urine sediment suggests acute glomerulonephritis. If a secondary form of hypertension is suspected, samples for plasma renin activity, aldosterone concentration, and plasma free catecholamines and metanephrines should also be drawn *before* initiation of treatment. Testing should be performed with the patient supine, and ideally, the patient should not be receiving β-blockers, especially labetalol, because of false-positive metanephrine and total catecholamine values. Electrocardiography to rule out myocardial ischemia and left ventricular strain or hypertrophy, as well as chest radiography, should be performed in every patient.[6] Renal ultrasound is also useful to rule out abnormalities such as differences in size or perfusion, especially in patients with altered renal function or with abnormalities on urinalysis.

Neurologic syndromes associated with hypertension, including subarachnoid hemorrhage, intracerebral hemorrhage, thrombotic stroke, and hypertensive encephalopathy, are difficult to distinguish from one another. Computed tomography (CT) or magnetic resonance imaging (MRI) provides a definite diagnosis of a hemorrhagic or thrombotic stroke. Echocardiography, thoracoabdominal CT or MRI, or abdominal ultrasound may be needed in patients with suspected aortic dissection or pheochromocytoma.[6]

Diagnostic Evaluation for Hypertensive Emergencies and Urgencies

History

Previous diagnosis and treatment of hypertension

Symptoms, previous diagnoses, and treatment of cardiac, cerebral, renal, and visual damage

Intake of pressor agents: sympathomimetics, illicit substances

Repeated Blood Pressure Measurements (first measurement in both arms)

Physical Examination

Cardiac

Vascular

Pulmonary

Neurologic

Optic fundi

Laboratory Studies

Complete blood count (red cells, platelets, white cells), urinalysis, creatinine, urea, electrolytes

Plasma renin activity, aldosterone, and catecholamines if secondary hypertension is suspected

Electrocardiography

Chest Radiograph

Further Investigations (according to clinical presentation)

Renal ultrasound

Brain CT scan or MRI

Echocardiography (transthoracic, transesophageal)

Thoracoabdominal CT scan or MRI

Box 37-2 Diagnostic evaluation for hypertensive emergencies and urgencies. *CT,* Computed tomography; *MRI,* magnetic resonance imaging.

TREATMENT

General Principles for Managing Hypertensive Emergencies

Although therapy with parenteral antihypertensive agents may be initiated in the ED, patients with a hypertensive emergency should be admitted to an ICU for continuous BP monitoring, clinical surveillance, and continued parenteral administration of an appropriate agent (Tables 37-1 and 37-2). Specific BP levels do not determine the severity and the emergency of the situation because the autoregulatory structural and functional changes may vary among individuals, such that some may develop target organ damage at lower BP.

Understanding of autoregulation is crucial for therapeutic decisions; sudden lowering of BP into a "normal" range could lead to inadequate tissue perfusion.[10] Clinical data document that lowering BP in hypertensive emergencies is beneficial: papilledema and exudates regress, hypertensive encephalopathy vanishes, pulmonary edema resolves, and renal function improves. However, there is also evidence that abrupt lowering of BP can be harmful. For example, the use of sublingual nifedipine with potent but unpredictable BP lowering may shunt blood away from the penumbra of the brain

Treatment of Hypertensive Emergencies

Drug	Mechanism of Action	Dose	Onset of Action	Duration of Action	Adverse Effects*	Special Indications
Vasodilators						
Nicardipine hydrochloride	Calcium channel blocker	5-15 mg IV every hour	5-15 min	15-30 min, may exceed 4 hr	Tachycardia, headache, flushing, nausea, vomiting, local phlebitis	Most hypertensive emergencies except acute heart failure
Fenoldopam mesylate	Dopamine-1 receptor agonist	0.1-0.3 μg/kg/min IV infusion	>5 min	30 min	Tachycardia, headache, nausea, flushing	Most hypertensive emergencies; caution with glaucoma
Clevidipine butyrate	Calcium channel blocker	1-2 mg/hr IV infusion; increase every 5-10 min up to 16 mg/hr	2-4 min	5-15 min	Tachycardia, headache, flushing, heart failure deterioration	Most hypertensive emergencies; caution with severe aortic stenosis, acute heart failure
Sodium nitroprusside	↑ Cyclic GMP, blocks intracellular Ca^{2+} increase	0.25-10 μg/kg/min IV infusion†	Immediate	1-2 min	Nausea, vomiting, muscle twitching, thiocyanate and cyanide intoxication, impaired cerebral autoregulation, coronary steal syndrome	Caution in situations associated with CNS manifestations, hepatic or renal failure; probably should be avoided if given other agents, especially fenoldopam
Nitroglycerin	↑ Nitrate receptors	5-100 μg/min IV infusion	2-5 min	5-10 min	Headache, vomiting, methemoglobinemia, tachyphylaxis, tolerance with prolonged use	Coronary ischemia, pulmonary edema
Enalaprilat	ACE inhibitor	1.25-5 mg every 6 hr IV	15-30 min	6-12 hr	Precipitous fall in BP in high-renin states, variable response, acute renal failure	Acute left ventricular failure; avoid in acute myocardial infarction
Isradipine	Calcium channel blocker	0.15 μg/kg/min IV, increase by 0.0025 μg/kg/min every 15 min. Maintenance infusion 0.15 μg/kg/min	1-10 min	1-2 hr	Headache, flushing, peripheral edema, dizziness, tachycardia	Perioperative, pregnancy
Hydralazine hydrochloride	Opens K^+ channels	10-20 mg IV	10-20 min	1-4 hr	Tachycardia, flushing, headache, vomiting, aggravation of angina	Must be given with concomitant IV β-blockers to avoid precipitation of angina but *not* a preferred initial choice or treatment
Adrenergic Inhibitors						
Labetalol hydrochloride	α_1-, β-Blocker	20-80 mg IV bolus every 10 min *or* 0.5-2 mg/min IV infusion	5-10 min	3-6 hr	Nausea, vomiting, scalp tingling, bronchoconstriction, dizziness, heart block, heart failure	Most hypertensive emergencies except acute heart failure
Esmolol hydrochloride	β_1-Blocker	0.5-2.0 mg/min IV infusion *or* 250-500 μg/kg/min IV bolus, then 50-100 μg/kg/min by infusion; may repeat bolus after 5 min or increase infusion to 300 μg/min	1-2 min	10-30 min	Nausea, asthma, first-degree heart block, heart failure, thrombophlebitis, COPD	Aortic dissection, perioperative, increased heart output or heart rate
Urapidil	α_1-Blocker, serotonin (5-HT1A) receptor agonist	12.5-25 mg IV bolus followed by 5-40 mg/hr IV infusion	3-5 min	4-6 hr	Headache, dizziness	Perioperative
Phentolamine	α-Blocker	5-15 mg IV bolus	1-2 min	10-30 min	Tachycardia, flushing, headache	Catecholamine excess

Table 37-1 Pharmacologic agents for treatment of hypertensive emergencies. *IV,* Intravenous(ly); *GMP,* guanosine monophosphate; *CNS,* central nervous system; *ACE,* angiotensin-converting enzyme; *BP,* blood pressure; *COPD;* chronic obstructive pulmonary disease. *Hypotension may occur with all agents. †Requires light-resistant delivery system.

Management of Specific Types of Hypertensive Emergencies

Type of Emergency	First-Choice Drug(s)	Second-Choice or Additional Drug(s)	Drugs to Avoid	Aim of BP Reduction
Cardiac				
Coronary ischemia/ infarction	Nitroglycerin, nicardipine, clevidipine	Sodium nitroprusside, labetalol, esmolol if heart failure absent	Diazoxide, hydralazine	Improvement in cardiac perfusion
Heart failure, pulmonary edema	Nitroglycerin, fenoldopam	Sodium nitroprusside, enalaprilat; diuretics	Diazoxide, hydralazine; β-blockers	Decrease in afterload
Aortic dissection	Labetalol or combination of esmolol with sodium nitroprusside or fenoldopam or nicardipine		Diazoxide, hydralazine	Decrease of aortic wall stress with systolic BP reduction <100-120 mm Hg in 20 min (if possible)
Renal				
Acute glomerulonephritis, collagen vascular renal disease, or renal artery stenosis	Fenoldopam	Nicardipine, labetalol, clevidipine; diuretics for volume overload	Sodium nitroprusside; ACE inhibitors and ARBs	Reduction in vascular resistance and volume overload without compromise of renal blood flow or glomerular filtration rate
Scleroderma crisis	Enalaprilat or other ACE inhibitor	Angiotensin receptor blocker, fenoldopam	Corticosteroids,* diuretics	Decrease in BP to <140/90 mm Hg with long term goal of <130/85
Neurologic				
Hypertensive encephalopathy	Nicardipine, fenoldopam, labetalol, clevidipine	Nitroprusside, esmolol, urapidil		20%-25% reduction in mean BP over 1-2 hr
Ischemic stroke	Nicardipine, labetalol, clevidipine	Nitroprusside, nimodipine, esmolol, urapidil		Reduction of BP if above 220/120 mm Hg (mean BP >130) by no more than 10%-15% within first 24 hours to avoid impairing cerebral blood flow in penumbra
Intracerebral hemorrhage	Nicardipine, labetalol, clevidipine	Fenoldopam, nitroprusside, esmolol, urapidil, nimodipine for subarachnoid hemorrhage		Decrease in BP below 185/110 to prevent further bleeding and hypoperfusion. For subarachnoid hemorrhage in normotensive patients, reduction to systolic BP of 130-160 mm Hg
Catecholamine Excess States				
Pheochromocytoma	Phentolamine or labetalol	β-Blocker in the presence of phentolamine	Diuretics	Control of BP paroxysms from sympathetic stimulation
Ingestion of cocaine or other sympathomimetic	Phentolamine or labetalol	β-blocker in the presence of phentolamine	Diuretics	Control of BP paroxysms from sympathetic stimulation
Perioperative/Postoperative Hypertension				
Coronary artery surgery	Nitroglycerin, nicardipine, clevidipine	Esmolol, labetalol, fenoldopam, isradipine, urapidil		Protection against target organ damage and surgical complications (keep BP<140/90 or mean BP <105 mm Hg)
Non-cardiac surgery	Esmolol, labetalol, fenoldopam, nicardipine, clevidipine, urapidil, nitroglycerin			Protection against target organ damage and surgical complications
Pregnancy Related				
Eclampsia	Labetalol, urapidil	Isradipine, $MgSO_4$, methyldopa, long-acting nifedipine	Nitroprusside, ACE inhibitors, ARBs	Control BP (typically <90 mm Hg diastolic but often lower) and protect placental blood flow

Table 37-2 Management of specific types of hypertensive emergencies. *BP,* Blood pressure; *ACE,* angiotensin-converting enzyme; *ARBs,* angiotensin receptor blockers. *Corticosteroids may worsen hypertension in scleroderma renal crisis.

(ischemic penumbra), resulting in a vascular infarct.[15] Thus, the goal of antihypertensive therapy is not to normalize BP rapidly, but to prevent target organ damage by gradually reducing BP while minimizing the risk of hypoperfusion.

For most patients with hypertensive emergency, the mean BP should be reduced by no more than 20%-25% within the first hour.[6] A diastolic BP target between 100 and 110 mm Hg or a reduction of 25% compared with the initial baseline, whichever is higher, is an appropriate goal within the next 2 to 6 hours. Reduction of diastolic pressure to less than 90 mm Hg or by 35% of the initial mean BP has been associated with major organ dysfunction, coma, and death. If the degree of BP reduction is well tolerated and the patient is clinically stable, further gradual reductions toward levels below 140/90 mm Hg should be implemented within the next 24 to 48 hours.

An important consideration before initiation of intravenous (IV) therapy is assessment of the patient's volume status. Because of pressure natriuresis, patients with hypertensive emergency may be volume depleted, and diuretics should not be used; rather, fluid administration may help restore organ perfusion and prevent a precipitous fall in BP.[8] Diuretics especially should be avoided in hypertensive emergencies because of catecholamine excess states (pheochromocytoma, monoamine oxidase inhibitor crisis, cocaine intoxication), since these patients are usually volume depleted.

Major exceptions to these treatment recommendations include (1) patients with acute stroke, in whom there is no clear evidence to support immediate BP lowering, and a more cautious approach is needed (see Chapter 42); (2) patients with aortic dissection, who should have their systolic BP lowered to less than 100 mm Hg if tolerated; and (3) patients in whom BP should be further lowered to enable the use of thrombolytic agents.[6,11]

After BP has been controlled for a suitable period, typically 12 to 24 hours, allowing autoregulation to reestablish, the IV medication is gradually reduced and replaced by oral agents. Typically, a calcium channel blocker (CCB), α- and β-blocker, or RAS blocker can be used, depending on the suspected cause and possible ongoing investigations for secondary hypertension.[10]

Specific Aspects of Antihypertensive Drug Use for Hypertensive Emergencies

The need for gradual and tightly controlled BP reduction requires the use of short-acting IV drugs (Table 37-1), the effects of which can be promptly reversed if response is excessive. Previous systematic reviews and meta-analyses showed minor differences in the degree of BP lowering and no differences in morbidity or mortality among these agents, because of the relative paucity of large, randomized controlled trials (RCTs) with appropriate follow-up.[16,17] Thus, treatment practices were mainly empiric. Recent evidence, however, suggests benefits of novel agents, a result expected to change clinical practice.

For several years, *sodium nitroprusside* was considered the first-choice drug for almost all hypertensive emergencies. It is easily titrated, is inexpensive, and has a long record of effectiveness.[6,10,18] It also has several drawbacks, including accumulation of toxic metabolites (thiocyanate and cyanide) when used for more than 48 hours, especially in patients with renal or hepatic dysfunction, and the need for invasive BP monitoring and an administration system that protects it from light. High-dose nitroprusside increases intracranial pressure. It also obliterates cerebral autoregulation and reduces regional coronary blood flow. These attributes of nitroprusside limits its usefulness in patients with neurologic complications or acute coronary syndromes.[8,11]

Clevidipine butyrate is a new, ultra-short-acting (within 1 to 2 minutes) third-generation CCB that acts through inhibition of extracellular calcium influx via the L-type channel and reduces peripheral vascular resistance without affecting venous vascular tone or cardiac filling pressure. Clevidipine is rapidly hydrolyzed by blood esterases, and thus its metabolism is not affected by renal or hepatic function.[8,11,19] In clinical studies, clevidipine was shown to be effective and safe in the control of perioperative hypertension and hypertensive emergencies.[19,20] The Evaluation of Clevidipine in the Perioperative Treatment of Hypertension Assessing Safety Events (ECLIPSE) report included three randomized trials with more than 1500 patients with perioperative acute hypertension that compared clevidipine, nitroglycerin, sodium nitroprusside, and nicardipine.[21] In this study, no difference was observed among clevidipine, nitroglycerin, or nicardipine in the primary end point of death, myocardial infarction, stroke, or renal dysfunction at 30 days, but clevidipine was more effective in maintaining BP within the prespecified target range and, most important was associated with lower mortality than nitroprusside.[21] In view of these data, nitroprusside should be abandoned for the treatment of hypertensive emergencies.[7,11]

Nicardipine is a dihydropyridine CCB with intermediate onset and duration of effect, prolonged half-life, and strong cerebral and coronary vasodilatory activity. It is useful for most hypertensive emergencies, especially in patients with coronary artery disease. Nicardipine potentiates curare effects and interacts with inhalant anesthetics.[10,18] In a recent randomized controlled trial of 226 patients with acute systolic BP of 180 mm Hg or higher, those receiving nicardipine reached physician-specified target range slightly more often (92% vs. 83%, $P = .039$) than those receiving labetalol.[22]

Fenoldopam mesylate is a selective agonist of dopaminergic 1 receptors located mainly in the renal and splanchnic arteries, with lesser density in the coronary and cerebral arteries.[8,10,18] IV fenoldopam does not cross the blood-brain barrier and has no central nervous system activity because it is a poorly lipid-soluble molecule. In clinical studies, compared with sodium nitroprusside, fenoldopam demonstrated similar BP-lowering efficacy and beneficial renal effects (increased diuresis, natriuresis, creatinine clearance).[23] Thus, fenoldopam is mostly useful for BP reduction in patients with renal impairment, those with heart failure, and those undergoing vascular surgery. Fenoldopam must be administered with caution, if at all, to patients with glaucoma because it increases intraocular pressures.[10,18]

Labetalol is a nonselective α_1- and β-blocker (in 1:7 ratio) given intravenously that can be used in many hypertensive emergencies because it has rapid onset of action, potent and sustained effect, and low toxicity. Labetalol reduces peripheral vascular resistance without a reflex increase in systolic volume, while cerebral, renal, and coronary blood flow is maintained. Its main indications are aortic dissection, acute coronary syndromes, hypertensive encephalopathy, and adrenergic crisis. Labetalol can be also used in pregnancy-induced hypertensive crisis as little placental transfer occurs because of its negligible lipid solubility.[6,8,11] *Esmolol* is a β_1-blocker with an immediate onset and a short duration of action, whose metabolism is not dependent on renal or hepatic function. Esmolol is used particularly in patients with severe postoperative hypertension, and it can be useful in those with increased cardiac output and heart rate.[8,18] Both labetalol and esmolol are contraindicated in patients with heart failure or heart block. Labetalol may be used in chronic obstructive pulmonary disease if the patient has no history of an asthmatic component.[24]

Table 37-1 provides pharmacologic characteristics and adverse effects of other agents that have been used in the treatment of hypertensive emergencies. Table 37-2 includes a general guide for use of these drugs according to the type of hypertensive emergency.

Treatment of Hypertensive Urgencies						
Drug	**Mechanism of Action**	**Dose**	**Onset of Action**	**Duration of Action**	**Adverse Effects***	**Special Indications**
Captopril	ACE inhibitor	12.5-25 mg PO every 1-2 hr	15-30 min	4-6 hr	Angioedema, cough, acute renal failure	
Clonidine	Central α_2-agonist	0.1-0.2 mg PO every 1-2 hr	30-60 min	6-8 hr	Sedation, dry mouth, bradycardia, rebound hypertension after withdrawal	
Labetalol	α_1-, β-Blocker	200-400 mg PO every 2-3 hr	30-120 min	6-8 hr	Bronchoconstriction, heart block, congestive heart failure	
Furosemide	Loop diuretic	20-40 mg PO every 2-3 hr	30-60 min	8-12 hr	Volume depletion, hyponatremia, hypokalemia	
Isradipine	Calcium channel blocker	5-10 mg PO every 4-6 hr	30-90 min	8-16 hr	Headache, tachycardia, flushing, peripheral edema	

Table 37-3 Pharmacologic agents for treatment of hypertensive urgencies. Shown are short-acting agents that are commonly used in the emergency room setting. However, as noted in the text, sometimes longer-acting drugs can be used. *PO,* Taken orally.

Treatment of Hypertensive Urgencies

There is no proven benefit from rapid BP reduction in asymptomatic patients without evidence of acute target organ damage; thus, all authorities agree that BP lowering should occur over a longer time than for a hypertensive emergency. BP reduction to levels below 160/100 mm Hg may be accomplished within 2 to 4 hours in the ED with the oral drugs described later. This may be particularly important for patients without ongoing target-organ damage, who are judged to be at high risk for cardiovascular events over the next days because of severe hypertension (e.g., those with known history of aortic aneurysm, repeated pulmonary edema). However, there are many different types of patients who may present as a hypertensive urgency. Because there is no proven benefit from rapid reduction of BP in these patients, less aggressive lowering of BP (over several hours to days) is also proposed by some, using strategies like resumption of antihypertensive therapy (in nonadherent patients), initiation of antihypertensive therapy with long-acting agents (if patients are treatment naive), or addition of another antihypertensive drug (in patients who are currently treated). In short, the most important aspect of treatment of hypertensive urgency is not achieving a BP goal but rather ensuring adequate follow-up, generally within 1 week, to an appropriate site of care for chronic hypertension.[6,8,10]

Patients with hypertensive urgency should be provided a quiet room in which to rest because this maneuver was associated with BP fall ≥20/10 mm Hg in one third of such patients.[25] Another major factor to consider before prescribing medication is assessment of pain. Patients with severe pain not secondary to cardiac or cerebral origin should be given analgesics first to improve pain. If such patients present with hypertensive urgency and are given acute acting medications such as clonidine or labetalol, they could become hypotensive once pain is alleviated with nonsteroidal agents, opioids, or steroids.

The choice of drugs for treatment of hypertensive urgencies is much broader than for emergencies, because almost all antihypertensives lower BP effectively over a reasonable time. Captopril, clonidine, labetalol, and other short-acting drugs have been used most often (Table 37-3).[6,8] A careful history to assess chronic antihypertensive treatment and patient adherence to medication is critical for drug and dose selection, and clinical surveillance is always advisable during the first few hours after drug administration. In an acute situation, if uncertain whether the patient may have a pheochromocytoma, it is advisable to avoid β-blockers because they can increase BP. This includes labetalol because its α-blocking effect is very small. An α-blocker should always be a first-line drug in these patients.

Oral *captopril* is typically given in a 12.5- to 25-mg dose; angiotensin-converting enzyme (ACE) inhibitors must be used with caution because they can cause or exacerbate renal impairment in the occasional patient with critical renal artery stenosis.[3,6] Oral clonidine, 0.1 to 0.2 mg, is one of the most common agents used in this setting. However, patients should not be discharged taking clonidine if they have a history of nonadherence to drug regimens, because of the risk of rebound hypertension if clonidine is abruptly stopped. Furosemide can also effectively lower BP if elevated pressure is related to volume overload, especially if renal dysfunction is present. However, a common physiologic response of the kidney to elevated BP is natriuresis, so many patients, especially those with normal renal function, are volume depleted rather than volume expanded.[6,8]

Sublingual short-acting nifedipine, although once frequently used, is now contraindicated secondary to a higher incidence of stroke, myocardial infarction, and death related to precipitous hypotensive episodes after ED release.[15] However, intermediate-acting dihydropyridine CCBs, such as IV nicardipine, may be used. Longer-acting CCBs, such as once-daily nifedipine or nifedipine XL, amlodipine, and sustained-release isradipine, do not have a role in management of hypertensive urgencies or emergencies and are used only in long-term management of these patients.

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CHAPTER 38

Interventional Treatments for Resistant Hypertension

Henry Krum, Markus P. Schlaich, and Paul A. Sobotka

This chapter discusses novel procedure-based and device-based strategies in the management of systemic hypertension refractory to conventional treatment. Two of the most promising approaches are percutaneous renal sympathetic denervation and baroreceptor activation therapy.

PATHOGENESIS

Sympathetic Nervous System in Hypertension and Cardiovascular Disease

The contribution of sympathetic activation to the genesis and progression of systemic hypertension and cardiovascular disease (CVD) has been well recognized for many decades.[1] A stepwise increase in muscle sympathetic nerve activity (MSNA) occurs from normal blood pressure (BP), high-normal BP, white coat hypertension, borderline hypertension, and established hypertension, with or without left ventricular hypertrophy (LVH).[2] These data are supported by other measures of sympathetic activation in humans, specifically spillover of noradrenaline into plasma. In a study of renal spillover from the kidneys, a significant increase was noted in patients with primary hypertension compared with normotensive controls.[3] This increase was particularly prominent in younger hypertensive participants (20 to 39 years).

Renal Efferent Sympathetic Activity

Renal sympathetic efferent nerves modulate autonomic control of the kidney. Renin secretion is activated by β1-adrenoceptor stimulation, enhanced tubular sodium reabsorption by α1B-adrenoceptors and reduced renal blood flow by α1A-adrenoceptors[4] (Fig. 38-1). Thus, sympathetic innervation is critical to renal control of regulatory hormones, modulation of total body volume status, and effects on the pressure-natriuresis curve. Renal sympathetic denervation shifts the diuresis and natriuresis curves to the left[5]; that is, an increase in water and sodium excretion for the same renal perfusion pressure is achieved in the denervated compared to the innervated animal.

Abrogation or disruption of renal sympathetic efferents therefore represents an attractive therapeutic target in the management of disorders characterized by renal sympathetic nerve activation. This has been supported through the preclinical literature in both low-renin and high-renin models of hypertension in animals.[6]

Renal Afferent Sympathetic Activity

The kidney and pelvic region is highly innervated by mechanosensitive and chemosensitive nerve receptors.[7] Renal afferent nerves transmit this information to the central sympathetic nervous system, which in turn modulates activity of key organs, including heart, kidney, and vasculature (Fig. 38-2). Indeed, dorsal rhizotomy (afferent denervation) reduces BP in animals with renal disease[8]; the renal afferent denervation abrogates increased CNS catecholamine levels. In renal transplant patients, denervation through nephrectomy of the nonfunctioning kidney reduced both renal sympathetic efferent activity and BP.[9] Similarly, in patients with end-stage renal disease (ESRD) on dialysis, removal of the nonfunctioning kidney has simultaneously reduced MSNA and calf vascular resistance, confirming the kidney as a seminal source of sympathetic stimulation.[10]

Carotid Baroreflex Sensitivity

Abnormalities of the baroreflex are well described in the setting of systemic hypertension.[11] Arterial baroreceptors are rapidly reset in response to sustained BP elevation but also buffer short-term fluctuations in BP.[11] As BP increases, firing of baroreceptor afferents also increases. If BP elevation is sustained despite this, however, the baroreceptor response diminishes over time, and a new threshold for activation is established. Thus, baroreceptors become less sensitive to any given change in BP in patients with chronic hypertension. The reasons for this baroreceptor resetting are not well understood. This contribution of reduced baroreflex activity to chronic hypertension and its associated multiorgan involvement has been widely described.

SURGICAL SYMPATHETIC DENERVATION

In the era preceding the emergence of modern antihypertensive pharmacotherapy, surgical denervation of the renal arteries was perhaps the only effective approach to treating patients with significant elevations in BP. Case series comparing this surgical approach to medical therapies (such as existed) demonstrated about 50% improvement in survival with denervation in patients for the same starting BP values.[12] The magnitude of the BP reduction correlated with the starting preoperative mean BP. However, sympathetic denervation was accompanied by significant adverse events, limiting the clinical utility. In particular, patients experienced impotence, incontinence, and almost invariably, orthostatic hypotension, essentially rendering them unable to maintain upright posture for long periods.[13]

Percutaneous and Minimally Invasive Approaches to Renal Sympathetic Denervation

Novel approaches have been developed to achieve specific renal sympathetic denervation while avoiding the complications of the earlier

surgical approaches, as outlined earlier. Most of these approaches focus on the sympathetic nerve plexus that surrounds the main trunk of each renal artery. These nerves reside within the adventitia of the main artery (or immediately adjacent). These novel methods include various approaches to radiofrequency (RF) energy application, use of ultrasound waves, direct injection of neurotoxins such as guanethidine or ethanol, and even extracorporeal approaches that are completely noninvasive. By far the most advanced and best investigated of these strategies is percutaneous RF ablation[14] (see Fig. 38-2). This procedure involves cannulation of the femoral artery and subsequent placement of the catheter tip in the distal renal artery, where energy is applied to target adjacent sympathetic nerve trunks. The catheter is then withdrawn 1 to 2 cm and circumferentially rotated with further RF energy applications performed, such that four to six applications on average (often more) are applied to the individual renal artery. The same procedure is applied in both main renal arteries.

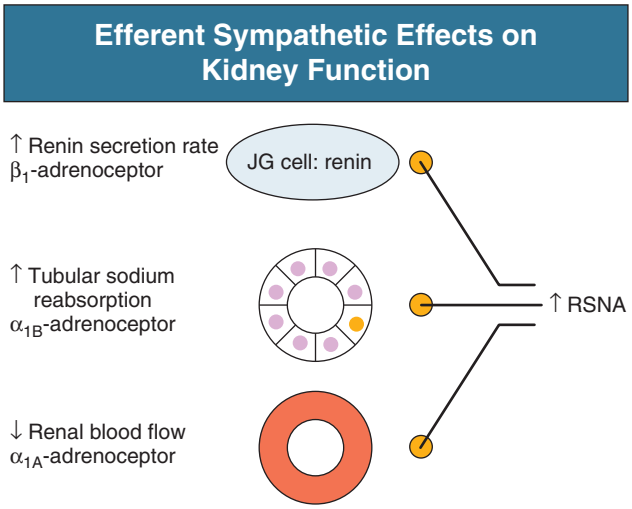

Figure 38-1 Efferent sympathetic effects on kidney function. *RSNA,* Renal sympathetic nerve activity; *JG,* juxtaglomerular.

Published Experience with Percutaneous Renal Sympathetic Denervation

Symplicity Hypertension 1 Study

Symplicity HTN-1 was a 12-month evaluation of safety and BP-lowering efficacy (without a control group) as a first-in-human experience with the denervation procedure.[15] Inclusion criteria involved patients with a systolic BP greater than 160 mm Hg despite three or more antihypertensive medications, including a diuretic or confirmed intolerance to medications. Furthermore, estimated glomerular filtration rate (eGFR) was required to be greater than 45 ml/min/1.73 m^2. The key exclusion criteria included known secondary causes of hypertension, type 1 diabetes mellitus, central sympatholytic drug use, and evidence of renovascular abnormalities, including renal artery stenosis, prior renal procedure, and dual renal arteries. Enrolled patients had a mean BP greater than 170 mm Hg systolic and 100 mm Hg diastolic, despite taking on average five antihypertensive drug classes. Almost all patients were taking ACE inhibitor and/or angiotensin receptor blocker (ARB) as well as diuretics, and 75% were taking β-blockers. After 12 months, BP was reduced by 27/17 mm Hg compared to baseline (Fig. 38-3). Limited ambulatory blood pressure monitoring (ABPM) data showed an increase in patients shifting from "nondipper" to dipper status with the procedure. However, the magnitude of the ABPM response to denervation in this study (and Symplicity HTN-2) was substantially less than that of office BP decreases, suggesting a "white coat" component may be contributory to the observed office response.

The key mechanistic question in Symplicity HTN-1 was whether sympathetic denervation of the kidney is achieved by the renal denervation (RDN) procedure. In humans, evidence of renal

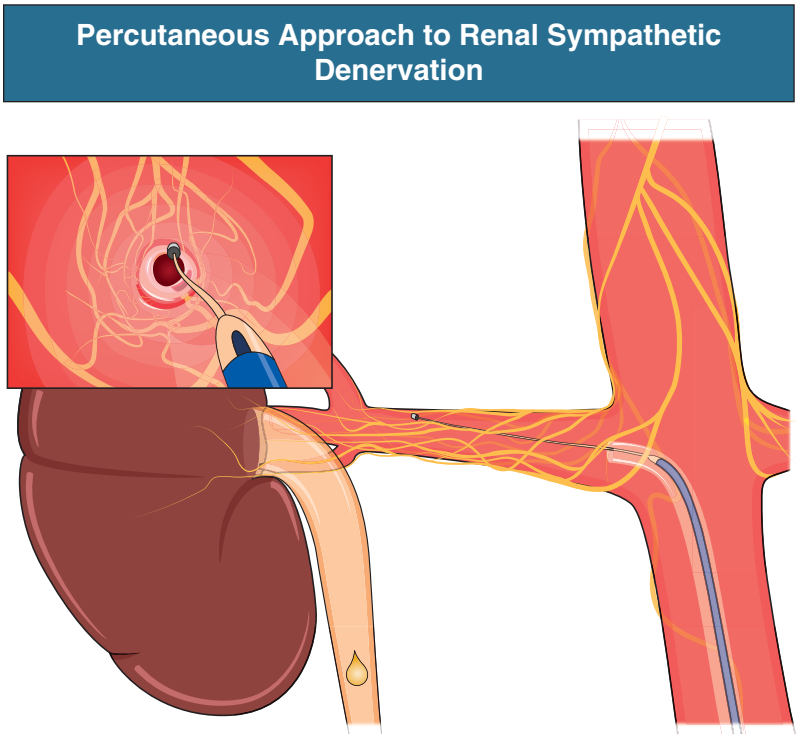

Figure 38-2 Percutaneous approach to renal sympathetic denervation. Using a femoral artery approach, the distal tip of the catheter is placed in distal portion of the renal artery and initial radiofrequency energy applied.

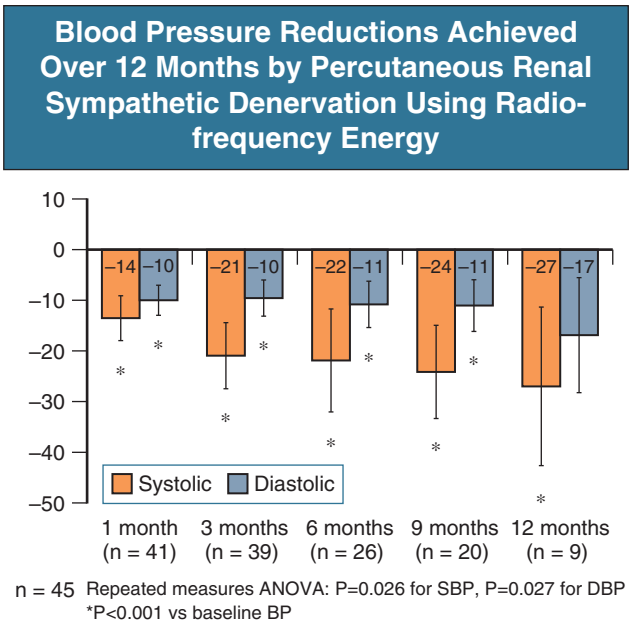

Figure 38-3 Blood pressure reductions achieved over 12 months by percutaneous renal sympathetic denervation using radiofrequency energy. *(Data from Symplicity HTN-1 trial.)*

denervation was observed with a substantial reduction in renal norepinephrine spillover rate in a case study in which BP decreased. In these patients, MSNA (indicative of efferent sympathetic output) also progressively decreased out to 12 months.[16] Sympathetic nerve activity reduction after RDN has been confirmed in a larger series.[17] However, it remains uncertain at the time of the procedure whether denervation has been successfully achieved. The extent of efferent and afferent denervation remains unquantifiable and the importance of complete denervation uncertain; there are as yet no simple clinical tools to address this question.

The Symplicity HTN-1 experience has been extended to 36 months in a larger cohort.[18] Of the 153 patients followed, however, only 24 actually reached the 36-month follow-up visit. Nonetheless, the mean reduction in clinic BP persisted, with a mean 33/19 mm Hg reduction compared to baseline at 36 months. This is consistent with the surgical experience in which many years of improved BP control are observed after the surgical intervention. There is no evidence of loss of BP-lowering effect during the 36 months.

In this cohort, "responders" were arbitrarily defined as those with an office systolic BP reduction greater than 10 mm Hg versus baseline.[18] At 12 months, only 79% had achieved this response in the Symplicity HTN-1 expanded cohort. By 36 months, however, all study patients had achieved this "response." This raises the important issue of what physiologic mechanisms may occur after denervation to produce a late (but not early) BP effect. Possibilities include progressive vascular remodeling, resetting of the baroreflex, and alterations in renal blood flow and sodium excretory status, all of which may require time to "reset." Whether different energy or ablation modalities could alter the responder rate or the time course of BP reduction remains unknown.

To date, no subgroups of patients have been identified who are more likely to respond or not to respond to the procedure. In particular, age greater or less than 65 years, presence or absence of diabetes mellitus, impaired or preserved renal function, and high or low heart rate resulted in no heterogeneity in BP response. However, larger numbers of participants, such as from a global registry, will be required to answer this important question.

Symplicity Hypertension 2 Study

Symplicity HTN-2[19] used similar entry criteria as Symplicity HTN-1.[15] The key differences included a 2-week observation period, after which baseline systolic BP measures were required to remain above 160 mm Hg. In this way, concerns in Symplicity HTN-1 about regression to the mean and Hawthorne effect could at least be partially overcome. Patients who meet BP criteria then underwent anatomic screening with magnetic resonance angiography (MRA), computerized tomography angiography (CTA) or duplex scanning. If renal arteries were free of major atherosclerotic disease, patients were then randomized to a control or treatment group, with a 6-month primary end point assessment of safety and efficacy. The initial 6-month results demonstrated acceptable safety (see later) and a 32/12 mm Hg reduction from baseline in the RDN group ($n = 49$) compared to a 1/0 mm Hg increase in BP in the control group ($n = 51$).This was achieved despite more patients decreasing their medication and fewer patients increasing their medication in the RDN group than in the control group.

At the end of the 6-month primary end point, the control patients were offered the RDN procedure, and all patients were then followed for another 6 months. This analysis found that in the initial RDN group ($n = 47$), BP lowering was maintained for the 12 months, with a reduction of 28/10 mm Hg compared with baseline.[20] In the crossover group ($n = 35$) evaluated 6 months after denervation, mean reduction was 24/8 mm Hg compared to their 6-month pre-RDN value of +7/1 mm Hg versus baseline.

Impact on Renal Function: Studies in Patients with Hypertension and Renal Failure

Although patients in the Symplicity HTN-2 trial had a mean eGFR of 77 ml/min/1.73 m^2, and patients with eGFR less than 45 ml/min/1.73 m^2 were excluded, renal function was unchanged at 6 months.[19] Furthermore, longer-term follow-up data of Symplicity HTN-1 demonstrated that during the first year of follow-up, eGFR remained stable.[18] In no patient did serum creatinine value double. Although it was a nonrandomized study, the relatively modest decline in renal function observed in this 24-month follow-up suggested that there might be an intrinsic beneficial effect of the procedure on the kidney to maintain renal function, which is greater than that achieved with BP reduction alone. Indeed, after successful RDN, renal resistive index decreased from 0.691 ± 0.01 at baseline to 0.674 ± 0.01 and 0.670 ± 0.01 at 3 and 6 months follow-up, respectively; the proportion of patients with microalbuminuria and macroalbuminuria decreased by 10% and 23%, respectively, at 3 and 6 months of follow-up, without effects on GFR.[21]

A pilot study assessed bilateral RDN in 15 patients with resistant hypertension and stage 3 or 4 chronic kidney disease (mean eGFR 31 ± 9 ml/min/1.73 m^2).[22] An average of five ablation treatments per artery were delivered without complications in any of the treated patients. Angiographic evaluation directly after RDN showed no compromise of treated arteries. Importantly, eGFR remained stable in this patient cohort, with five patients followed up to 12 months. Mean baseline BP was 174 ± 22/91 ± 16 mm Hg despite the use of 5.6 ± 1.3 antihypertensive drugs. Office systolic and diastolic BP decreased by 33 ± 20/19 ± 20 at 12 months ($P < .001$). RDN also diminished mean and maximum nighttime BP and restored a physiologic dipping pattern in 9 of 10 patients.

Increased activity of the sympathetic nervous system contributes substantially to the elevated BP often seen in patients with ESRD.[23] Preliminary data were reported on the feasibility of RDN and its effects on BP and sympathetic nerve activity in 12 patients with ESRD and uncontrolled BP.[24] BP was measured on dialysis-free days at baseline and follow-up, and measures of renal noradrenaline

spillover and MSNA were available from five patients at baseline and two patients at 12-month follow-up and beyond. The average office BP was 171 ± 17/89 ± 121 mm Hg despite the use of a mean of four antihypertensive drugs. MSNA and noradrenaline spillover were substantially elevated in all five patients, Of note, 3 of 12 patients could not undergo RDN because of atrophic renal arteries, which made it impossible to position the RF treatment catheter appropriately. Compared with baseline, office systolic BP was significantly reduced at 3, 6, and 12 months after RDN, from 166 ± 16 to 148 ± 11, 150 ± 14, and 138 ± 17 mm Hg, respectively, whereas no change was evident in the three untreated patients. These data suggest that RDN is effective in patients with ESRD as long as it is technically possible.

Safety with Percutaneous Renal Sympathetic Denervation

Initial studies of RDN focused primarily on the safety and tolerability of the procedure. Diffuse visceral pain occurs with the application of RF energy, suggesting that somatic afferent C fibers travel with the sympathetic nerves, which are the targets of the ablation. Patients require prophylactic intravenous analgesia and/or sedation. Imaging studies (e.g., MRA, CTA) at 1 to 2 weeks and 6 months showed no major atherosclerotic progression in response to the RF energy application in denervated arteries.

One episode of renal artery dissection occurred during the catheter procedure (but before application of RF energy) and was successfully stented. Several patients also had impaired hemostasis in the groin, but at a rate consistent with other arterial cannulation procedures involving the femoral artery.

There are rare case reports of renal artery stenosis following RDN, although it is unclear whether the late stenosis is related to mechanical arterial manipulation or the RF denervation. In one report, the patient with late stenosis was successfully treated with dilation and stenting.[25] Alternative technologies developed to minimize renal artery stenosis and other potential local complications include use of catheters with multiple electrodes, to minimize catheter time in the vessel, and ultrasound-based approaches to minimize endothelial damage. No cases of vessel thrombosis or kidney embolization have been reported.

Ongoing Percutaneous Renal Denervation Studies: Symplicity Hypertension 3 Study

Symplicity HTN-1 and HTN-2 have provided strong safety and efficacy data to support the utility of percutaneous renal denervation in refractory hypertension patients. However, the U.S. Food and Drug Administration (FDA) mandated a definitive study (Symplicity HTN-3) that required more aggressive achievement of target dose, or at least highest tolerated dose, of background antihypertensive medications. The qualifying BP requirement included systolic greater than 135 mm Hg by ABPM (as well as subsequent office systolic BP >160 mm Hg), as confirmed after initial screening.[26] The study also concluded a sham procedure performed in the renal artery of controls. Because the operator was aware of which patients received the active procedure, a separate group of investigators performed the end point assessments.

The Symplicity HTN-3 trial has recently reported its full results. The primary efficacy end point was change in office systolic blood pressure between the denervation and the control arm with a superiority margin of 5 mm Hg. However, the decrease in systolic blood pressure in the denervation group was 2.4 mm Hg versus sham control at 6 months, with a starting systolic blood pressure of 180 mm Hg in both groups. There was a nonsignificant interaction effect (p = 0.09) in African Americans versus non–African Americans, suggesting that these subjects derived less benefit in terms of blood pressure reduction. There were no other prespecified subgroup interactions of note.There was no significant increase in safety events with denervation. Thus, the study failed to meet its primary efficacy end point and considerable discussion has ensued as to why that may be the case. This may relate to use of the specific catheter (Flex) with concerns that denervation was not actually achieved in a significant number of patients; the trial design, which allowed background medication uptitration up to 2 weeks prior to the procedure being performed; suboptimal background management of patients referred in from nontertiary centers; and the possibility that denervation itself is not an effective procedure (even if achieved). Further investigation will be required to sort this out and in particular to develop a simple test to ascertain the achievement and completeness of denervation while patients are still on the table during the denervation procedure.

Novel Approaches to Percutaneous Renal Denervation

Radiofrequency Ablation

Newer denervation systems use multiple RF ablation electrodes mounted on steerable basket-shaped catheters (St. Jude Medical EnligHTN system), spiral catheters (Medtronic Multi-electrode Radiofrequency RDN System), and cooled balloon catheter RF ablation (Covidien One-Shot). Preliminary 6-month data on the EnligHTN system ($n = 46$) has shown efficacious BP reduction, with 76% of patients achieving systolic BP reduction of 10 mm Hg or more at 6 months. Mean BP reduction at 6 months was −26/−10 mm Hg from 176/96 mm Hg at baseline. The Covidien One-Shot system uses a saline-irrigated balloon catheter, with a spiral RF electrode on the balloon. The Vessix V2 RSD system is an over-the-wire low-pressure balloon catheter with multiple bipolar RF electrodes mounted on the exterior of the balloon.

Ultrasound

The ReCor Medical PARADISE RSD system uses a catheter with a cylindrical transducer, within a low-pressure balloon, that emits ultrasound energy circumferentially, effecting RDN. It is claimed that this allows complete circumferential denervation and deeper therapeutic penetration, which is hoped to be more consistent and effective, with improved vascular safety, than the standard RF ablation strategy. In a small study ($n = 11$), this ultrasound renal sympathetic denervation (RSD) method was shown to be a safe and effective treatment for resistant hypertension.[27]

All these new devices allow for simultaneous application of ablation energy at multiple different points in the renal artery lumen to denervate the renal sympathetic nerves. This permits shorter procedure time and thus shorter periods of pain during the application of the ablation energy on the renal sympathetic nerves. There is also a theoretical reduced volume of nephrotoxic contrast used. The newer multielectrode catheters will also allow ablation of smaller and shorter renal arteries.

BAROREFLEX ACTIVATION THERAPY

Devices to stimulate the baroreceptor have been commercialized and are currently undergoing preclinical and clinical testing. The Rheos (CVRx, Minneapolis) implantable carotid sinus stimulator has been studied in patients with severe hypertension refractory to drug

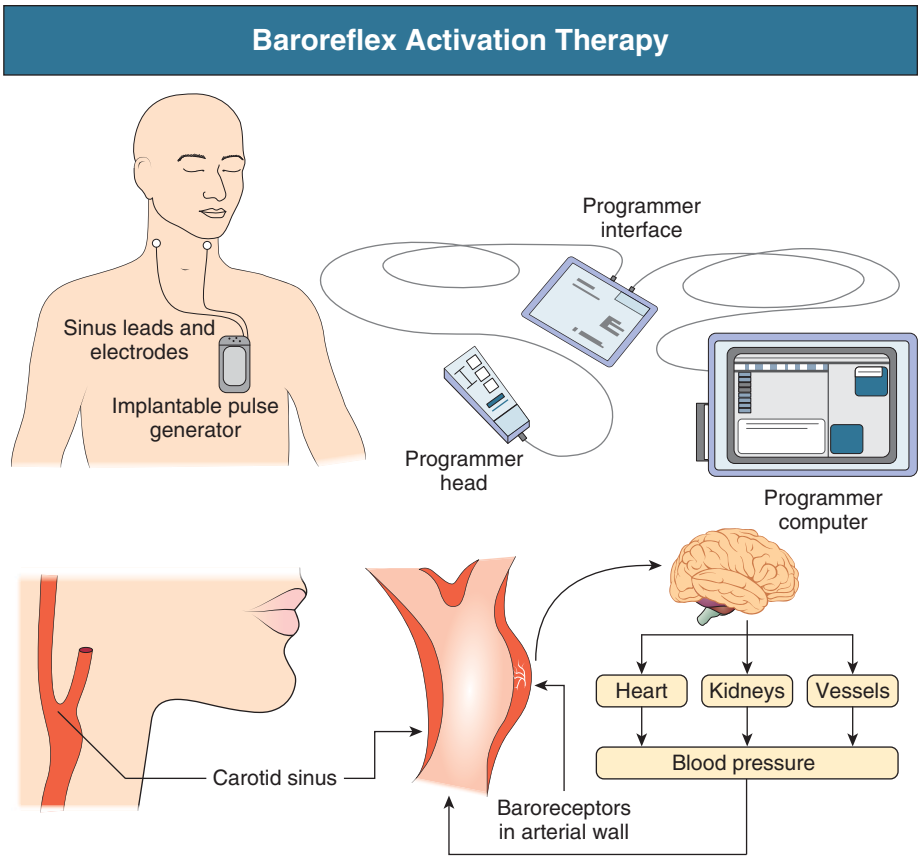

Figure 38-4 **Baroreflex activation therapy.**

therapy[28] (Fig. 38-4). Implantation involves both carotid sinuses being surgically exposed and electrodes placed around the carotid adventitial surface bilaterally. The leads are subcutaneously tunneled and connected to an implantable stimulation device placed in the subclavian subcutaneous position on the anterior chest wall. Electrical baroreflex activation is then initiated on both carotid sinuses simultaneously, with incremental voltage increases until the chronic stimulation level is achieved.

In animal models, activation of central baroreflex pathways results in suppression of medullary sympathoexcitatory cells in both acute and chronically hypertensive dogs, as well as inhibition of renal sympathetic nerve activity. This induces beneficial effects such as natriuresis, along with sustained reductions in BP and heart rate.[29]

DEBUT Study

The multicenter DEBUT feasibility study in patients with treatment-resistant hypertension demonstrated a clinically and statistically significant reduction in office BP of over 20 mm Hg systolic after 3 months of carotid baroceptor stimulation in 37 participants.[30] In 17 participants followed for up to 3 years, BP reductions were sustained (Fig. 38-5). ABPM confirmed the pressure drop during baroceptor activation therapy (BAT), with reductions both during daytime and nighttime. Recent data indicate that lowering BP during activation of the BAT device is associated with a reduction of MSNA.[31]

In DEBUT, 7 of 42 patients experienced a procedure-related adverse event and one a BAT device–related event. One patient had fatal angioneurotic edema (cause unknown) a few days after the procedure but before device activation. Three patients had the device explanted before activation because of infection. Three additional procedure-related adverse events included perioperative stroke with minimal residual effects; tongue paresis (no abnormalities on brain MRI) most likely caused by injury to the hypoglossal nerve; and moderate pulmonary edema that resolved within 6 days. Because most complications occurred early during the study, greater experience with the technique might reduce the number of adverse events.

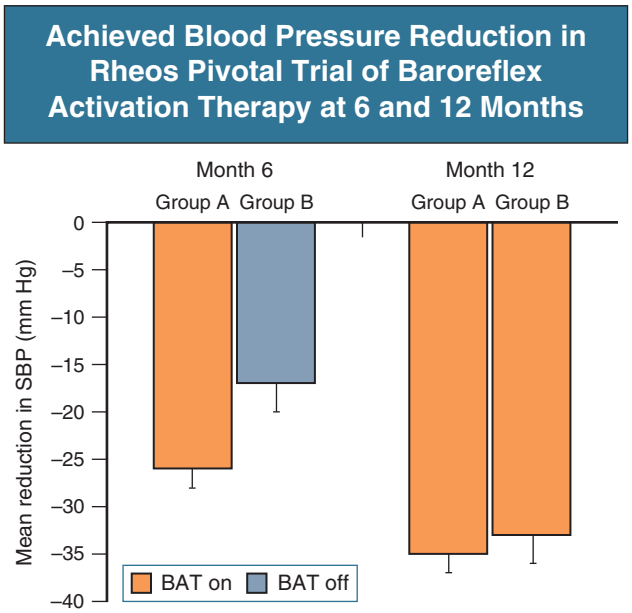

Figure 38-5 **Achieved BP reduction in of baroreflex activation therapy (BAT) at 6 and 12 months.** Group A had BAT device turned on and group B had BAT device turned off for first 6 months. *(Data from Rheos Pivotal trial.)*

A 6-minute walk test at 1 year increased significantly by 48 m (~158 ft) in 14 participants. At the start of the trial, renal function was in the normal range in all patients. Serum creatinine significantly increased after 1 year of therapy in 22 participants, although the rise was less than 20%. In the other 20 patients, it remained stable or even improved. None of the patients developed carotid artery stenosis by the 1-year visit. No evidence for orthostatic hypotension was found, and no events of collapse or syncope were reported in the 32 participants with readings at baseline and after 3 months of BAT.

Rheos Pivotal Trial

The Rheos Pivotal trial of baroreflex sensitization randomized 265 patients to have the BAT device implanted, with half these patients having the device turned on and half with it turned off for 6 months.[32] End point evaluations (efficacy and safety) were performed at this time, and then all patients had the device turned on for longer-term follow-up. Mean BP was 169 to 169/100 to 101 mm Hg, and patients were taking 5.2 different antihypertensive medications. A greater percentage of patients with the BAT device on (42%) achieved systolic BP less than 140 mm Hg at 6 months than those with the BAT device off (24%), but the acute systolic BP responder date (>10 mm Hg reduction) was not significant. Both groups had systolic BP reduction of 25 mm Hg by 12 months.

Ongoing Studies

With the second-generation BAT device, a small European trial has showed a 26 mm Hg reduction in systolic BP at 6 months.[33] Larger studies are planned.

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CHAPTER 39

Renovascular Hypertension and Ischemic Nephropathy

Stephen C. Textor and Barbara A. Greco

Few areas in nephrology generate more controversy than management of renovascular disease. Advances in medical therapy, management of atherosclerotic comorbidity, diagnostic imaging, and endovascular intervention have combined to reshape the tools available and the range of clinicians involved with managing these disorders. Restoring blood flow to a critically ischemic kidney offers the potential to improve blood pressure and recover kidney function. However, several recent prospective, randomized controlled trials have failed to identify major additional benefits from revascularizing the kidney when added to optimal medical therapy. Although these trial results have diminished enthusiasm for renal artery revascularization for many patients, nephrologists will continue to encounter patients who can benefit from endovascular or surgical intervention for advanced renovascular disease as well as intensive risk factor management. As with many vascular diseases, the issue is most often one of *timing,* rather than simply choosing one therapy over another indefinitely. This chapter provides an overview of the pathophysiology of renovascular hypertension and clinical management of renal artery stenosis.

DEFINITION AND ETIOLOGY

Renovascular disease with reduced perfusion of the kidney can produce a range of clinical syndromes, most frequently a rise in arterial pressure, designated *renovascular hypertension* (RVH), with or without associated ischemic and hypertensive renal injury. RVH is usually caused by renal artery (RA) stenosis and is a common secondary form of hypertension. Recognition that reduction of renal perfusion pressure activates a series of hormonal and neuronal responses that raise systemic arterial pressure remains one of the seminal observations in blood pressure (BP) regulation. Not surprisingly, high BP in patients with RA stenosis frequently leads to the assumption that the stenosis is the cause of the hypertension. Often, however, patients have preexisting hypertension unrelated to renovascular disease. Final proof that a patient has RVH rests with the demonstration that the hypertension is improved or eliminated by RA endovascular or surgical revascularization or by removal of the kidney distal to the stenosis.

Renovascular hypertension is defined as a syndrome of elevated BP (systolic and/or diastolic) produced by any condition that interferes with arterial circulation to the kidneys. The majority of patients with RVH have significant main RA stenosis with reduced renal perfusion pressure**.** Most conditions cause reduced perfusion to one kidney, while a second "contralateral" kidney is exposed to elevated systemic pressures, called "two-kidney" hypertension by analogy to experimental models of "2-kidney–1-clip hypertension" discussed later. When both kidneys are affected, as may occur with atheroembolic disease or a RA stenosis in a solitary functioning kidney without a normal "contralateral" kidney, the designation "one-kidney" RVH is given.

Of the conditions that may produce the syndrome of RVH, main vessel RA stenosis is by far the most common. The two major causes of main renal artery disease are *fibromuscular dysplasia* (FMD) and *atherosclerotic renal vascular disease* (ASRVD). Box 39-1 lists other conditions that can cause RVH by impairing renal blood supply. Many of these are rare, but all lead to reduced renal perfusion pressure.

The term *ischemic nephropathy* or *ischemic renal disease* (IRD) refers to the reduced glomerular filtration rate (GFR) associated with reduced renal blood flow beyond the level of renal autoregulatory compensation.[1] Critical RA stenosis can lead to renal atrophy and progressive renal impairment. As with RVH, establishing the causal relationship between proximal RA stenosis and the development and progression of chronic kidney disease is often difficult. Collateral renal blood supply can preserve renal viability in the face of proximal atherosclerotic renovascular occlusive disease, and small vessel and parenchymal disease often coexist with main RA atherosclerotic disease. Renal revascularization of ischemic kidneys in some cases can succeed in recovering renal function, but there are few predictors to guide therapeutic choices in these patients, who are often at high risk for complications of interventions.

PATHOPHYSIOLOGY OF RENOVASCULAR HYPERTENSION

Renovascular occlusive disease from any cause can activate pressor pathways that tend to restore renal artery perfusion pressures. Most notable among these is activation of the renin-angiotensin aldosterone (RAAS) system. Activation of plasma renin only occurs after poststenotic pressures fall by at least 10% to 20% compared with aortic pressures.[2] A fall in renal perfusion pressure sufficient to initiate RVH only occurs when luminal occlusion is relatively severe, usually in the 70% to 80% cross-sectional occlusion range (Fig. 39-1, *left*).

When critical stenosis develops and reduces renal perfusion pressure, multiple mechanisms are activated in the kidney to restore renal blood flow. Central to this process is the release of renin from the juxtaglomerular apparatus, leading to activation of the RAAS. This is mediated in part by stimulation of neuronal nitric oxide synthase and cyclooxygenase-2 in the macula densa. Blockade of the RAAS during creation of an experimental RA lesion prevents development of hypertension. Studies in transgenic mice without

receptors to angiotensin confirm that development of RVH requires an intact RAAS.[3] In the absence of RAAS blockade, systemic arterial pressures increase until renal perfusion is restored. Studies in both experimental models and humans indicate that additional mechanisms contribute to long-term BP elevation in the presence of RA stenosis, including activation of the sympathetic nervous system, impairment of nitric oxide generation, and release of endothelin, as well as hypertensive microvascular injury to the nonstenosed kidney.[4]

Mechanisms responsible for sustained RVH differ depending on whether one or both kidneys are affected by significant stenoses, either pathologic or created in animal models using clips (Fig. 39-2). The nomenclature distinguishes between a situation in which one clip is present with a normal contralateral or unclipped kidney ("1-clip–2-kidney hypertension") and a situation in which the entire renal mass is affected with no contralateral kidney ("1-clip–1-kidney hypertension"). Both these situations depend on impaired renal perfusion and initial activation of the RAAS with sodium retention. However, the presence of a normal contralateral kidney allows pressure natriuresis to occur, in which the elevated perfusion pressure mediates natriuresis in the nonstenotic kidney. Because the nonstenotic kidney functions to eliminate the excess sodium, the level of perfusion to the stenotic side remains reduced, leading to sustained activation of the RA stenosis. This sequence of events produces angiotensin II (Ang II)–dependent hypertension and secondary aldosterone excess with hypokalemia (Fig. 39-2, *A*).

By contrast, 1-clip–1-kidney hypertension represents a model in which the entire renal mass is exposed to reduced pressures beyond a stenosis. There is no normal or nonstenotic kidney to counteract increased systemic pressures. As a result, sodium is retained and blood volume expanded, which eventually feeds back to inhibit the RAAS (Fig. 39-2, *B*). Therefore, 1-clip–1-kidney hypertension is typically not angiotensin dependent unless removal of volume is achieved that reduces renal perfusion pressure and activates the RAAS.

These differences have clinical implications. Many diagnostic studies used to evaluate the functional significance of RA lesions depend on comparisons of the different physiologic response of the two kidneys, which may give a false impression if both kidneys are involved. Furthermore, diagnostic tests that depend on differences in responses to alterations in sodium status (e.g., measuring renal vein renin levels after sodium depletion or individual kidney sodium reabsorption) may be problematic, because high levels of Ang II and aldosterone stimulate sodium reabsorption in both the stenotic and the nonstenotic kidney. This partly accounts for the less frequent use of such tests in recent years.[5]

Renovascular Hypertension: Classification

"Two-Kidney Hypertension"*
Unilateral fibromuscular dysplasia
Unilateral atherosclerotic renovascular disease
Renal artery aneurysm
Renal artery embolism
Traumatic arterial occlusion
Arteriovenous fistula
Renal artery dissection or thrombosis
Aortic dissections with compromise to renal ostium
Page kidney (i.e., post-traumatic perirenal fibrosis)
Metastatic tumor compressing renal parenchyma
Pheochromocytoma compressing renal artery
Phakomatosis pigmentovascularis type IIb
Neurofibromatosis
Behçet disease
Covering of origin of renal artery by aortic stent graft
Renal artery spasm

"One-Kidney Hypertension"†
Stenosis to solitary kidney
Bilateral arterial stenosis
Coarctation of the aorta
Vasculitis involving renal arteries
Congenital vascular anomalies
Atheroembolic renal disease

Box 39-1 Classification of renovascular hypertension. Examples of renovascular disease with associated renovascular hypertension or ischemic renal disease. *Two-kidney hypertension implies that a contralateral, nonaffected kidney is present. †One-kidney hypertension implies that the entire renal mass is beyond the vascular lesion, either bilateral disease or a solitary functioning kidney.

Hemodynamic Effects of Stenotic Lesions

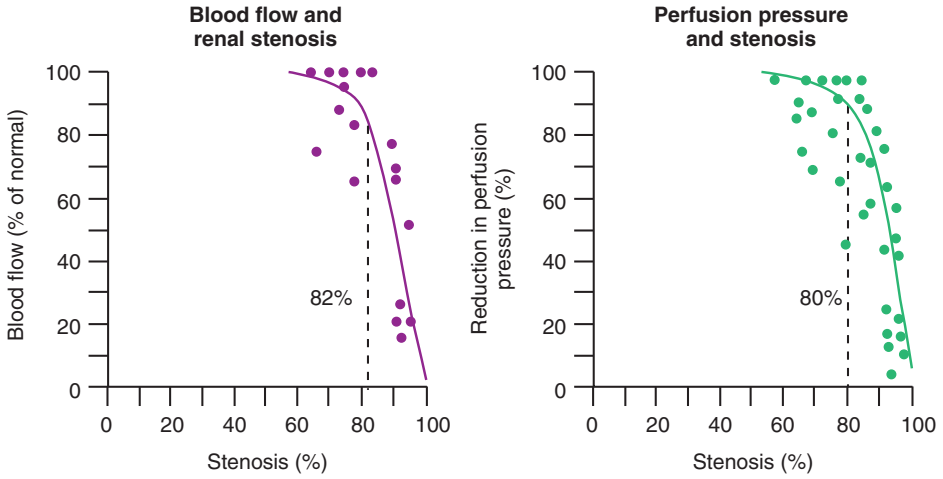

Figure 39-1 Hemodynamic effects of stenotic lesions. Changes in blood flow and arterial pressure across a carefully quantitated arterial lesion are barely detectable until cross-sectional area diminishes by 75% to 80%. *(From reference 91.)*

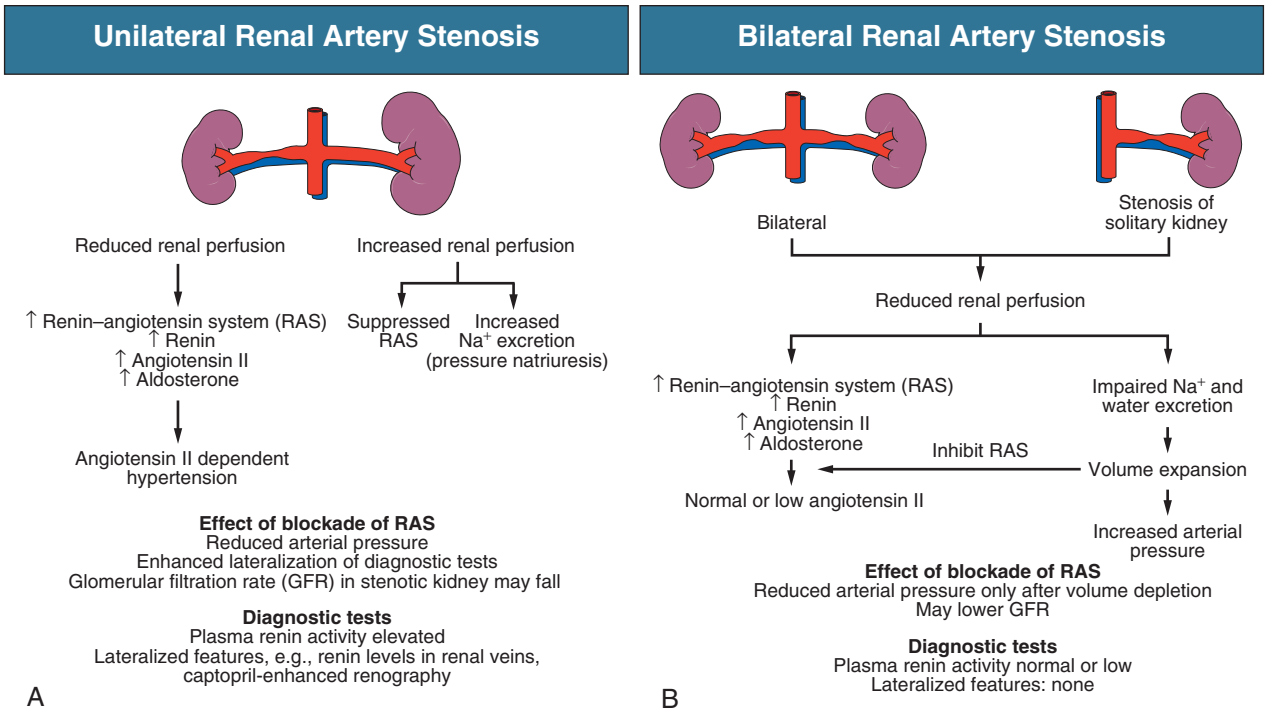

Figure 39-2 Pathogenesis of renovascular hypertension in one-kidney versus two-kidney model. A, In unilateral stenosis with two kidneys, opposing forces between the stenotic kidney, which has reduced perfusion pressures, and the nonstenotic contralateral kidney, which has increased perfusion pressures, result in laboratory and clinical features of angiotensin-dependent hypertension. **B,** In unilateral stenosis with a solitary functioning kidney or in a patient with bilateral critical renal artery stenosis, reduced perfusion pressure to the stenotic kidney in the absence of a normal kidney excreting sodium leads to sodium and volume retention, ultimately associated with hypertension without persistent activation of the RAS.

Variations in the natural history of RVH complicate our understanding of primary pathogenic mechanisms. Rarely is it known exactly when critical levels of stenosis develop. In experimental models, the relative importance of pressor mechanisms, including measurable activation of the RAAS, changes with time. Levels of circulating plasma renin activity decrease, as does the responsiveness of BP to short-term blockade of the renin system. Several mechanisms have been proposed to explain such changes, including a slowly developing pressor action of Ang II, a transition to alternate pressor mechanisms, and intrinsic renal injury to the nonstenotic kidney, which ultimately sustains hypertension despite reversal of the vascular lesion. In experimental models, this translates into a time limit for reversibility of RVH.

There are several clinical correlates with this variable time course. First, it is not known how best to identify when revascularization will fail to improve BP control, although a brief duration of hypertension suggests a more favorable response to intervention. As a result, many of the diagnostic studies that depend on lateralization of effects have only modest predictive value when negative. As a general rule, studies are most reliable when positive, meaning that high-grade lateralization accurately predicts an improvement after revascularization. Second, coexistent intrarenal disease, such as arteriolosclerosis with glomerulosclerosis, is associated with persistent hypertension despite correction of RA stenosis, particularly for patients with ASRVD.[6] In these patients, a long duration of hypertension allows the development of arteriolosclerotic lesions and renal injury in the contralateral kidney (Fig. 39-2, *A*). Thus, older age and a long duration of hypertension (e.g., >3 to 5 years) predict a poorer outcome of intervention in this patient population. Most elderly patients with ASRVD also have impaired renal function related to microvascular renal injury in addition to main RA stenosis.

ATHEROSCLEROTIC RENOVASCULAR DISEASE

Epidemiology

Atherosclerotic narrowing of the renal arteries generally occurs in older patients (>50 years) and is associated with systemic atherosclerosis. Younger patients with premature atherosclerosis are also at risk. ASRVD is the most common cause of RVH and can contribute to loss of renal function, leading to end-stage renal disease (ESRD) (Fig. 39-3). Atherosclerotic plaque often arises in the first or second centimeter of the renal artery or may extend from the aorta into the renal ostium. Aortic and renal vascular calcification is often present. ASRVD is a manifestation of systemic atherosclerosis and is associated with coronary, cerebrovascular, peripheral vascular, and aortic disease.[7,8] The prevalence of ASRVD appears to be increasing. Although this partly reflects improved imaging and selection bias, this trend likely also reflects that more people are surviving to ages when atherosclerotic vascular disease in the visceral abdominal vessels reaches critical levels, producing RVH when the kidney is affected. In patients undergoing angiography of the peripheral or coronary circulation, ASRVD is found in 11% to 42%.[9] Predictors of ASRVD include a history of hypertension, presence of renal functional impairment, coexisting vascular or coronary artery disease, the presence of abdominal bruits, and a history of smoking. RA lesions are bilateral in 20% to 40% of such patients.

Estimates of the prevalence of ASRVD depend on the population screened. One population-based study of 870 patients older than 65 screened with RA duplex ultrasound found a 6.8% prevalence of ASRVD, defined as greater than 60% stenosis. No differences were detected between African Americans and Caucasians.[10] Autopsy

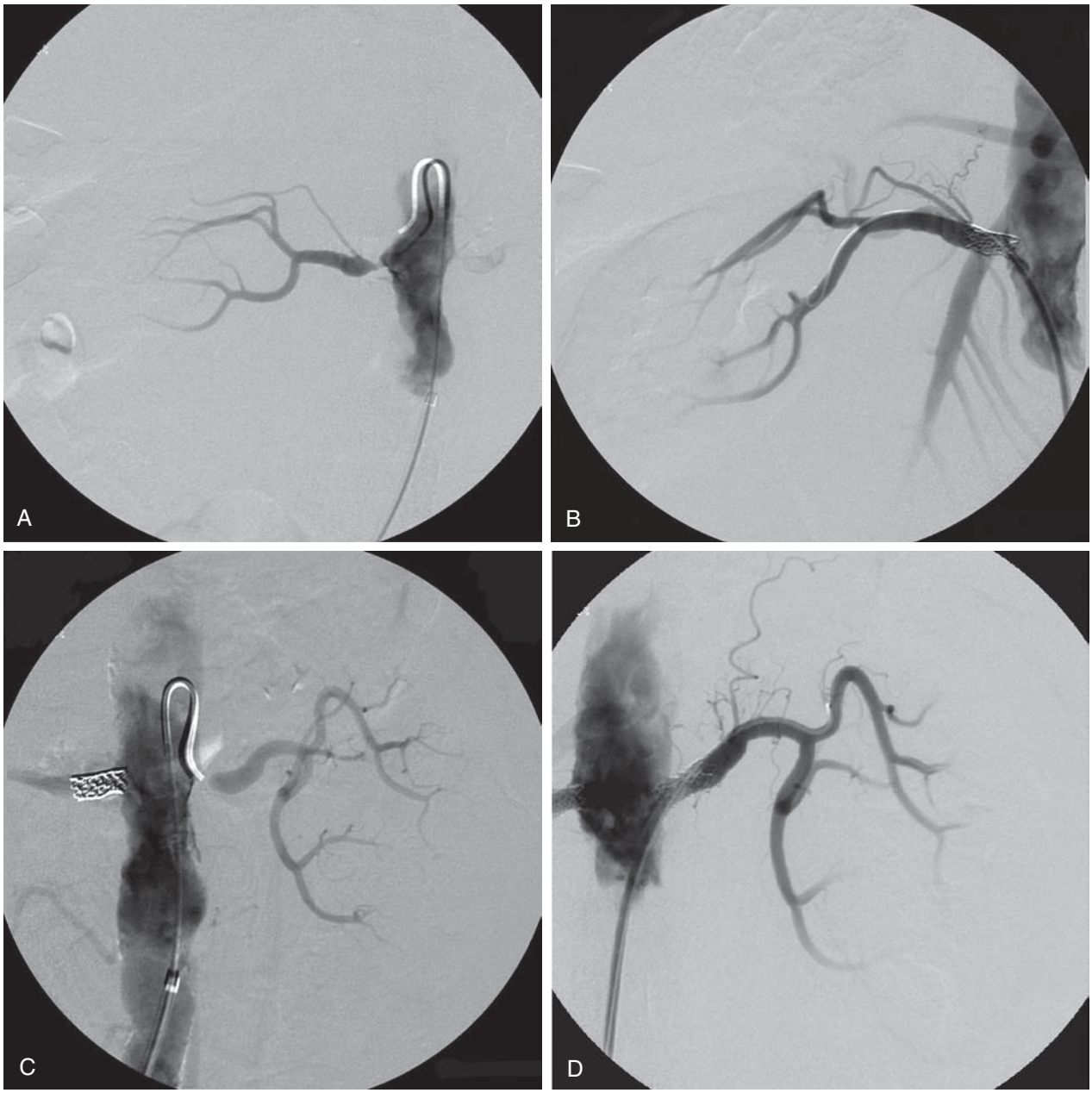

Figure 39-3 Angiograms of atherosclerotic renal artery stenosis. A, Proximal, high-grade stenosis near the ostium. **B,** Restoration of vessel patency by endovascular stent placement. **C,** Image of contralateral, high-grade stenosis of the left kidney. **D,** Improved flow after endovascular stenting.

series report an overall prevalence of 4% to 20%, with progressively higher rates for those older than 60 years (25% to 30%) and 75 years (40% to 60%). These studies suggest that ASRVD is common among elderly hypertensive patients. Furthermore, RA stenosis from ASRVD has been reported to contribute to the decline in renal function in 15% to 22% of patients reaching ESRD.[11,12]

Relationship to "Ischemic" Renal Disease

Activation of pressor mechanisms producing RVH can occur without loss of kidney size or function. However, the more common clinical scenario in patients with ASRVD involves both increasing severity of hypertension and deteriorating renal function, often with loss of kidney volume. Because mechanisms underlying parenchymal renal damage differ from those responsible for generating hypertension, improved BP control after revascularization in some cases may be achieved without improvement in kidney function.

Transition from "reversible" loss of function to "irreversible" tissue fibrosis is not well understood. Basal renal energy requirements are met with less than 10% of blood flow, consistent with its filtration function. Studies using blood oxygen level–dependent (BOLD) magnetic resonance imaging (MRI) indicate that despite reductions in blood flow and GFR, many patients maintain normal cortical and medullary tissue oxygenation.[13] Thus, many poststenotic kidneys have no more "ischemia" than normal kidneys. These observations explain the relative stability and infrequent progression of renal injury in prospective trials of medically treated patients with ASRVD, such as Angioplasty and Stenting for Renal Atherosclerotic Lesions (ASTRAL).[14,15] Nonetheless, reduced renal perfusion ultimately activates numerous mechanisms of tissue injury. Figure 39-4

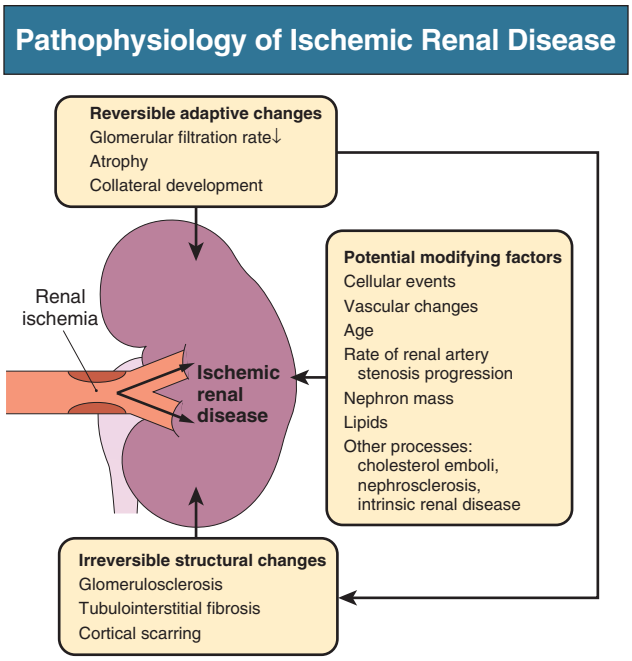

Figure 39-4 Pathophysiology of ischemic renal disease. Chronic ischemia of the kidney is associated with reversible functional involution and atrophy as well as with irreversible structural changes. A number of external factors influence the renal response to chronic ischemia. *(Modified from reference 92.)*

summarizes the activation of vasoactive and inflammatory pathways.[16] Over time, inflammation, fibrosis, and microvascular rarefaction occur, leading to irreversible changes.[16,17]

Activation of the RAAS and endothelial systems such as endothelin and oxidative stress pathways have been demonstrated with RA stenosis models.[16] These systems stimulate inflammation and drive fibrosis. Under acute conditions of reduced blood flow with persistent filtration and tubular function, levels of deoxygenated hemoglobin increase in the renal medulla, representing medullary hypoxia.[18] Medullary oxygen levels are normally lower than cortical levels and are heavily dependent on the level of solute transport. Reductions in GFR and associated energy-dependent solute transport allow "adaptation" to reduced blood flow without development of tissue hypoxia. Only when more severe vascular occlusion develops beyond the limits of such adaptation can one identify overt cortical ischemia associated with increased deoxyhemoglobin.[19] This results in macrophage accumulation with progressive tubular cell loss and fibrosis.[20] Glomeruli are usually preserved, although collapsed.

Clinical Manifestations

Renovascular Hypertension

Clinical studies suggest that for any level of BP, patients with RVH have higher nocturnal pressures ("nondipper") and have more severe target organ manifestations, including left ventricular hypertrophy, than patients with essential hypertension[21] (Box 39-2). Likelihood of RVH in patients with treatment-resistant hypertension increases with elevated cholesterol, impaired renal function, lower body mass index, and smoking; but none of these features is sufficiently sensitive or specific to offer diagnostic precision. Some reports indicate that RVH rarely may be associated with nephrotic-range proteinuria, which can regress with correction of the vascular lesions.[22]

Blood pressure elevations from RVH vary widely. Acute RA occlusion may only gradually produce BP increase or may cause a rapid increase in hypertension that precipitates a hypertensive urgency or emergency (see Chapter 37). Before the current era of antihypertensive agents, 30% of Caucasian patients appearing in an emergency department with hypertensive urgency (defined as grade III or IV hypertensive retinopathy) were ultimately found to have RVH. Syndromes of polydipsia and accelerated hypertension with hyponatremia and hypokalemia, sometimes attributed to the dipsogenic actions of Ang II, also have been observed.

Recent consensus documents emphasize the need for effective population-wide BP control, while limiting the number and expense of diagnostic studies. As a result, most patients with hypertension simply are treated and subjected to few laboratory investigations. For those who reach acceptable BP control without adverse effects, no further studies are performed. Therefore, many if not most cases of RVH are not detected (Fig. 39-5), unless hypertension becomes more difficult to treat or renal dysfunction ensues.

In recent years, widespread application of RAAS blockers for indications other than hypertension, including congestive cardiac failure, diabetic nephropathy, and other proteinuric renal disease, increases the exposure of individuals with undetected RA stenosis to these drugs.[23]

A consequence of these changes has been the emergence of distinctive clinical syndromes that merit evaluation in patients at risk for ASRVD (see Box 39-2). As a result, patients that typically undergo diagnostic evaluation and renal revascularization are a subset of the patient population with RVH. This subset is characterized generally by more severe hypertension, decreasing renal function, propensity for rapid volume accumulation manifested as "flash" pulmonary edema, and occasionally advanced renal failure.

Renovascular Hypertension: Clinical Manifestations

Features of Renovascular Hypertension

- Activation of renin-angiotensin-aldosterone system (RAAS)—early
- Parenchymal symptoms: sympathetic nervous system activation
- Abnormal circadian rhythm: loss of nocturnal pressure fall
- Accelerated target organ damage
  - Left ventricular hypertrophy
  - Microvascular disease
  - Renal injury: fibrosis
- Hyponatremic hypertensive syndrome
- Nephrotic range proteinuria
- Unstable cardiac chest pain

Clinical Syndromes Associated with Atherosclerotic Renal Artery Stenosis

- "Incidental lesion": no hemodynamic effect
- Renovascular hypertension (see above)
  - New-onset hypertension
  - Acceleration in previously hypertensive patient
- Acute kidney injury
  - ACE or ARB-induced acute kidney injury
  - Acute or chronic kidney disease impairment
- Unexplained chronic kidney disease: especially in elderly patients
- Circulatory congestion: "flash pulmonary edema"

Box 39-2 Clinical manifestations of renovascular hypertension. *ACE*, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker.

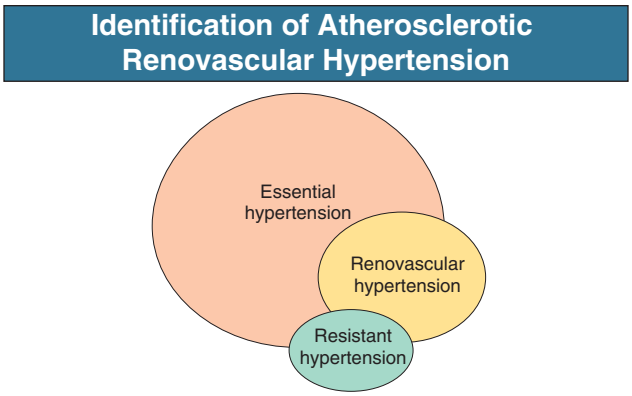

Figure 39-5 Identification of atherosclerotic renovascular hypertension. Venn diagram indicates that many patients with renovascular hypertension are indistinguishable from patients with primary hypertension. A subset develops problematic or resistant hypertension, which brings them to clinical attention and consideration for renal revascularization.

Ischemic Renal Disease

The diagnosis of IRD (ischemic nephropathy) should be considered in several clinical settings (see Box 39-2).

Renal Impairment in Patients with Renovascular Hypertension or in Atherosclerotic Age Range Ischemic nephropathy should be considered as a cause of chronic kidney disease (CKD) in the atherosclerotic age group, particularly when other vascular disease is detected. Many but not all will have a history of hypertension. It remains difficult to separate primary vascular disease from renal parenchymal injury associated with nephrosclerosis from other vascular insults. Clues to IRD include asymmetry of kidney size or recent deterioration of renal function, as opposed to slowly progressive CKD. An asymmetrically small kidney in an adult over age 50 has a 70% chance of being associated with ipsilateral RA stenosis.[24]

The development of renal impairment in patients treated medically for longstanding hypertension should raise suspicion for possible IRD. Given the high frequency of bilateral RA stenosis (30% to 50%), the possibility of IRD should always be considered in patients with known prior RA stenosis. The most common presentation of ASRVD is unilateral involvement in a patient with CKD associated with longstanding hypertension. In this case, renal impairment cannot be attributed solely to IRD because the RA stenosis affects only one kidney. The kidney supplied by the stenotic vessel may have reduced blood flow, resulting in diminished GFR, RVH, and atrophy. The contralateral kidney with a patent renal vessel often hypertrophies and compensates with hyperfiltration. However, over time, this kidney develops parenchymal injury. In some cases, the kidney with the patent RA has worse renal function than the poststenotic kidney.[25]

Acute Kidney Injury After Starting Antihypertensives/RAAS Blockade Patients with hemodynamically significant RA stenosis to the entire functioning nephron mass are at risk for the development of "functional" acute kidney injury (AKI) after starting RAAS blockers. The sudden reduction in systemic BP in the patient with critical RA stenosis may reduce RA pressure below levels needed to sustain glomerular filtration by autoregulation (see Medical Therapy). This can occur with reduction in BP by any antihypertensive agent. With medications that block the production or action of Ang II, alterations in glomerular hemodynamics may result in acute reduction in GFR, which is independent of effects on systemic BP.[26] Normally, activation of Ang II causes efferent arteriolar vasoconstriction, which preserves transcapillary filtration pressures at the glomerulus when preglomerular pressures are reduced, thereby maintaining GFR. The loss of this compensatory mechanism induced by agents that inhibit or block the RAAS can result in functional AKI. This typically occurs within a few days from the start of therapy and is usually, but not always, reversible.

In patients without RA stenosis, AKI can also occur with the use of RAAS inhibitors. This most frequently occurs in patients with cardiac or hepatic dysfunction or patients with intravascular volume depletion because, in these settings, GFR is also Ang II dependent. In a prospective study, the observation of 20% increase in serum creatinine or more after administration of an angiotensin-converting enzyme (ACE) inhibitor detected most cases of bilateral severe RA stenosis.[27] When prospectively challenged, more than 90% of a cohort followed in the United Kingdom tolerated RAAS blockade, including 78% of those with high-grade, bilateral ASRVD.[28] Because of the potential change in GFR, kidney function should be rechecked within 1 to 2 weeks of instituting therapy with RAAS blockers.[29]

"Flash" Pulmonary Edema Some patients with bilateral RA stenosis or ischemic nephropathy develop severe hypertension and extracellular fluid volume excess caused by impaired pressure natriuresis. Such conditions may produce the sudden ("flash") onset of pulmonary edema in association with rapid development of circulatory congestion.[30] This has been attributed in part to rapid loss of contractile strength of the left ventricle caused by sudden increases in afterload. Impaired diuresis can result in exaggerated swings in BP, circulatory congestion, and renal function.[31] Such patients have increased mortality and hospitalization rates compared with those who have congestive heart failure (CHF) without renovascular disease.[32] Case series suggest that renal revascularization can facilitate fluid volume management, reduce hospitalization, and occasionally improve cardiac function independent of interventional procedures for the heart itself, even in patients with poor preoperative cardiopulmonary status.[33,34] In one series, 41% of patients with bilateral RA stenosis had a history of pulmonary edema, compared with 12% with unilateral renovascular disease. Of patients with bilateral RA stenosis, 77% had no further pulmonary edema after RA stent placement in one or both arteries. The patients who did have recurrent pulmonary edema all had evidence of stent thrombosis or restenosis.[35]

No prospective clinical studies have examined the effect of optimal medical therapy of BP and volume status on the frequency of events in these patients. Observational, retrospective studies indicate that ASRVD in patients with CHF imparts a worse survival and that renal revascularization lowers the rates of recurrent pulmonary edema and hospitalization as compared to those treated medically.[32] Reports from prospective, randomized controlled clinical studies such as ASTRAL, however, demonstrate no differences in hospitalizations or episodes of CHF between intensively treated patients with or without RA stenting.[14] An important caveat related to this observation is that patients considered "likely to benefit" from revascularization were excluded from ASTRAL.[36]

Oligoanuric Acute Superimposed on Chronic Kidney Disease Patients with high-grade RA stenosis are at risk for renal artery occlusion. When RA stenosis is bilateral or unilateral in the patient with a single functioning kidney, progression to total occlusion can present as oligoanuric AKI, sometimes associated with a hypertensive emergency. A clinical clue to this diagnosis is abrupt onset oligoanuria. In this setting, the kidney parenchyma may be viable despite lack of filtration; in some patients collateral vessels maintain renal viability in the face of proximal RA occlusion. Clues to renal viability include preserved kidney length and evidence of renal contrast enhancement ("renal blush") seen on delayed or venous phase images during renal angiography. When these factors are present and the clinical course is consistent with recent occlusion, there is a chance of retrieval of renal function if revascularization is feasible clinically and anatomically. In this setting, urgent vascular surgical

consultation should be sought, and the nephrologist should assume that the kidneys may be viable for weeks to months.

Incidental Renal Artery Stenosis As mentioned, ASRVD is highly correlated with disease in both the coronary and the peripheral vasculature. Disease is usually identified incidentally at angiography or computed tomography (CT) for other indications. Most of these patients with coexisting ASRVD and coronary artery disease have only moderate degrees of RA stenosis (50% to 75%) with minimal hemodynamic impact. However, the presence of RA lesions is an independent risk factor for mortality, which may reach 30% over 4 years in high-risk groups.[37] Since no data support intervention for asymptomatic RA stenosis, the use of screening renal aortography at coronary angiography should be limited to patients who have demonstrated clinical manifestations, as summarized earlier, and in whom documentation of RA disease is likely to influence management.

Natural History

Early, retrospective angiographic studies (1980s) suggested ASRVD typically progresses over 2 to 5 years. "Progression" is usually defined as a greater than 25% luminal diameter narrowing or as severe stenosis progressing to vascular occlusion. Over 4 to 5 years, 6% to 16% of stenoses advance to occlusion. Prospective studies between 1990 and 1997 using Doppler ultrasound in patients with atherosclerotic RA lesions indicated hemodynamic progression in 30% over 3 years, varying by degree of initial stenosis, although total occlusion occurred in only 3%.[38] Measurable loss of kidney length (>1 cm) is less common but accompanies progressive vascular occlusion. Changes in serum creatinine are often minimal.[39]

Progression is most likely in patients with more than 60% stenosis. It often occurs without changes in BP control. Therapy with statins appears to reduce the risk of progression and occasionally induces regression of atherosclerotic RA stenosis.[40] Statins also appear to attenuate renal parenchymal injury associated with experimental ASRVD.[41]

Follow-up studies of patients with incidentally detected, high-grade RA stenosis (>70%) treated medically indicate that fewer than 10% required later revascularization for intractable hypertension.[42] Another report noted that few patients with incidental RA stenosis progressed to ESRD over follow-up of 8 to 9 years.[43] Patients followed after simultaneous renal angiography at cardiac catheterization noted no difference in serum creatinine between those with and without RA stenosis at follow-up.

Risk of Mortality

Both ASRVD and ischemic nephropathy (IRD) are associated with limited long-term survival, consistent with widespread atherosclerotic disease. Retrospective analyses report 3-year to 5-year mortality rates of 30% to 35% in patients with RA stenosis, largely caused by cardiovascular events or cerebrovascular accident (stroke). In follow-up of more than 1200 patients who underwent coronary and renal angiography, patients with RA stenosis had a 65% 4-year survival versus 85% for those without RA stenosis at catheterization. The 5- and 10-year survival rates for patients reaching ESRD caused by IRD are as low as 18% and 5%, respectively.[44]

Whether renal revascularization improves overall survival in patients with ASRVD remains controversial.[45] In one study, patients with bilateral ASRVD who were treated medically had better follow-up renal function than those who had undergone revascularization, but there was no difference in survival.[46] Other studies suggest that intervention directed at improving renal function may improve survival in these patients. An observational study reported 2-year survival of 80% in patients with ischemic nephropathy who underwent endovascular stenting.[47] Reports from combined UK and German cohorts treated prospectively indicated that improvement in renal function was more likely in revascularized patients and associated with substantial survival benefit compared with those treated with medications alone.[48] The morbidity and mortality associated with complications of endovascular interventions must be considered in the risk/benefit analysis of optimizing treatment of patients with ASRVD.[49,50] Prospective randomized controlled trials comparing renal artery stenting with medical therapy, including the recently published Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial, have failed to demonstrate a benefit of intervention on mortality or cardiovascular or renal end points.[51] CORAL is expected to publish important natural history data from a prospectively studied subgroup followed by serial duplex ultrasound studies.

FIBROMUSCULAR DYSPLASIA

Fibromuscular dysplasia (FMD) is a noninflammatory, nonatherosclerotic arteriopathy and the second most common cause of RVH. It usually involves the middle to distal renal artery or branches (Fig. 39-6). The vascular distribution of FMD involves primarily the renal and cerebral arteries. Renal arteries are involved with FMD in 65% to 70% of cases. Bilateral RA disease is seen in 25% to 35% of adult cases, in up to 78% of syndromic childhood FMD, and in most familial cases.[52] Associated midaortic syndrome should be considered in pediatric cases.[53] Cerebrovascular involvement is present in 25% to 30% of adult cases. Up to 65% of patients with renovascular FMD have concomitant cerebrovascular involvement. Less common extrarenal sites of involvement with FMD include coronary, mesenteric, celiac, splenic, aortic, and peripheral vasculature, with two sites involved in 30%, three sites in 20%, and more than three sites in 10% of patients.

Epidemiology

The prevalence of clinically apparent renovascular FMD is estimated at 4 in 1000, with a lower prevalence of cerebrovascular involvement of 1 in 1000.[54] Data from screening angiography in potential kidney donors suggest that the prevalence may be higher, with FMD observed in 3% to 6% of individuals. FMD has a female predilection, with about 90% of cases occurring in women. FMD is reported to be more common in whites than in blacks. Of those enrolled in the United States registry of patients with FMD, 95% are Caucasian, and the mean age of onset of hypertension 43 years.[55] It is unclear whether this racial predilection represents recruitment or geographic bias. Familial FMD occurs in approximately 10% of patients[54] and has been associated with subclinical evidence of carotid flow abnormalities in first-degree relatives, consistent with an autosomal dominant inheritance pattern.[56] FMD may also complicate other hereditary syndromes (e.g., Alport, Ehlers-Danlos, Marfan). Box 39-3 lists clinical disorders associated with FMD.

Pathophysiology

The pathophysiology of FMD is unknown. No unifying genetic mutations have been identified. It is likely that numerous disturbances in vascular collagen and structural processes can result in the FMD angiographic phenotype. Genes being investigated include collagen III *(COL 3A1),* α_1-antitrypsin, angiotensin I–converting

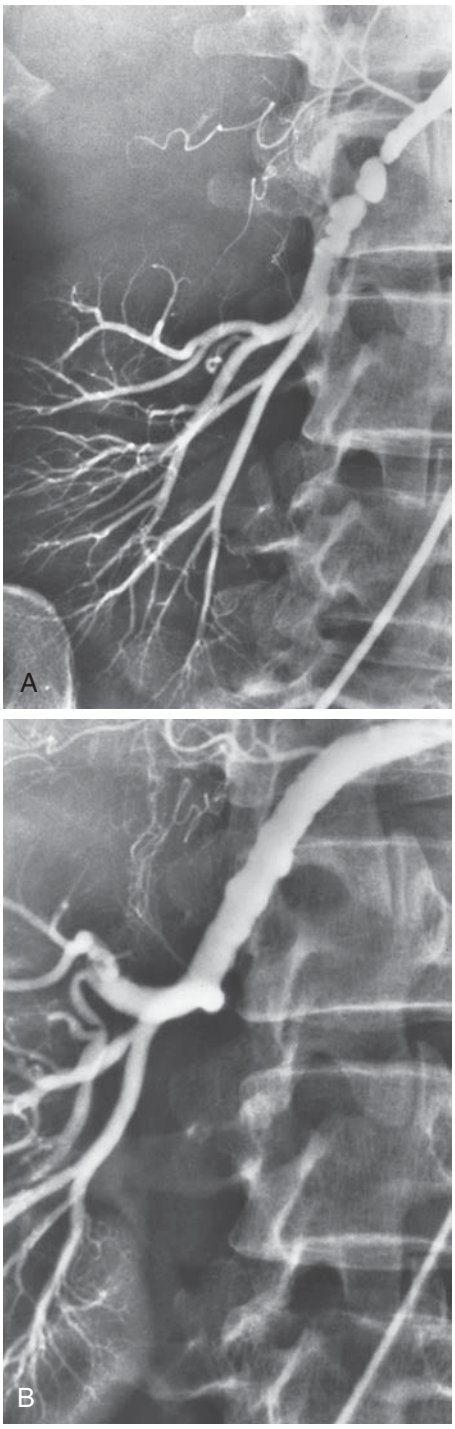

Figure 39-6 Fibromuscular dysplasia. A, Selective renal arteriogram illustrating the beaded appearance of fibromuscular dysplasia with multiple webs characteristic of medial fibroplasia in a 39-year-old woman. **B,** Selective injection of the same renal artery after technically successful percutaneous transluminal renal angioplasty. *(Courtesy Michael McKusick, MD, Mayo Clinic, Rochester, Minn.)*

enzyme, and JAGGED 1 (encodes for a ligand for Notch receptors). Other implicated etiologic factors include cigarette smoking, hormonal influences (based on the female predilection), and vascular trauma or stretching of the renal artery.[57]

Histologically, abnormal vascular wall structure is associated with irregular bands of collagen deposits and in some cases disruption of elastic membrane. Several subtypes of FMD have been described on

Fibromuscular Dysplasia: Clinical Manifestations and Associated Disorders

Clinical Manifestations

- Incidental finding (e.g., living kidney donors)
- Renovascular hypertension
- Renal infarction
- Loin or flank pain
- Hematuria
- Retroperitoneal hemorrhage
- Cerebrovascular accident (stroke)
- Transient ischemic attack
- Headaches
- Pulsatile tinnitus
- Horner syndrome
- Neck pain
- Dizziness
- Imaging finding of aneurysm dissection
- Amaurosis fugax
- Myocardial infarction
- Ischemic chest pain/dyspnea
- Postprandial abdominal pain
- Weight loss
- Hemobilia
- Claudication

Associated Disorders

- Tuberous sclerosis
- Marfan syndrome
- Ehler-Danlos syndrome
- Cystic medial necrosis
- Coarctation of the aorta
- Alport syndrome
- Renal agenesis or dysgenesis
- α_1-Antitrypsin deficiency
- Medullary sponge kidney
- Pheochromocytoma
- Infantile myofibromatosis
- Ergotamine preparation, methysergide
- Cigarette smoking
- Collagen III glomerulopathy
- Atherosclerotic renovascular disease
- Alagille syndrome
- Ask-Upmark kidney
- Celiac disease
- Cocaine exposure—intrauterine
- Crohn disease
- Homocystinuria
- Macrophagic myofasciitis
- Neurofibromatosis
- Williams syndrome

Box 39-3 Clinical manifestations and disorders associated with fibromuscular dysplasia.

the basis of the predominant layers of the arterial wall involved, but these are not mutually exclusive. In up to two thirds of cases examined histologically, more than one arterial wall layer is involved. The histologic features coincide with the arteriographic phenotypes outlined in Table 39-1. The three main types of FMD are medial fibroplasia, accounting for 85% to 100% of cases, and intimal and adventitial fibroplasia. In *medial* fibroplasia, alternating thin and thick ridges of collagen and elastic tissue deposits result in discrete stenoses alternating with aneurysmal sections characterized by fragmented internal elastic lamina. This produces the recognizable "string of beads" appearance on angiography. The loss of elastic structural integrity leads to ballooning or beading of the vessels such that the diameter of the beaded segment is larger than the diameter of the artery lumen. In *intimal* FMD, the angiographic pattern is smooth focal or elongated lumen narrowing and results from concentric intimal deposition of collagen with fragmentation and duplication of the internal elastic lamina. In *adventitial* or *periarterial* FMD, the rarest histologic variant, dense collagen replaces the normal fibrous tissue in the adventitia, resulting in concentric, smooth narrowing of the lumen.[58] Unlike atherosclerotic RA stenosis, FMD generally appears beyond the first 2 cm from the RA origin. FMD and atherosclerotic disease may also coexist. The differential diagnoses for angiographic lesions consistent with FMD include ASRVD, although this is usually easily distinguishable; renal vasculitis, particularly Takayasu arteritis; segmental arterial mediolysis;

Fibromuscular Dysplasia: Histologic Classification and Angiographic Phenotypes			
Type	**Frequency**	**Histology**	**Angiographic Appearance**
Medial			"String of beads"
Medial fibroplasia	85%-100%, most common	Alternating ridges of collagen/loss of elastic membrane	Medial: bead diameter is larger than lumen diameter
Perimedial fibroplasia	Rarer (10%-15%)		Perimedial: bead diameter is smaller than lumen diameter
Medial hyperplasia	Rarest	True smooth muscle hyperplasia: no fibrosis	Medial hyperplasia: smooth stenosis without beads
Intimal	<10%	Circumferential deposition of collagen in intima: fragmented or duplicated internal elastic lamina	Concentric smooth stenosis: long smooth narrowing
Adventitial	<1%	Dense collagen replaces fibrous tissue in adventitia and surrounding tissue	Smooth stenosis or diffuse attenuation of vessel lumen

Table 39-1 **Histologic classifications of fibromuscular dysplasia and angiographic phenotypes.**

and an artifact of imaging known as "standing arterial waves," thought to be caused by catheter-induced vasospasm.[59]

Renal artery aneurysms may also be seen in FMD. The frequency is unclear. Aneurysms were identified in only 5.6% of the patients in the U.S. FMD registry, but some series report up to 50% having aneurysms. Aneurysms in FMD are most common in the renal vasculature compared with other beds. When present, 17% of patients with an aneurysm at any vascular site have more than one vascular site involved, with some having up to four.[55]

Clinical Manifestations

Clinical manifestations of FMD are summarized in Box 39-3. Because it is usually asymptomatic for many years, FMD is sometimes detected as an incidental finding during angiography. The most common adult clinical presentation is early-onset hypertension between ages 15 and 50 years, more often in women than men. FMD is also the most common cause of RVH in children. Although RVH in women under age 50 is the most common presentation of renal FMD, the presence of lesions in other vascular territories can lead to other symptoms. Headaches, pulsatile tinnitus, and bruits over the carotid arteries, epigastrium, and femoral regions are common. Stroke, transient ischemic attacks, or amaurosis fugax may occur. FMD should be considered in patients with early stroke or subarachnoid hemorrhage caused by cerebral aneurysms or when extrarenal vascular aneurysms or dissection occurs. Therefore, young patients presenting with spontaneous carotid artery dissection or occlusion should be considered at risk for renovascular FMD, and vice versa. In addition, FMD with associated aneurysms of the renal artery can present as renal infarction from renal artery dissection, embolism from clot within the aneurysm, or retroperitoneal hemorrhage with flank pain and hemorrhagic shock (Box 39-3).

Natural History

The natural history of FMD has not been adequately studied. Progression of disease can be manifest as the development of new focal lesions within the same arterial bed, worsening arterial luminal narrowing within a specific lesion, involvement of a new vascular territory, or development or enlargement of arteriovenous fistulas or aneurysms. It appears that up to 27% of patients may demonstrate angiographic progression of FMD when serial studies are undertaken. This appears to be limited to younger patients, with few patients developing new or progressive lesions after age 50 years. FMD rarely causes ESRD unless hypertension remains uncontrolled, or thrombosis or dissection of the renal vessel results in renal infarction. Renal cortical atrophy has been reported in more than half of patients with untreated FMD.[60]

DIAGNOSIS OF RENOVASCULAR HYPERTENSION

In addition to consideration of age of onset and quality of hypertension, the diagnosis of RA disease–induced RVH requires both demonstration of a critical stenotic vascular lesion and activation of the RAAS. From the imaging standpoint, conventional angiography remains the reference standard to define the anatomy of the renal vasculature against which other screening modalities are compared. Common noninvasive screening modalities include RA duplex ultrasound, computed tomographic angiography, and magnetic resonance angiography (see Chapter 5) (Table 39-2). The goal of noninvasive screening is to limit further invasive testing. These methods provide different information and may vary between institutions in both availability and reliability.

Renal artery duplex scanning is often used to identify and to follow hemodynamic effects of vascular lesions serially. It is relatively inexpensive and requires no contrast. It is most effective in detecting lesions of the main RA near the ostium, making it a better screening test for ASRVD than for FMD. However, the reliability of this method depends on the skill of the ultrasonographer and on the body habitus of the patient. Duplex ultrasound provides little functional information regarding the kidney beyond the vascular lesion, although many important structural features may be determined, including kidney size and presence of ureteral obstruction. The diagnostic criteria for hemodynamically significant RA stenosis by duplex ultrasound includes acceleration of blood flow through the stenotic area that exceeds the flow in the aorta, as well as abnormal waveforms representing blood flow in the affected vessel (see Chapter 5). Parameters measured using this modality include peak systolic velocity (PSV) at various sites along the aorta and renal artery, acceleration time and index, and intrarenal resistive index. The resistive index has been associated with intrinsic small vessel renal disease, and a value greater than 80 has a strong negative predictive value on likelihood of BP response to intervention. PSV in the range of 250 to 350 cm/sec is considered the threshold for identifying a 60% to 70% RA stenosis.

Magnetic resonance angiography (MRA) offers the potential to provide both structural vascular imaging and functional information. MRA with gadolinium contrast gives excellent imaging of the

Relative Value of Imaging Methods for Evaluation of Renal Vasculature

Methods	Images of Vessels	Tissue Perfusion	Function (GFR)	Advantages	Disadvantages
Spiral computed tomographic angiography	+++	+	±	Provision of three types of images, examination of venous structures, might be useful for evaluating transplant donors	High contrast requirement
Contrast angiography	+++	++	±	Nephrography estimates volume of viable tissue; gold standard	Risk of catheter-induced injuries and contrast nephropathy
Captopril renography	–	+++	++	Change in GFR might estimate reversibility of lesion; widely available, noninvasive; totally normal renogram effectively excludes significant vascular disease.	
Duplex ultrasound	++	++	–	Precise measurement of flow velocity, suitable for serial studies, relatively inexpensive	Produces little functional information; is not suitable for accessory vessels
Magnetic resonance angiography	++	++	±	No radiation exposure	Gadolinium contrast not used for eGFR <30 ml/mg; concern for nephrogenic systemic fibrosis

Table 39-2 Relative value of imaging methods for evaluating the renal vasculature. The available techniques vary in their ability to image the renal vessels, to assess tissue perfusion, and to measure glomerular filtration rate (*GFR; eGFR,* estimated).

main renal arteries. Limitations of MRA include interobserver variability, a recognized tendency to overestimate luminal narrowing, and limited sensitivity for middle and distal vascular lesions. Caution is advised in the use of gadolinium agents in patients with reduced GFR, based on reports of nephrogenic fibrosing dermopathy in patients with advanced CKD exposed to these agents. Studies are underway to improve the sensitivity and negative predictive value of non–gadolinium-enhanced MRA in the detection of RA stenosis (Fig. 39-7).

Computed tomographic angiography (CTA) with vascular reconstruction achieves image qualities almost equivalent to those of angiography but requires more iodinated contrast. CTA is becoming the noninvasive study of choice in patients whose risk of contrast-associated nephrotoxicity is minimal. However, CTA may overestimate the degree of stenosis with false-positive rates, which vary according to reconstruction protocols, vascular calcification, and regional differences in experience. CTA is highly sensitive for identifying lesions associated with FMD and is a good screening test for these patients, who generally have good kidney function[61] (Fig. 39-8).

Angiography remains the gold standard for defining the degree of stenosis associated with ASRVD and for identification of FMD. Aortography provides important anatomic and functional information in cases of tight stenosis or occlusion, including the demonstration of delayed perfusion of the kidney and distal reconstitution of the proximally occluded renal vessel. This is important in consideration of surgical revascularization for retrieval of renal function. In experienced hands, selective renal angiography to identify significant RA stenosis can be performed with as little as 20 ml of iodinated contrast. In very-high-risk cases, carbon dioxide can be used in place of contrast to assess the renal ostium and proximal vessel where atherosclerosis typically develops.

Unfortunately, few tests can accurately predict favorable response to intervention. Two tests used for this purpose in cases of unilateral RA disease include captopril renography and measurement of renal vein renin levels. Figure 39-9 illustrates a captopril-enhanced renogram in a patient with RA stenosis. This examination provides no direct image of the renal vessel, but does provide a view of the rate of isotope appearance and washout, reflecting the sequence of renal blood flow and filtration. The study provides functional information

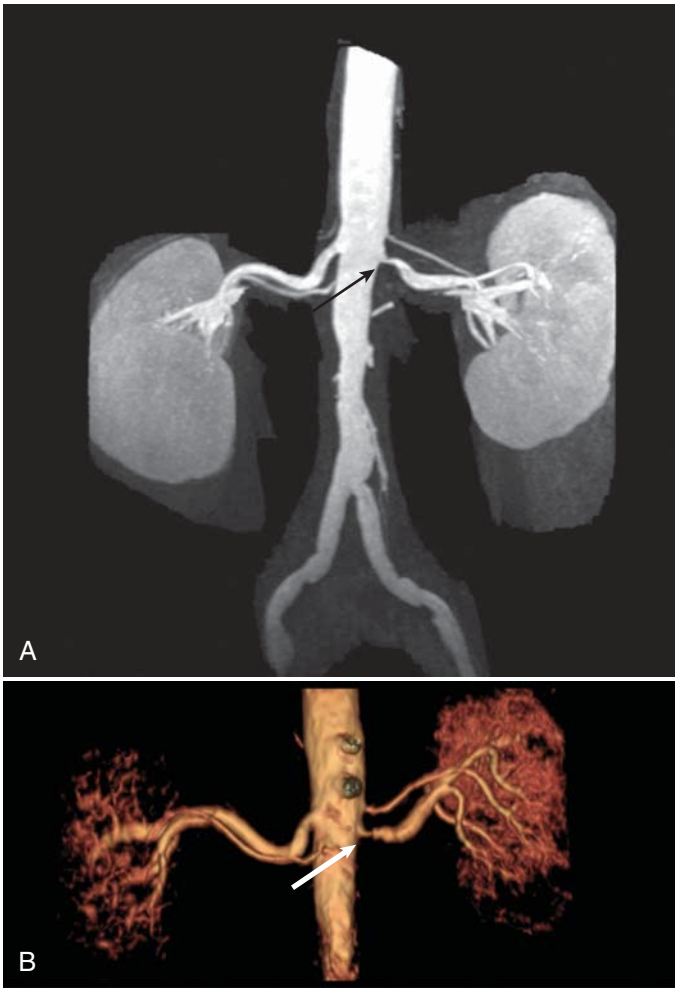

Figure 39-7 Magnetic resonance angiogram with and without gadolinium contrast enhancement. A, High-grade stenosis affecting the left inferior renal artery is evident, with functioning kidney tissue as reflected by gadolinium nephrogram *(arrow)*. Concerns about the role of gadolinium in the development of nephrogenic systemic fibrosis have greatly reduced the use of this contrast agent. **B,** As a result, methods to image the vasculature without contrast material are being developed that produce excellent reconstructed images *(arrow)*.

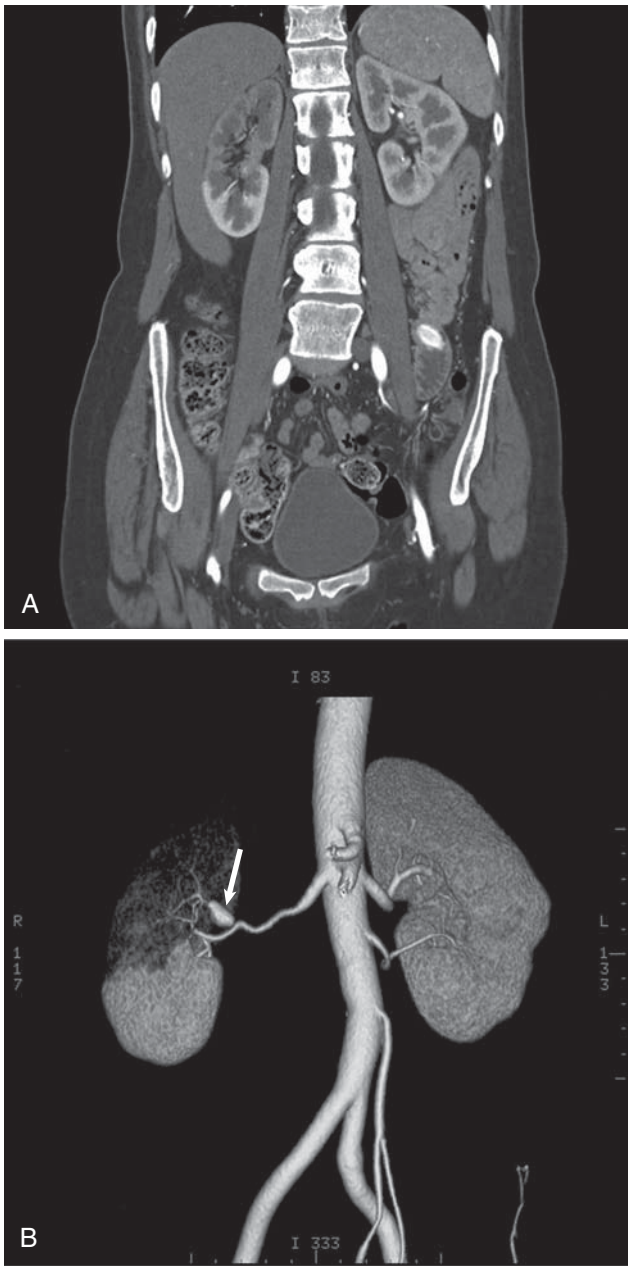

Figure 39-8 Computed tomography angiogram of renal artery aneurysm with area of renal infarction in right kidney. A, Coronal image demonstrates area of intact tissue with no blood perfusion within the kidney parenchyma. **B,** Reconstructed view with vascular aneurysm *(arrow)* and minimal flow in the distribution beyond this segment, consistent with near-total occlusion. This patient presented with accelerated renovascular hypertension treated primarily with renin-angiotensin system (RAS) blockade.

regarding the size and excretory capacity of the kidney, as well as emphasizing the role of Ang II in maintaining GFR. This test has a high negative predictive value when completely normal.[62] Many intrinsic renal abnormalities unrelated to the main RA may change these curves, which limits its value in the presence of reduced GFR (serum creatinine >2.0 mg/dl, or 176 µmol/l).

Renal vein renin measurements may help predict the BP response to renal revascularization.[5,63] Previous studies indicated that lateralization of renal vein levels (>1.5:1 stenotic-nonstenotic kidney ratio) predicts a favorable BP response for more than 90% of patients. Because failure to lateralize also carried a favorable response in almost half of patients, the negative predictive value is limited. Some

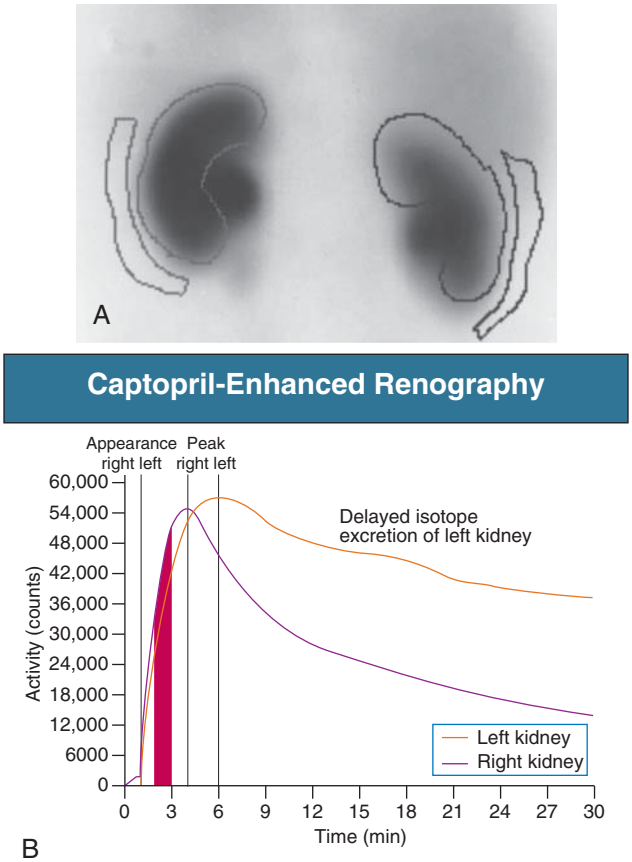

Figure 39-9 Captopril-enhanced renography. A, Scan in a patient with newly developing hypertension. **B,** Renogram demonstrates delayed arrival and excretion of isotope (MAG3) in the affected left kidney.

clinicians use these measurements to verify the role of a pressor kidney before undertaking nephrectomy.

TREATMENT OF RENOVASCULAR DISEASE

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) stated that the goal of hypertension therapy is to reduce morbidity and mortality "by the least intrusive means possible." In RVH, this entails balancing the risks and benefits of several modalities, ranging from medical therapy to surgical or endovascular repair. Whether renal revascularization improves outcomes in the era of effective medical therapy has been the subject of several prospective randomized controlled trials, including ASTRAL and the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study in the United States.

Medical Therapy

Most patients with RVH are treated initially with conventional lifestyle modification, control of the metabolic syndrome and antihypertensive medications (see Chapter 36). Regimens using agents that interfere with the RAAS, such as ACE inhibitors, renin inhibitors, and angiotensin receptor blockers (ARBs), as well as the use of diuretics and the dihydropyridine class of calcium channel blockers (CCBs), allow achievement of target BP levels in most patients. RAAS blockade is considered fundamental. Successful renal revascularization rarely leads to withdrawal of all antihypertensive

medications in the current era. Therefore, it may be questioned whether the costs and risks of renal revascularization are warranted for patients whose BP and kidney function are stable on an acceptable antihypertensive regimen.

When there is critical RA stenosis, reduction of arterial pressure has the potential for reduction of renal blood flow below levels needed to sustain glomerular filtration. RA pressures beyond the stenosis may decrease below that needed for autoregulation of blood flow and GFR, estimated at 60 mm Hg in humans.[26] Such a reduction in blood flow can develop with any antihypertensive drug and can rarely lead to thrombotic occlusion.

The RAAS blockers remove the vasoconstrictive action of Ang II at the efferent arteriole. When preglomerular pressures are reduced for any reason, Ang II preserves glomerular transcapillary filtration pressures by constricting the efferent arteriole preferentially. This maintains glomerular filtration despite marginal blood flow. Inhibition of this Ang II effect under these conditions can lead to AKI.[64] The decrease in GFR is apparent clinically under conditions in which the entire renal mass is affected, including bilateral RA stenosis or stenosis to a solitary functioning kidney.[65] Although the functional decrease in GFR induced by RAAS inhibitors is usually reversible, occasionally patients do not recover renal function. Thus, these agents are a double-edged sword in RVH. They have unique properties, allowing more effective BP control than previously possible in this particular situation, but at the same time have the potential for early loss of filtration pressure in patients with critical levels of RA stenosis.

Clinical experience with RAAS blockers in the treatment of RVH is reassuring, however. Postmarketing surveys of >15,000 prescriptions in the United Kingdom after the release of enalapril indicated few, but important, adverse experiences. Most often, these occurred in patients with preexisting renal dysfunction who were taking potassium-sparing diuretics and had other known atherosclerotic disease.[26] Registry data and prospective follow-up studies in patients with ASRVD indicate that blockade of the RAAS is usually well-tolerated and associated with reduced morbidity for patients.[23,28] Nevertheless, hyperkalemia and increasing creatinine values during treatment with RAAS blockade (Table 39-3) in the setting of critical RA stenosis affecting the entire renal mass are indications to consider alternative therapy and/or renal revascularization. Furthermore, medical therapy including RAAS blockade may be insufficient to adequately control BP and cardiac manifestations of RA stenosis including recurrent episodes of pulmonary edema. These patients may benefit from renal revascularization regarding both level of BP control and stabilization of renal and cardiac function.

Guidelines for Limiting Renal Toxicity with ACE Inhibitors

Guideline	Specific Conditions/Interventions
Recognize predisposing condition	Widespread atherosclerotic disease Associated renal artery stenosis Impaired pretreatment renal function Solitary functioning kidney Activated renin-angiotensin system Low sodium intake Diuretic therapy Other volume losses: vomiting, diarrhea Vasodilator administration Low cardiac function: hypotension, hyponatremia Other agents affecting kidney function (e.g., nonsteroidal anti-inflammatory agents)
Monitor effects of initiating ACE inhibitor therapy	Serum creatinine: measure over first days and at weeks 2 and 4, especially in high-risk patients. Elevated serum potassium: withhold potassium supplements; withhold potassium-sparing agents; use low-potassium diet.
Manage volume	Temporarily withhold diuretics. Titrate dose of both diuretics and ACE inhibitor. Liberalize sodium intake, and replace volume; consider rechallenge with ACE inhibitor after volume repletion.

Table 39-3 Guidelines for limiting renal toxicity with angiotensin-converting enzyme (ACE) inhibitors.

Success Rates with Percutaneous Transluminal Renal Angioplasty

	1989–1995 (%)	1981–1987 (%)
Patients	1359	691
Arteries	1664	—
Fibromuscular Disease		
Cured	42	53
Improved	36	38
Cured plus improved	78	91
Failed	21	8
Atherosclerotic Renovascular Disease		
Cured	14	18
Improved	51	48
Cured plus improved	65	67
Failed	34	32

Table 39-4 Technical success and clinical effect of percutaneous transluminal renal angioplasty (PTRA). Summary of 17 reports of PTRA comprising more than 2000 patients, beginning in 1981. *(Modified from references 69 and 93.)*

Renal Revascularization

Restoring the renal blood supply is a rational goal of treating hypertension related to renovascular disease. In a young person with FMD, a permanent cure of hypertension is sometimes achieved. Revascularization offers such a patient the potential for relief from a lifelong regimen of antihypertensive medications and cardiovascular risk associated with high BP. In practice, however, cures are infrequent. More often, renal revascularization allows improved BP control and stabilization of kidney circulation.

Percutaneous Transluminal Renal Angioplasty for Fibromuscular Dysplasia

Currently most centers treat hypertension associated with FMD with percutaneous transluminal renal angioplasty (PTRA) without stenting.[66] Approximately 86% of patients require less antihypertensive medication after technically successful PTRA. "Complete cure," defined as normal arterial pressure without medications, occurs in 35% to 45% of cases.[67] Predictors of hypertensive response include lower levels of preintervention systolic BP, younger patient age, shorter duration of hypertension, and positive result of simplified captopril renogram.[68] Table 39-4 summarizes 17 reported series assessing technical success and clinical effect of PTRA in patients with RVH caused by FMD.[69] Although primary technical success rates for PTRA are high (>90%) for FMD, restenosis from either inadequate initial treatment or recurrent fibrosis has been reported in up to 34% of cases. This appears to be most common with the "string of beads"

angiographic variant, which has multiple areas of stenosis.[70,71] Some interventionalists recommend the use of intravascular ultrasound to guide adequate endovascular treatment of these lesions, allowing for visualization of web-like membranes often present within them.[72]

Intimal hyperplasia is associated with higher rates of technical failure and early restenosis. Restenosis can be treated by repeated PTRA if needed or, in the case of intimal and adventitial disease, may require surgical revascularization.[73] As patients with FMD age, they are at significant risk of developing essential hypertension or ASRVD, such that the effectiveness of intervention on freedom from hypertension wanes with age.[74]

When FMD is associated with large aneurysmal dilations exceeding 1.5 cm in diameter, surgical revascularization has been the standard of care. Endovascular management of RA aneurysms sometimes can be achieved by use of "covered" stent grafts to exclude the aneurysm. Women of childbearing age with RA aneurysms should be treated surgically or with a covered stent graft before pursuing pregnancy because of the risk of ruptured aneurysm during pregnancy or delivery.

Atherosclerotic Disease: Endovascular Stents

Primary endovascular RA stenting has become standard for the interventional treatment of atherosclerotic RA stenosis in most centers. Comparisons between PTRA alone versus PTRA with stent placement establish superior immediate and long-term results with stents.[75] With current techniques, target vessel patency rates regularly exceed 95%. Short-term use of platelet inhibitors (e.g., clopidogrel) for several weeks to prevent vessel occlusion is standard.

Functional changes and BP changes may develop over weeks and months, when antihypertensive medications can be adjusted. A rise in BP should raise the question of vessel restenosis that occurs in 14% to 30% of patients over the first year. Most occur within 6 months of revascularization and are more common for smaller vessels.

Table 39-5 summarizes results from observational reports of more than 1000 patients undergoing renal artery stent placement for either hypertension or renal function preservation. BP control rates were improved in 50%, with 68% of patients experiencing "stabilization" or "improvement" in renal function over a mean of 17 months.[76] The effects of RA stenting on the course of CKD in patients with RA stenosis remain ambiguous. In almost all studies reporting renal function outcome after stenting, the percentage of patients experiencing improvement in renal function is offset by a group with worsening renal function. Those whose renal function improves the most tend to be those whose renal function was actively deteriorating over the preceding year.[77] Patients with deterioration of renal function after stenting likely experience complications such as cholesterol embolization or contrast nephropathy. Patients with advanced CKD at intervention tend to progress over time to require renal replacement therapy despite technically successful restoration of blood flow.[78]

Common complications of PTRA include contrast nephrotoxicity, which is usually reversible, and atheroembolism, from which patients usually do not recover (Table 39-6). Recent reviews suggest

Complications of Percutaneous Transluminal Renal Angioplasty

Type (Frequency)	Complications
Total (63/691 or 9.1%)	—
Fatal (3/691)	Cholesterol embolism Cerebral hemorrhage Bowel infarction
Most frequent	Cholesterol embolism Contrast-associated nephrotoxicity Renal artery dissection Renal artery thrombosis/occlusion Segmental renal infarction Hematoma at puncture site
Classified as indirect	Cerebrovascular accident (stroke) Myocardial infarction Anterior spinal artery thrombosis Branchial artery thrombosis Bowel infarction

Table 39-6 Complications of percutaneous transluminal renal angioplasty (PTRA). *(Modified from reference 93.)*

Renal Function Outcomes After Endovascular Stenting

Year	Author	No. of Patients	Follow-up	Renal Function Outcome (%)			Restenosis (%)
				Improved	*Stable*	*Worse*	
1991	Rees	100*	7 mo	36	36	28	25
1994	Hennequin	100*	32 mo	17	50	33	20
1995	Van de Ven	92*	6 mo	36	64	0	13
1996	Iannone	86*	10 mo	36	45	19	14
1997	Boisclair	100*	13 mo	41	35	24	ND
1997	Harden	100*	6 mo	34	34	32	13
1998	Shannon	100*	9 mo	43	29	28	0
1998	Dorros	163*	6–48 mo		66-75‡	25-33	
2000	Baumgartner	107†	12 mo	33	42	25	21
2000	Watson	25	8 mo	72	28	0	ND
2000	Burket	37†/127*	15 mo	43	24	33	ND
2001	Bush	69	20 mo	22	48	25	ND
2001	Beutler	63	23 mo	12	68	19	17-19

Table 39-5 Renal function outcomes after endovascular stenting. *ND,* Not done. *Includes patients with and without renal impairment. †Patients with renal impairment. ‡Includes those with stable or improved renal function at last follow-up; the 75% and 25% values represent those stented for bilateral renal artery stenosis. *(Modified from reference 76.)*

Blood Pressure Outcome for Surgical Revascularization in Renovascular Hypertension		
Outcome (%)	Fibromuscular Disease (*n* = 1014)	Atherosclerosis of Renal Arteries (*n* = 631)
Cured	58 (14-100)	37
Improved	30	46
Cured plus improved	88	84
Failed	12	15

Table 39-7 Blood pressure outcome for surgical revascularization in patients with renovascular hypertension. Summary of results for more than 1200 patients. Follow-up procedures and definitions of blood pressure cure varied greatly between series. Surgical mortality was 1.3% to 5.8% in patients with stenosis from atherosclerosis and nil in those with fibromuscular disease. *(Modified from references 67 and 94.)*

that 7.5% to 9% of patients have a major, procedure-related complication,[76] including local arterial dissection, aortic dissection, and segmental renal infarction.

Surgical Revascularization

Prior to the introduction of PTRA with stents, surgical revascularization was the standard treatment for patients with IRD and RVH (Table 39-7). Such procedures involve major vascular surgery and carry considerable risk, cost, and morbidity. Risks are reduced with preoperative screening and treatment of associated coronary and carotid disease. As a result, surgical intervention for renovascular disease is reserved for patients refractory to medical therapy for whom endovascular therapy fails[79] or who have associated aortic disease that is not amenable to endovascular therapy.[80] Despite these caveats, successful surgical revascularization in well-selected cases provides durable restoration of kidney blood supply and long-term survival (81% at 5 years).[81] Overall, the effects of surgical revascularization on BP and renal function response in patients with ASRVD mirrors those for endovascular therapy. Diabetic patients form an important subgroup of those with IRD. Surgical revascularization in this group is associated with similar renal functional responses but an inferior rate of BP response and higher postoperative mortality risk or eventual dialysis dependence.

Some dialysis-dependent patients and some with advanced CKD with IRD experience recovery of renal function after surgical revascularization.[82] The best predictor of successful and sustained withdrawal from dialysis is a rapid and recent preoperative decline in GFR, often associated with occlusion of a critically stenotic main RA and a kidney with preserved size and extensive collateral supply.

Some patients develop RVH associated with total occlusion of a preexisting RA stenosis resulting in nonfunctioning of that kidney. Hypertension in these patients may improve with nephrectomy, which can be undertaken with a laparoscopic procedure. Results from a recent series indicate that improved BP can be obtained in such patients without important loss of renal function. Estimates of renal function in this group were 11% in the removed kidney and 89% in the contralateral kidney.[83]

Realistic Outcomes and Controversies with Renal Revascularization

For some patients, technically successful renal revascularization leads to better BP control and improved kidney function. Antihypertensive medication requirements decrease, although rarely are eliminated entirely. Remarkably, the limited prospective data comparing medical therapy with renal revascularization in the current era at most have demonstrated modest benefit regarding renal or cardiovascular outcomes for atherosclerotic disease. Each of three small, randomized controlled trials in the 1990s could identify only minor differences in BP and renal outcomes.[84-86] Despite the lack of prospective trials, application of endovascular RA stenting in the United States rose more than fourfold between 1996 and 2005.[87] Most series report stabilization of renal function, meaning that average serum creatinine levels do not change. Some patients experience improved renal function, whereas others have clinically significant loss of renal function. In most series, this occurs in up to 18% to 20% of patients treated either with PTRA or surgery. Although group average values do not change, some patients experience adverse effects on renal function that should be considered for management decisions.

Among the few prospective, randomized trials related specifically to renovascular hypertension, the most prominent was the Dutch Renal Artery Stenosis Intervention Cooperative Study group (DRASTIC). It included 106 patients with relatively resistant hypertension randomized to medical therapy or PTRA. The lack of difference in BP after 1 year between patients treated with PTRA and treated medically led the authors to conclude that "angioplasty has little advantage over antihypertensive drug therapy."[84] The results of this study were analyzed under "intention-to-treat" statistical rules, but were confounded by 22 of 50 patients assigned to medical therapy (44%) who crossed over to the PTRA arm because of uncontrolled BP levels at 3 months. Despite their inclusion in the medical arm, many authorities reviewing these data argue that this group offers compelling evidence of medical treatment failure in some cases and the benefit of renal revascularization for such individuals.

Since then, additional trials have been undertaken. Reports from prospective registry data from the UK and Germany suggest that revascularization provides measurable slowing of renal functional loss and a survival advantage compared with patients managed with medications alone.[48] This has not been confirmed by randomized controlled trials. ASTRAL compared medical therapy and stenting to medical therapy alone in more than 800 subjects for whom clinicians were "uncertain" as to whether they would benefit from revascularization. Results demonstrated no differences in renal function, BP, CHF, or mortality end points over several years.[14] In ASTRAL, no definition of "certainty" was provided, nor were data regarding outcomes of patients not included in the trial, making it unclear how these results can be generalized to wider groups. The Stent Placement in Patients with Atherosclerotic Renal Artery Stenosis (STAR) trial randomized 140 patients to medical or stent therapy to evaluate loss of creatinine clearance over 2 years.[88] This trial was limited by imprecise definition of stenosis so that 28% of patients assigned to stent therapy were untreated because only trivial stenosis was found at angiography. A small, randomized trial extending more than 9 years failed to detect a mortality benefit with surgical revascularization.[89] The recently completed CORAL trial was the largest randomized controlled trial comparing medical therapy to medical therapy plus stenting in patients with significant renal artery stenosis and hypertension or chronic kidney disease. CORAL randomized 974 patients to well-defined medical therapy including RAAS blockade with or without stenting. CORAL results showed no differences in the composite end point of mortality, cardiovascular and renal events, or any of the individual components. Clinicians caring for patients with ASRVD should embark on aggressive cardiovascular risk factor reduction, incorporate RAAS blockade in the management of hypertension, and individualize consideration of endovascular treatments to avoid unnecessary loss of kidney function and to limit futile interventions.

Integrated Approach to Treating Renovascular Disease

Central to the management of patients' renovascular disease is the recognition of distinctive clinical syndromes, linking acceleration of hypertension with deteriorating renal function and, occasionally, episodic circulatory congestion ("flash" pulmonary edema). Many patients can be managed effectively by medical means, including vigorous measures to prevent atherosclerotic progression with statin therapy and smoking cessation. It must be emphasized that long-term care of such patients is an ongoing process that should be reviewed at regular intervals. When progressively more complex antihypertensive regimens become required, or renal function deteriorates, or for patients with recurrent flash pulmonary edema despite adequate medical and diuretic therapy, consideration should be given to identification and correction of critical vascular lesions affecting the kidneys.

Figure 39-10 provides a general algorithm for evaluating and managing the patient with renovascular disease. In general, a

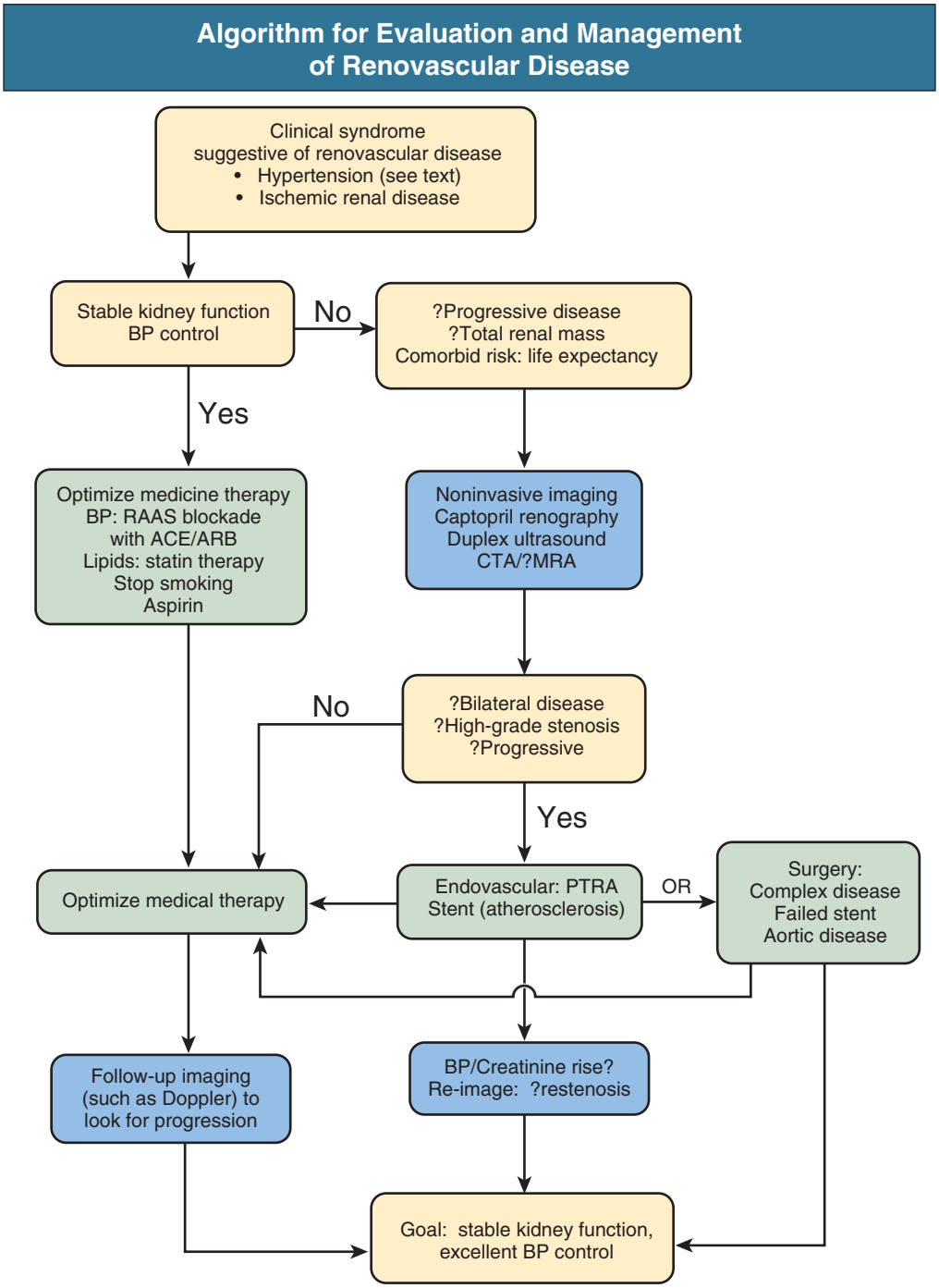

Figure 39-10 Algorithm for evaluation and management of renovascular disease. The intensity of imaging and revascularization depends on both the level of kidney function and the blood pressure, in addition to the comorbid disease risks for the individual patient. The overall goal should focus on stable kidney function and blood pressure levels. As with any other vascular disease, monitoring for disease progression and recurrence is an important element of long-term management. *ACE,* Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *CTA,* computed tomographic angiography; *F/U,* follow-up; *MRA,* magnetic resonance angiography; *PTRA,* percutaneous transluminal renal angioplasty; *RAAS,* renin-angiotensin-aldosterone system.

reasonable initial approach to patients with ASRVD is to optimize medical therapy for hypertension and cardiovascular risk factors, including smoking cessation, management of hyperlipidemia and diabetes mellitus. When ASRVD is associated with RVH, RAAS blockade is fundamental to control of blood pressure. Often, a multidrug regimen is needed, including diuretics. The decision to pursue diagnostic studies and revascularization should be individualized based on a number of factors, including response to medical therapy, age, kidney function trajectory, estimated risk of intervention, and cardiovascular status.

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CHAPTER 40

Endocrine Causes of Hypertension: Aldosterone

I. David Weiner and Charles S. Wingo

Recent advances in the diagnosis of aldosterone-induced hypertension have led to the recognition that primary hyperaldosteronism is more common than previously thought. Effective diagnostic strategies are available, and treatment regimens are highly efficacious.

ETIOLOGY AND PATHOGENESIS

Aldosterone is a steroid hormone normally produced by the zona glomerulosa of the adrenal glands (Fig. 40-1). Aldosterone synthase, which is encoded by the gene *CYP11B2,* is the generally accepted rate-limiting enzyme in adrenal aldosterone production. Table 40-1 summarizes factors known to stimulate or to inhibit aldosterone synthesis by the adrenal gland. Aldosterone exhibits a circadian change in serum concentration, greatest in the late morning and with peak values about 50% greater than the average concentration. The factors accepted as physiologically important regulators of aldosterone production include angiotensin II (Ang II), which stimulates aldosterone production through activation of the AT_1 receptor, and atrial natriuretic peptide and chronic hypokalemia, which inhibit aldosterone production.[1]

Substantial advances have been made recently in our understanding of the factors that lead to primary aldosteronism. In particular, mutations in the gene for the potassium channel KCNJ5 are now recognized as a frequent cause of primary aldosteronism. Germline mutations cause bilateral, familial primary aldosteronism, and somatic mutations are present in about 40% of aldosterone-producing adenomas.[3,4] Mutations in the genes *ATP1A1* (encoding a Na^+, K^+-ATPase) and *ATP2B3* (encoding a Ca^{2+}-ATPase) have also been identified in about 7% of aldosterone-producing adenomas.[5]

A less common genetic cause is *familial hypertension type 1* (FH-1), also known as *glucocorticoid-remediable aldosteronism* (GRA). In GRA, there is crossover between the *CYP11B1* and *CYP11B2* genes, resulting in a chimeric aldosterone synthase gene whose expression is regulated by adrenocorticotropic hormone (ACTH), leading to excessive aldosterone release.[6,7] GRA should be considered in children or young adults with refractory hypertension or in whom there is a family history of hypertension in the same age range or history of premature hemorrhagic stroke.[8] If suspected, genetic testing is the preferred diagnostic approach because of improved sensitivity and specificity over measurement of steroid metabolites or dexamethasone suppression testing.[8,9] If GRA is identified, corticosteroids are administered at the minimal dose necessary to suppress ACTH release, resulting in often dramatic improvement in blood pressure (BP) control (see Chapter 49).

Aldosterone regulates BP by several mechanisms, including effects on the kidneys, vasculature, central nervous system (CNS), and other endocrine hormones (Fig. 40-2). No single effect is sufficient to explain the hypertension that occurs in primary hyperaldosteronism; together the effects explain why primary hyperaldosteronism causes refractory hypertension. Aldosterone has multiple renal effects that regulate BP. First, aldosterone stimulates renal sodium chloride (NaCl) retention by increasing expression of the thiazide-sensitive NaCl cotransporter in the distal convoluted tubule, the amiloride-sensitive epithelial sodium channel (eNaC), in the collecting duct, and the chloride-reabsorbing protein, pendrin, in the cortical collecting duct.[10-12] Aldosterone also has acute effects on sodium reabsorption in these segments through mechanisms that do not require protein synthesis.[13]

Second, aldosterone alters BP through generation of hypokalemia. The increased Na^+ reabsorption enhances K^+ secretion. In addition, aldosterone increases extrarenal cellular potassium uptake by stimulating the ubiquitous Na^+,K^+-ATPase, further decreasing extracellular potassium.[14] As discussed in Chapter 9, potassium depletion raises BP through a variety of mechanisms.

Aldosterone has multiple effects on the vasculature. Aldosterone increases both basal vascular tone and vascular reactivity to circulating vasoconstrictors, including norepinephrine, epinephrine, Ang II, and vasopressin.[15,16] Aldosterone decreases flow-mediated vasodilation, perhaps because of decreased nitric oxide production resulting from decreased endothelial nitric oxide synthase expression.[17] In the central nervous system (CNS), aldosterone stimulates sympathetic nervous system tone, which further increases BP.[18] Finally, aldosterone causes perivascular fibrosis and stimulates vascular endothelin expression.[19]

Aldosterone mediates its physiologic and pathophysiologic effects predominantly by activating the *mineralocorticoid receptor* (MR).[20] The MR is located in the inactive state in the cytoplasm; aldosterone binding to MR promotes a conformational change and translocation to the nucleus, where it regulates gene transcription.

Cortisol is a naturally synthesized glucocorticoid with an affinity for MR similar to that of aldosterone, but cortisol is present in plasma at about 100-fold greater levels than aldosterone. The enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) is expressed in the aldosterone-sensitive distal nephron and collecting duct and metabolizes cortisol to cortisone, which binds to MR poorly, thereby preventing glucocorticoid-dependent MR activation. Either the genetic deficiency of or the ingestion of inhibitors of 11β-HSD can result in excessive activation of the MR and development of severe hypertension[21] (see Chapter 49). Aldosterone also has nongenomic effects, but their role in mineralocorticoid-dependent BP regulation remains unclear.[22,23]

Primary hyperaldosteronism may result from either unilateral or bilateral adrenal disease. Typically, unilateral disease results from adenoma and bilateral disease from hyperplasia. This association is not absolute and about 10% of patients with primary hyperaldosteronism exhibit either bilateral aldosterone-producing adenoma, which may be microscopic, or unilateral hyperplasia.

EPIDEMIOLOGY

The exact incidence of primary hyperaldosteronism varies with the patient population and the diagnostic criteria used. Early studies,

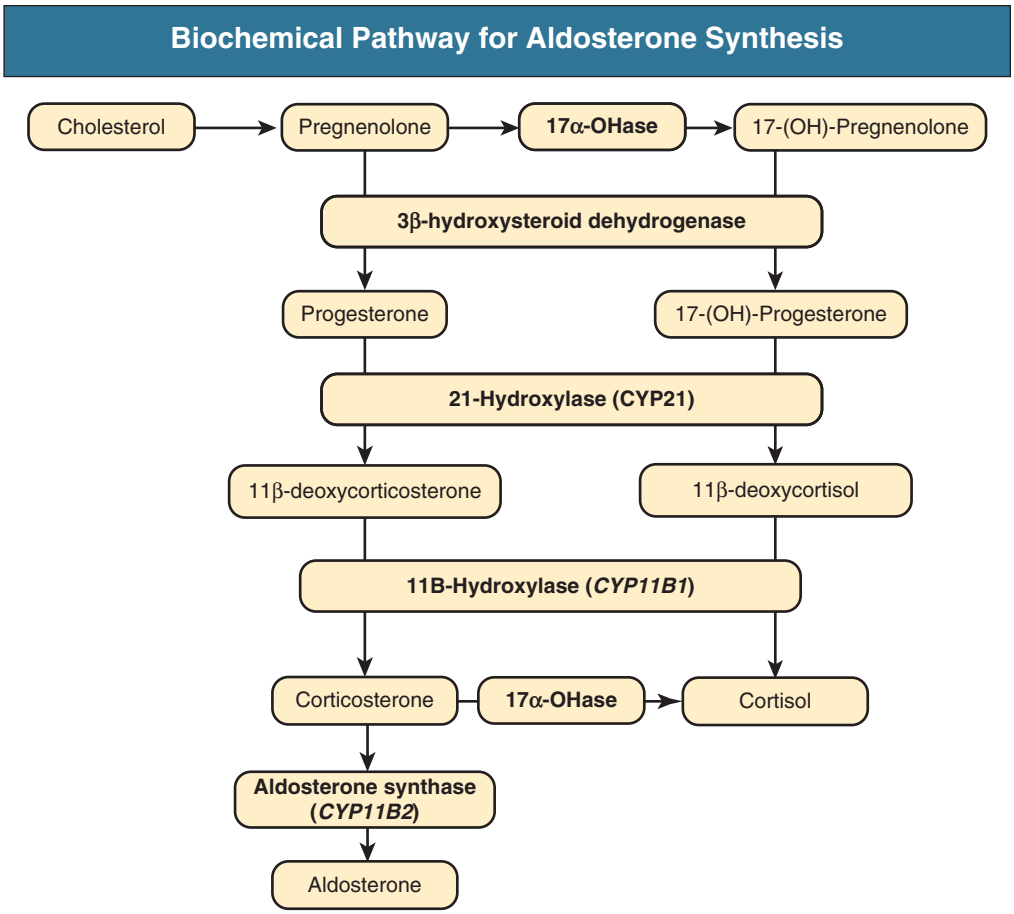

Figure 40-1 **Biochemical pathway for aldosterone synthesis.**

Factors that Regulate Aldosterone Release

Stimulatory	Inhibitory
Angiotensin II	*Atrial natriuretic peptide*
Adrenocorticotropic hormone	*Hypokalemia*
Acetylcholine	Calcitonin gene–related peptide
Adenosine triphosphate	Dopamine
Bradykinin	Nitric oxide
Cholecystokinin	Platelet-derived growth factor
β-Endorphin	Somatostatin
Endothelin	Transforming growth factor β
Enkephalins	Unsaturated fatty acids
Epidermal growth factor	
Hyperkalemia	
Melanocyte-stimulating hormone	
Neuropeptide Y	
Neurotensin	
Norepinephrine	
Parathyroid hormone	
Prolactin	
Serotonin	
Substance P	
Vasoactive intestinal peptide	
Vasopressin	

Table 40-1 **Factors that regulate aldosterone release.** The stimulatory and inhibitory regulators that exert significant effects on aldosterone release under the majority of clinical circumstances are noted in italics. *(Data from references 1 and 2.)*

which only recognized severe cases, suggested that primary hyperaldosteronism was rare, with an incidence less than 1% to 2%.[24] More accurate diagnosis has led to the recognition that primary hyperaldosteronism is relatively common. Patients with treatment-resistant hypertension—inadequately controlled hypertension despite treatment with three medications at appropriate dosages, including a diuretic—are highly likely to have primary hyperaldosteronism, with rates typically of 20% to 40% and as high as 67% in some studies.[25] Some studies have found a 1% to 2% incidence of hyperaldosteronism in normotensive patients (see Fig. 40-3), with the incidence increasing as BP increases.[26]

CLINICAL MANIFESTATIONS

Identifying patients with primary aldosteronism purely on clinical characteristics is difficult. Patients with primary hyperaldosteronism can have characteristics suggestive of secondary hypertension, such as early onset of hypertension or the need for multiple medications for BP control. Sometimes primary aldosteronism presents with either frank or easily provoked hypokalemia. Also, patients may have no distinguishing characteristics that differentiate them from individuals with essential hypertension. Figure 40-3 shows the frequency of primary hyperaldosteronism in individuals with different degrees of hypertension, and Table 40-2 summarizes characteristics of those with primary hyperaldosteronism.[27]

Because of the wide variety of presentations, from one indistinguishable from essential hypertension to one highly suggestive of secondary hypertension, we recommend screening all patients for primary aldosteronism who have characteristics of secondary hypertension, have baseline or easily provoked hypokalemia, or have hypertension not effectively controlled with routine antihypertensive therapy. It is important to recognize that both hypokalemia and metabolic alkalosis are no longer considered hallmarks of primary hyperaldosteronism, and in fact are absent in the majority of patients.

Effects of Aldosterone on Blood Pressure

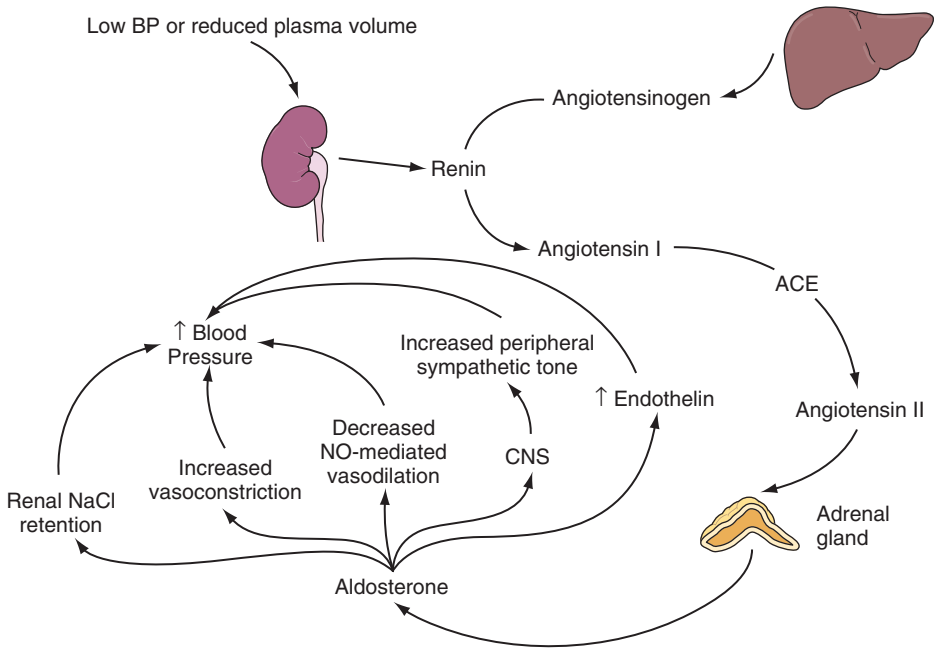

Figure 40-2 Summary of aldosterone's effects on blood pressure (BP) regulation. *ACE,* Angiotensin-converting enzyme; *CNS,* central nervous system; *NO,* nitric oxide.

Incidence of Primary Hyperaldosteronism in Patients with Differing Degrees of Hypertension

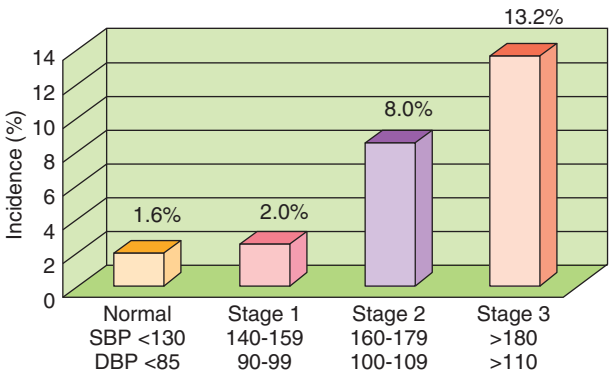

Figure 40-3 Incidence of primary hyperaldosteronism in patients with differing degrees of hypertension. *SBP,* Systolic blood pressure; *DBP,* diastolic blood pressure. *(From reference 26.)*

Typical Characteristics at Diagnosis of Primary Hyperaldosteronism

Patient Factor	Measured Value
Gender (female/male)	43:57 (%)
Age (yr)	52 ± 1 (range 29-74)
Hypertension duration (yr)	10 ± 1
Number of hypertensive medications	2.4 ± 0.1 (range 0-4)
Percentage requiring 3 or more medications	54%
Blood pressure controlled with current medical regimen	20%
Neither hypokalemic nor receiving 3 or more medications	52%
Plasma aldosterone (ng/dl)	
<15	37%
15-40	54%
>40	9%
Plasma renin activity (ng Ang I/ml/hr)	0.39 ± 0.04

Table 40-2 Typical characteristics of patients at diagnosis of primary hyperaldosteronism. *(Data from reference 27.)*

Diagnosing and treating primary aldosteronism is important for two major reasons. First, in many patients primary aldosteronism leads to very severe hypertension, which is poorly responsive to antihypertensive medications and thus increases cardiovascular risk. Indeed, a goal of hypertension management is to be able to identify and treat the underlying causative factor generating the individual's hypertension. Although not feasible for the majority of patients with hypertension, this is possible for the patient with primary aldosteronism. Second, and possibly more important, untreated primary aldosteronism leads to cardiovascular events at rates significantly greater than attributable solely to the hypertension. Diagnosing and treating the primary aldosteronism, whether with adrenalectomy or with MR blockers, as clinically appropriate, corrects this increased risk.[28]

PATHOLOGY

Primary hyperaldosteronism can result either from an aldosterone-producing adenoma (APA) or from hyperplasia of the zona glomerulosa (Fig. 40-4). Most APAs are unilateral and are large enough (>1 cm) to be identified by computed tomography (CT) scanning (Fig. 40-5). However, APAs may also be microscopic and may be bilateral. Hyperplasia is typically bilateral but may develop asynchronously in the two adrenal glands; hyperplasia also may be unilateral. The factors that cause development of either APA or hyperplasia are not completely understood.

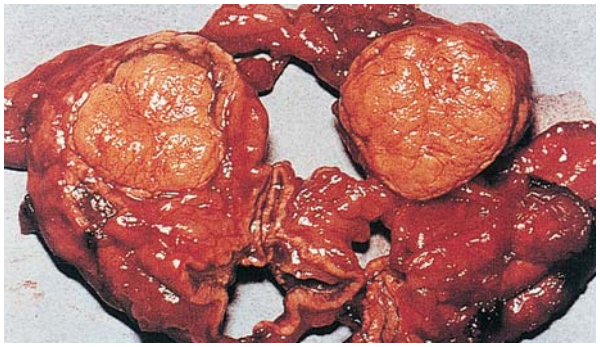

Figure 40-4 Adrenal adenoma. An aldosterone-producing adrenal adenoma with typical cholesterol-rich yellow appearance.

Figure 40-5 Adrenal adenoma by computed tomography scan. A normal linear image of the right adrenal gland *(white arrowhead)* and expansion of the left adrenal with aldosterone-producing adenoma (~1 cm) *(white arrow).*

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Evaluation of patients with suspected primary hyperaldosteronism is directed at (1) identifying those who have autonomous aldosterone release and then (2) determining whether treatment should be based on a medical or a surgical approach (Fig. 40-6).

Evidence of Ang II–independent aldosterone release is used to indicate autonomous aldosterone release and therefore primary hyperaldosteronism. Because Ang II cannot be assayed for routine clinical use, *renin* is used as a surrogate. A random blood sample is used to measure the ratio of plasma aldosterone to renin (ARR, aldosterone-renin ratio). If this value is elevated, there is significant Ang II–independent aldosterone release, thereby providing evidence of autonomous aldosterone production consistent with primary hyperaldosteronism.

Currently, two different renin assays are in routine clinical use. One measures renin activity, assayed as the rate of conversion of angiotensinogen to angiotensin I (Ang I), and the second measures the amount of immunoreactive renin. These two techniques yield results that correlate well with each other, but the units and numerical values obtained differ. For the plasma renin activity, the normal range is 1.9 to 3.7 ng Ang I/ml/hr, and the lower level of detectability is 0.2 ng Ang I/ml/hr, in most clinical laboratories. For the direct renin assay, the normal range is typically 13 to 44 IU/ml, and lower level of detectability is 6 to 8 IU/ml. Therefore, the normal ARR, for a patient with primary hypertension not receiving medications that alter the renin-angiotensin system (RAS), is about 10:1 when using the plasma renin activity, and 1:1 with the direct renin assay. The plasma renin activity assay is more sensitive at lower values than the direct plasma assay and currently is preferred for clinical use.

Whereas an elevated aldosterone and a low renin strongly suggest primary aldosteronism, an elevated ARR may also occur with low aldosterone if renin is suppressed. Combining an elevated ARR and "nonsuppressed" aldosterone levels decreases the rate of "false-positive" screening for primary hyperaldosteronism. The minimal plasma aldosterone level that may be associated with aldosteronism is unclear. We recommend using a minimal value of 10 ng/dl to make a diagnosis of primary aldosteronism.[29] Other investigators use cutoff values greater than 15 ng/dl,[30,31] and some do not recommend a cutoff.[8] This is partly because 36% to 48% of patients with primary aldosteronism have plasma aldosterone levels of 9 to 16 ng/dl,[26,32] and about 20% of those with unilateral autonomous adrenal aldosterone production have levels less than 15 ng/dl.[32]

Many common medicines may alter ARR.[31,33] β-Adrenergic receptor antagonists (β-blockers) can suppress renin release, typically by about 50%. However, β-blockers generally will not result in complete renin suppression and generally do not confound the diagnosis of primary hyperaldosteronism.[33] Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), along with diuretics, can increase renin release in normal individuals, which theoretically might decrease the sensitivity of ARR measurement. However, the effect of ACE inhibitors and ARBs to increase renin release can also be an advantage; in patients using either an ACE inhibitor or an ARB, a suppressed renin in combination with a nonsuppressed aldosterone (>10 ng/dl) is highly specific for primary hyperaldosteronism. MR antagonists such as spironolactone and eplerenone can elevate the plasma renin activity and impair the sensitivity of testing. How long to hold these medications before testing is not clear; we recommend 2 weeks if this can be done without excessive BP increases developing. Potassium-sparing diuretics such as amiloride and triamterene can generally be continued without difficulty. Other antihypertensive medications typically have little effect on ARR measurement and do not need to be held before testing.

An elevated ARR alone, while sensitive for detecting primary hyperaldosteronism, is not highly specific. In unselected populations or those with only mild or moderate hypertension, as many as 50% of patients with elevated ARR do not have primary hyperaldosteronism. If the diagnosis of primary aldosteronism is in doubt, several confirmatory tests can be used. Table 40-3 summarizes the various confirmatory testing methods in routine use. We recommend using these studies if only mild or easily controlled hypertension is present, if baseline hyperkalemia is present, or if MR antagonists are not well tolerated. However, some groups recommend confirmatory testing in all patients suggested to have primary aldosteronism.[8] Typically, performance of only one test is needed, the choice of which can be based on provider and patient preferences. If results are ambiguous, additional confirmatory testing can be performed.

The clinical importance in routine clinical practice of confirming the diagnosis of primary aldosteronism involves considering both the risks and the benefits of confirmatory testing.[29] None of the confirmatory tests has 100% sensitivity or specificity. Many tests require salt loading, which can raise BP and is problematic in the

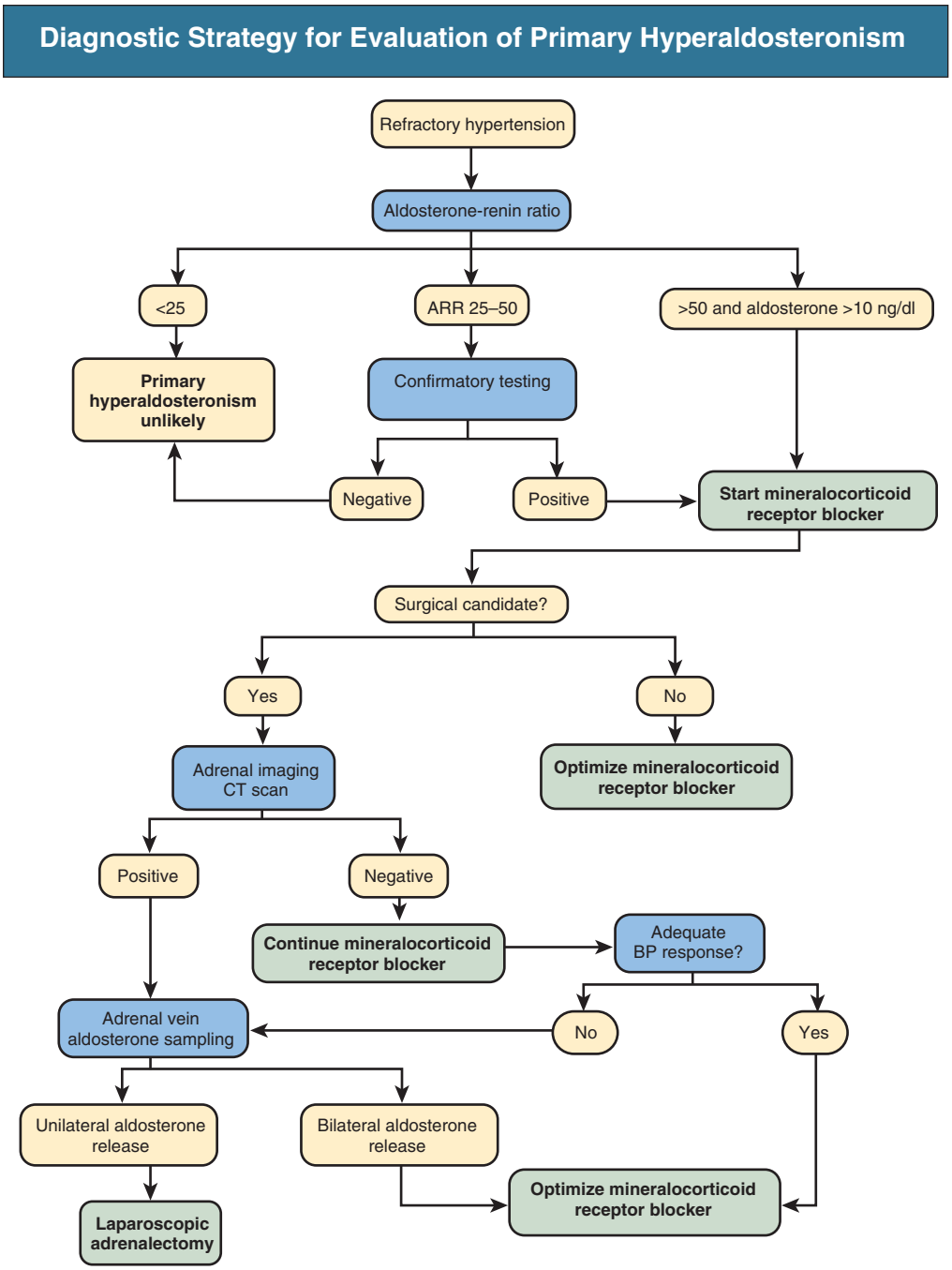

Figure 40-6 Diagnostic strategy for evaluation of primary hyperaldosteronism. Aldosterone-renin ratio *(ARR)* is calculated using measurement of plasma renin activity. If direct renin immunoassay is used, the resulting ARR calculation should be multiplied by 10 for use with this diagnostic algorithm. *BP,* Blood pressure; *CT,* computed tomography.

management of the patient who already has poorly controlled hypertension. Most tests require the patient not to use medications that interact with the renin-angiotensin-aldosterone system, which involves discontinuation of many highly effective antihypertensives, including β-blockers, ACE inhibitors, ARBs, direct renin inhibitors, and diuretics; this can lead to significant worsening of hypertension control.[29] Definitive diagnosis of primary aldosteronism would be necessary if it substantially altered the management of these patients. However, patients with resistant hypertension generally respond well to MR antagonists, with significant BP improvement even in the absence of primary aldosteronism.[34,35] Our experience is that almost all patients with nonsuppressed plasma aldosterone (i.e., >10 ng/dl) and ARR greater than 50 respond to MR antagonists with substantial (>20 mm Hg) decreases in BP. Because of these factors, some centers do not routinely perform confirmatory testing before initiating treatment with MR blockers for patients with presumed primary aldosteronism based on elevated ARR and nonsuppressed plasma aldosterone.

Once primary hyperaldosteronism is diagnosed, the clinician should determine whether unilateral aldosterone release is present, in which case adrenalectomy may be curative. If the patient is not a surgical candidate, this evaluation is not necessary. Because about 90% of patients with unilateral aldosterone release have an APA, an adrenal CT protocol is the next diagnostic step, using 2- to 3-mm slices; conventional abdominal CT using 10-mm slices may fail to identify small adrenal adenomas.

If an adrenal adenoma is identified, it is critical to determine by *adrenal vein sampling* whether the identified adenoma is aldosterone

Confirmatory Testing for Diagnosis of Primary Hyperaldosteronism			
Test	**Method**	**Evaluation**	**Limitations**
Oral sodium chloride (NaCl) loading	Oral NaCl intake >200 mmol/d for 3 days, with oral KCl as needed to prevent hypokalemia, with subsequent 24-hr urine aldosterone measurement	Urine aldosterone <10 μg/d, diagnosis unlikely; >12 μg/d, diagnosis likely	Avoid if severe uncontrolled hypertension, CKD, CHF, cardiac arrhythmias, or severe hypokalemia
Saline infusion test	Patient in recumbent position for 1 hr before testing and then throughout entire test Begin test between 8 and 9:30 AM. Measure plasma aldosterone, plasma renin activity, cortisol, and potassium at beginning of test and then after infusing 2 l NS IV over 4 hr.	Plasma aldosterone at end of infusion <5 ng/dl, diagnosis unlikely; >10 ng/dl, diagnosis likely; 5-10 ng/dl, indeterminate	Avoid if severe uncontrolled hypertension, CKD, CHF, cardiac arrhythmias, or severe hypokalemia
Fludrocortisone suppression test	Oral fludrocortisone, 0.1 mg every 6 hr for 4 days, plus oral NaCl, 30 mmol 3×/d, and high-salt diet combined with sufficient KCl to avoid hypokalemia	Upright plasma aldosterone on day 4 >6 ng/dl and plasma renin activity <1 ng/ml/h, diagnosis likely	Frequently requires hospitalization for patient monitoring of blood pressure and potassium
Captopril challenge test	Oral captopril, 20-50 mg, given with plasma aldosterone, and plasma renin activity obtained immediately before captopril and then 1-2 hr afterward, with patient seated throughout test	Plasma aldosterone decrease >30%, diagnosis unlikely	Probably more false-positive and false-negative results than other tests

Table 40-3 Confirmatory testing for primary hyperaldosteronism. *CHF,* Congestive heart failure; *CKD,* chronic kidney disease; *KCl,* potassium chloride; *l NS IV,* liters normal saline intravenously. *(From reference 8.)*

producing (APA) or is a nonfunctional adenoma ("incidentaloma"). In as many as 20% to 30% of patients with primary aldosteronism and an adrenal adenoma, the adenoma is nonfunctional. A nonfunctional adenoma is relatively unusual in younger patients (<40 to 45 years), so the additional benefit of adrenal vein sampling is less clear in this patient population.

Many issues complicate adrenal vein sampling studies. First, the procedure is technically difficult and should be performed in specialized centers by a specific interventional radiologist using a standardized procedure. Second, biochemical confirmation of successful adrenal vein sampling, by demonstrating cortisol concentrations significantly greater than present in the blood from the inferior vena cava, is necessary. Third, stimulation of cortisol production with ACTH or an analogue increases the ease of confirming successful adrenal vein sampling. However, ACTH and its analogues can alter aldosterone production, which may result in misleading interpretations as to whether aldosterone secretion is unilateral or bilateral and, if unilateral, which side is the predominant source. Thus, interpretation requires careful evaluation of the biochemical studies resulting from adrenal vein sampling, in conjunction with imaging modalities.

Occasional patients will have unilateral aldosterone release but not have an adenoma detectable on CT. These patients may have either unilateral adrenal hyperplasia or micronodular APA. This diagnosis should be considered when the response to MR antagonists such as spironolactone and eplerenone is suboptimal or requires high doses. Despite a negative CT scan, adrenal vein sampling is used to identify whether the patient has surgically treatable unilateral autonomous adrenal aldosterone release.

Many other diagnostic tests have been suggested in the evaluation of primary hyperaldosteronism, but none has widespread acceptance. The postural stimulation test may help differentiate bilateral adrenal hyperplasia from APA. All medicines that affect the RAS, including diuretics, β-blockers, ACE inhibitors, and ARBs, must be discontinued before testing, but the difficulty in controlling BP in these patients without medicines often limits the utility of this test. Its main role is in the evaluation of the patient with an adrenal adenoma and unsuccessful adrenal vein sampling.[8]

NATURAL HISTORY

The natural history of untreated primary hyperaldosteronism is uncertain. Although there are case reports of remission of untreated primary hyperaldosteronism, these all followed adrenal venography, and thus may reflect related complications. However, studies comparing patients with newly diagnosed primary aldosteronism to those with primary hypertension of the same severity and duration suggest untreated primary aldosteronism is associated with numerous end-organ complications, including increased risk of coronary heart disease, atherosclerotic peripheral vascular disease, cardiac arrhythmias, left ventricular hypertrophy, low bone mineral density, and development of chronic kidney disease.[28,36,37] Effective treatment of primary aldosteronism appears to reverse these increased risks. Therefore, treatment either with MR blockers or with adrenalectomy is recommended for patients with primary aldosteronism.

TREATMENT

Patients with an aldosterone-producing adenoma who are acceptable surgical candidates should undergo surgical laparoscopic adrenalectomy. Laparoscopic adrenalectomy is associated with a shortened hospital stay, decreased postoperative morbidity, and a quicker return to normal health than open surgical adrenalectomy. Patients who undergo laparoscopic adrenalectomy have a 30% to 60% chance of hypertension cure.[38-40] Patients most likely to have their hypertension cured are less than 50 years of age and have few family members with primary hypertension. Those not cured have a greater than 95% chance of BP improvement.[39,40] The lack of complete cure may reflect intrarenal microvascular disease that developed as a consequence of the poorly controlled hypertension.

Patients who are not candidates for surgical adrenalectomy or who have bilateral aldosterone production should be treated with MR antagonists, currently spironolactone and eplerenone. These should be started at modest doses and titrated slowly. Most patients find that the responses are delayed, and monthly dose adjustments should be done until an optimal dose is identified. The choice of MR

blocker involves consideration of side effects, cost, and effectiveness. Spironolactone has off-target effects on sex-steroid hormone receptors, which can lead to a dose-dependent risk of breast enlargement (gynecomastia) in men and breast tenderness (gynecodynia) and menstrual irregularities in women. Eplerenone is more selective than spironolactone for the mineralocorticoid receptor, and the risk of these side effects is less but not eliminated. These differences initially led many to prefer the use of eplerenone to spironolactone. However, recent evidence showed spironolactone was significantly more effective than eplerenone at improving blood pressure, with almost twice as great a BP reduction and a substantially greater proportion of patients experiencing a significant BP improvement.[41] The overall incidence of side effects was similar. Accordingly, spironolactone may be the preferred agent for medical treatment of primary aldosteronism.

The clinician should also be familiar with additional side effects of MR blocker therapy. Muscle cramps can occur with both spironolactone and eplerenone. MR blockers can cause neuropsychiatric side effects that are often nonspecific and can include symptoms of feeling out of touch with reality, difficulty thinking, and decreased attention and performance in various memory tasks.[41,42] In general, these effects are temporary and resolve within a few weeks. Hyperkalemia is common when MR blockers are used for conditions other than primary aldosteronism, such as congestive heart failure,[43,44] but is relatively uncommon in patients with primary aldosteronism. However, hyperkalemia can occur late in therapy, often following years of MR blocker administration, and may require either a decrease in the MR dose or addition of diuretics.

Treatment with an MR antagonist usually results in dramatically improved BP control. Many patients will respond to a low dose, 25 to 50 mg daily, as initial therapy. Both systolic BP and diastolic BP frequently decrease by about 25 mm Hg over a few weeks to months. Dosage of the MR antagonists can be increased as necessary but generally should not be changed more than every 2 to 4 weeks. If present, hypokalemia and metabolic alkalosis improve. Potassium supplements can be tapered rapidly with improvement in hypokalemia. With time, BP can be controlled in many patients with an MR antagonist and a single alternative agent. We typically use ACE inhibitors because renin activity, which is suppressed initially, typically increases after starting MR antagonist therapy. Synergistic use of an ACE inhibitor may prevent development of a renin-stimulated, Ang II–dependent component of hypertension. However, many antihypertensive combinations can be used successfully with the MR antagonist.

Inhibitors of the RAS are widely used to slow the progression of chronic kidney disease (CKD) and to decrease cardiovascular mortality in patients with congestive heart failure (CHF). These treatment regimens usually involve either ACE inhibitors or ARBs, which by blocking Ang II–dependent stimulation of aldosterone production, should decrease plasma aldosterone levels. However, many patients develop aldosterone breakthrough, in which the initial decrease in plasma aldosterone level is followed by a later rise in aldosterone levels to greater than that prior to ACE inhibitor or ARB treatment. Aldosterone breakthrough is associated with faster loss of glomerular filtration rate (GFR) in patients with CKD, reduced exercise capacity and reduced venous compliance in patients with CHF, and adverse effects on left ventricular mass index in hypertensive patients.[45-47] In addition to patients taking ACE inhibitors who manifest aldosterone breakthrough, obese individuals may also show higher aldosterone levels in the absence of ACE inhibitors.[48] This may result from adipocyte release of compounds that stimulate adrenal aldosterone production.[49] Neither of these conditions results in the elevated ARR observed with primary aldosteronism. Nevertheless, use of spironolactone in these patients may aid in BP control. In addition, patients with CKD who develop aldosterone breakthrough have a greater rate of GFR loss, and treating these patients with low doses of MR antagonists, such as oral spironolactone 25 mg once daily, appears to decrease proteinuria, predicting a renoprotective benefit.[50]

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CHAPTER 41

Endocrine Causes of Hypertension

A. Mark Richards and M. Gary Nicholls

The true incidence and prevalence of hypertension with endocrine etiology are unknown. However, primary aldosteronism may be present in up to 12% of patients with newly diagnosed hypertension, and overall, an endocrine contribution to high blood pressure (BP) may be present in more than 12% of cases. *Endocrine hypertension* often remains undiagnosed because physicians consider it rare and therefore unlikely, and access to the required specialized tests is limited.

Endocrine hypertension may occur in the absence of readily observed signs and symptoms or abnormalities in routine biochemical tests. However, certain features should trigger a simple screen (Fig. 41-1), such as a family history of inherited conditions, including pheochromocytoma, neurofibromatosis, multiple endocrine neoplasia, and aldosteronism. Resistant hypertension (i.e., BP resistant to administration of three antihypertensive drugs of different classes) mandates consideration of secondary hypertension once iatrogenic factors and noncompliance have been ruled out. The differential diagnoses for endocrine hypertension will include renal parenchymal disease and renovascular disease.

Symptoms and signs may be present. Severe hypokalemia is rare but when present may cause weakness, polyuria, and cardiac arrhythmia. Hyperadrenergic symptoms occur with pheochromocytoma. Changes in temperature tolerance, body weight, hair and skin condition, and bowel habit are clues in thyroid dysfunction or hypercortisolism. Thyroid disease, Cushing syndrome, and acromegaly are associated with typical changes in body habitus. Abnormal sweating occurs in pheochromocytoma, thyrotoxicosis, and acromegaly.

Hypokalemia and diabetes mellitus are hallmarks of endocrine pathologic processes in hypertension. Hypokalemia in the absence of diuretic use should suggest diagnoses such as primary aldosteronism, pseudoaldosteronism, renin-secreting tumor, Cushing syndrome, and accelerated hypertension of any cause. Therefore, concurrent high BP and hypokalemia should prompt consideration of endocrine hypertension. Hyperglycemia is common to Cushing syndrome, pheochromocytoma (especially when epinephrine levels are increased), acromegaly, and primary aldosteronism. Diagnosis of endocrine forms of hypertension offers the chance of cure, of altering an otherwise catastrophic natural history (e.g., in pheochromocytoma), and of applying specific and effective therapies that ameliorate other elements of the disease beyond BP control. Chapter 40 discusses aldosteronism; this chapter describes other types of endocrine hypertension.

CUSHING SYNDROME

Definition

This syndrome of sustained glucocorticoid excess is most often secondary to production of adrenocorticotropic hormone (ACTH) by a pituitary adenoma (Cushing disease). Less frequently, Cushing syndrome is the result of cortisol overproduction from an adrenal adenoma or carcinoma, and rarely it may be secondary to ectopic ACTH (corticotropin) secretion.[1] It can also result from exogenous corticosteroid administration. The incidence of endogenous Cushing syndrome is 5 to 10 cases per 1 million population per year. Cushing disease and cortisol-secreting adrenal tumors are four times more common in women than in men. Approximately 0.5% of patients with bronchogenic carcinoma (more common in men than women) develop ectopic ACTH syndrome.

Etiology, Pathogenesis, and Epidemiology

Hypertension is present in 80% of patients with Cushing syndrome (less often when caused by exogenous synthetic corticosteroid administration) and results from an increase in both cardiac output and total peripheral resistance. The mechanisms underlying these hemodynamic changes are complex.[2]

In some patients, Cushing syndrome may be caused by concurrent overproduction of mineralocorticoids such as aldosterone, 11-deoxycorticosterone, and corticosterone. Although cortisol is capable of binding the mineralocorticoid receptor (MR), usually it does not because of the renal enzyme 11β-hydroxysteroid dehydrogenase type 2 (β-HSD2), which inactivates cortisol to corticosterone, thereby preventing its binding to the MR. However, in the patient with low β-HSD2 activity or extremely high cortisol levels (e.g., ectopic ACTH syndrome), there may be sufficient excess cortisol that MR binding occurs. Furthermore, alterations in oxidation-reduction (redox) status, potentially triggered by metabolic disturbance and cytokine activation, may alter the effects of corticosteroids at the MR function, converting cortisol from its receptor antagonist role seen in health to an agonist in inflammatory states.[3]

Subsequent cardiac and vascular MR activation may foster adverse cardiovascular inflammatory, hypertrophic, and fibrotic changes. Inhibition of the vasodilator nitric oxide (NO) by cortisol may also contribute to the hypertension, along with enhanced pressor responsiveness to catecholamines and angiotensin II (Ang II), heightened cardiac inotropic sensitivity to β-adrenergic stimulation, and increased plasma volume.[2] If affected, the sympathetic nervous system (SNS) and renin-angiotensin system (RAS) are suppressed, even though circulating levels of renin substrate are increased. Some have proposed that elevated levels of vasoconstrictor hormones (vasopressin, endothelin-1, thromboxane, insulin) or subnormal concentrations of vasodilator systems (kallikrein-kinins, prostaglandins) contribute to the hypertension of Cushing syndrome, but the evidence is weak.[2] The vasodilator atrial natriuretic peptide (ANP) is elevated in Cushing syndrome, although biologic responses to ANP are impaired; in theory, ANP resistance could also contribute to the hypertension.[4] Adipokines, including leptin and resistin, plus release of proinflammatory cytokines (tumor necrosis factor α, interleukin-6) may also contribute to the increased cardiovascular risk observed in Cushing syndrome.[5]

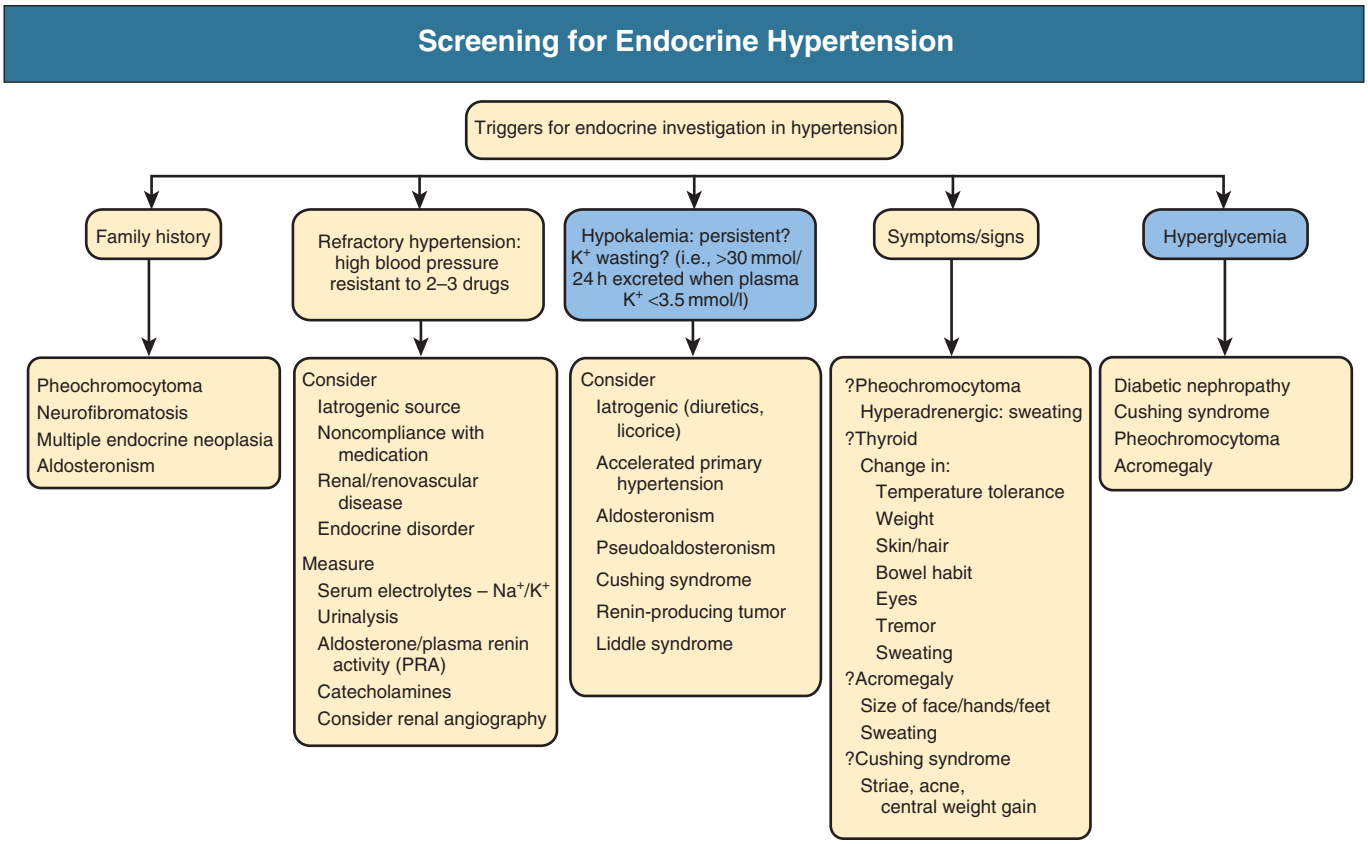

Figure 41-1 Screening algorithm for endocrine hypertension. Clinical observations suggesting investigation into endocrine causes of hypertension in hypertensive patients.

Figure 41-2 Striae and central obesity in a patient with Cushing syndrome.

Successful treatment of Cushing disease or removal of an underlying adrenal adenoma usually results in BP reduction and partial return of the previously impaired nocturnal fall in arterial pressure, although hypertension persists in a sizable minority of patients.

Clinical Manifestations

Clinical features in Cushing disease result from elevated circulating levels of pro-opiomelanocortin hormones, including ACTH (increased pigmentation) and cortisol (central adiposity, insulin resistance or diabetes, muscle wasting/weakness, plethoric facies, purple striae [Fig. 41-2], easy bruising, osteoporosis, psychological problems). In some patients, androgen effects are observed (hirsutism, acne, virilization) and may be striking in those with adrenal adenoma or carcinoma. Ectopic ACTH syndrome caused by small cell bronchial carcinoma or other tumors (e.g., bronchial or thymic carcinoid) presents typically as a wasting disease, often with hyperpigmentation and hypokalemia. Hypertension is often associated with left ventricular hypertrophy, which can be disproportionate to BP, and frank cardiac failure is occasionally the presenting feature.[6]

Differential Diagnosis

Pseudo–Cushing syndrome can occur with a sustained high intake of alcohol by inducing augmented cortisol secretion and reduced cortisol metabolism caused by hepatic damage. Routine diagnostic tests are unable to distinguish alcoholic pseudo–Cushing syndrome from true Cushing syndrome, and reassessment after alcohol withdrawal may be required.[7]

Depression is associated with increased cortisol level. In obesity, the plasma clearance rate of cortisol is increased, leading to a slightly elevated production rate of cortisol, although plasma levels are normal. Careful psychological and physical screening will usually differentiate these patients from those with Cushing syndrome.

Diagnosis

An elevated urinary free cortisol excretion (or early-morning cortisol-creatinine ratio) and absence of suppression of 8 AM plasma cortisol after a low dose of dexamethasone (1 mg at midnight) are the usual initial tests. Screening may also incorporate checks for elevated late-night salivary cortisol.

Further key investigations include computed tomography (CT) and magnetic resonance imaging (MRI) of the pituitary and adrenal glands and plasma ACTH (suppressed in cortisol-secreting adrenal tumors but elevated in ectopic ACTH syndrome). Further tests will depend on findings at this point. A high-dose dexamethasone suppression test partially suppresses ACTH in patients with pituitary tumors but not with ectopic ACTH. The response of plasma ACTH to a dose of corticotropin-releasing hormone may also help distinguish pituitary from adrenal or ectopic tumors. Simultaneous bilateral inferior petrosal sinus sampling for ACTH measurements is useful in differentiating Cushing disease from ectopic ACTH syndrome, when the previous tests give equivocal results. Imaging of the thorax, abdomen, and pelvis is indicated when ACTH-producing carcinoid tumors are suspected.

Treatment and Prognosis

Untreated, patients with Cushing syndrome have 50% 5-year mortality because of cardiovascular risk from hypertension, along with glucose intolerance and insulin resistance, hyperlipidemia, obesity, and elevated fibrinogen levels.[8]

Cure rates in treatment of Cushing disease are 80% to 90% by selective removal of a pituitary microadenoma and 50% for pituitary macroadenomas. Cushing syndrome caused by adrenal adenoma is almost always cured by unilateral adrenalectomy. However, in adrenal carcinoma, median survival is less than 2 years. The prognosis is also poor when Cushing syndrome results from ectopic ACTH syndrome caused by small cell bronchial carcinoma. If the ACTH-producing tumor is benign and can be located, however, removal usually leads to cure. After cure of Cushing syndrome, approximately 30% of patients have persistent hypertension.[9]

In managing the hypertension from Cushing syndrome, no evidence supports the use of any antihypertensive class over another. Potassium-losing diuretics can exacerbate both hypokalemia and glucose intolerance, whereas potassium-sparing diuretics, usually in combination with other antihypertensive agents, may correct hypokalemia and reduce edema while lowering BP.

PHEOCHROMOCYTOMA

Definition

Pheochromocytoma has challenged and fascinated clinicians since its first description by Frankel in 1886. Because clinical manifestations can mimic a wide spectrum of other disorders, the diagnosis is frequently delayed or missed altogether, sometimes with fatal consequences.[10]

Pheochromocytoma refers to a dusky tumor whose cells stain brown with chromium salts. Such tumors arise most frequently within the adrenal glands (Fig. 41-3), but approximately 10% are extra-adrenal (paraganglioma). Although the majority of pheochromocytomas are benign, 10% metastasize to regional lymph nodes and beyond. Histologic features are not a reliable guide to malignant behavior. The tumors can secrete a wide variety of hormones but most characteristically produce norepinephrine, epinephrine, and dopamine, with patterns differing among patients. Few paragangliomas produce epinephrine. Very high dopamine production is associated with malignant disease or a large tumor mass.

Etiology, Pathogenesis, and Epidemiology

The prevalence of pheochromocytoma in patients with hypertension in general medical outpatient clinics is 0.1% to 0.6%.[11] As with a firm diagnosis, however, the prevalence may be considerably higher because many people die with unsuspected pheochromocytoma.[12]

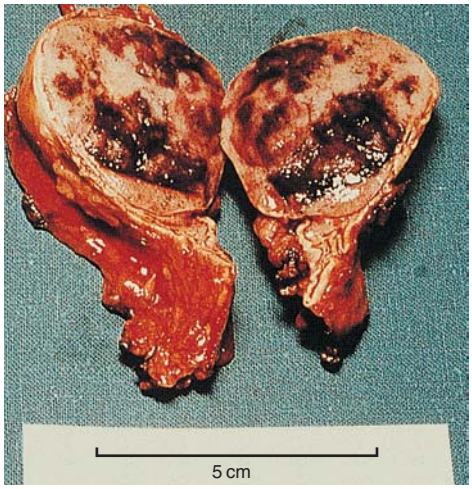

Figure 41-3 **Large adrenal pheochromocytoma with areas of hemorrhagic necrosis.**

Pheochromocytomas can be sporadic or familial. Whereas sporadic cases are usually unicentric and unilateral, familial pheochromocytomas are often multicentric and bilateral. Familial pheochromocytomas are the result of a germ-line mutation in one of five genes: the *RET* gene leading to multiple endocrine neoplasia type 2; the von Hippel–Lindau *(VHL)* gene, which causes the von Hippel–Lindau syndrome; the neurofibromatosis type 1 *(NF1)* gene resulting in von Recklinghausen disease; and the genes encoding the B and D subunits of mitochondrial succinate dehydrogenase (*SDHB* and *SDHD*), which are associated with familial paragangliomas and pheochromocytomas. More recently, mutations in *KIF1Bβ, TMEM127,* and *MAX* genes have also been associated with pheochromocytoma.[13]

Table 41-1 outlines clinical features of syndromes associated with pheochromocytoma. For patients with apparently sporadic pheochromocytomas, an underlying germ-line mutation of the genes mentioned may be present in about 20% of cases and should be considered in younger patients (<50 years) and those with multifocal or extra-adrenal tumors.[10,14] Patients found to harbor a germ-line mutation need to be identified for appropriate guidance of medical management for them and their families.

Clinical Manifestations

Clinical features of pheochromocytoma reflect episodic or continuous overproduction of catecholamines and depend in part on which catecholamine dominates. Symptoms include headache, sweating, palpitations, anxiety, and pallor (Fig. 41-4).[15] Hypertension or diabetes mellitus, with or without symptoms, may be the initial manifestation. Alternatively, pheochromocytoma may present as a tumor mass, usually an enlarging primary lesion in the abdomen or a paraganglioma in the neck, ear, thorax, or abdomen. On occasion, a metastatic lesion may be the presenting sign. Physical examination may reveal labile (66%) or persistent (33%) hypertension, sometimes with strikingly reciprocal changes in BP and heart rate when the tumor secretes predominantly norepinephrine.[16] The patient may have cool, mottled extremities and a low-grade fever with tachycardia and postural hypotension. Patients may also present as an emergency with severe hypertension with or without heart failure and a variety of symptoms attributable to high plasma catecholamine

Main Clinical Features of Syndromes Associated with Pheochromocytoma

Associated Syndrome	Clinical Manifestations
Von Hippel–Lindau Syndrome	
Type 1 (no pheochromocytoma)	Renal cell cysts and carcinomas Retinal and CNS hemangioblastomas Pancreatic neoplasms and cysts Endolymphatic sac tumors Epididymal cystadenomas
Type 2 (with pheochromocytoma)	2A. Retinal and CNS hemangioblastomas Pheochromocytomas Endolymphatic sac tumors Epididymal cystadenomas 2B. Renal cell cysts and carcinomas Retinal and CNS hemangioblastomas Pancreatic neoplasms and cysts Pheochromocytomas Endolymphatic sac tumors Epididymal cystadenomas 2C. Pheochromocytomas only
Multiple Endocrine Neoplasia (MEN) Type 2*	
Type 2A (MEN-2A)	Medullary thyroid carcinoma Pheochromocytoma Hyperparathyroidism Cutaneous lichen amyloidosis
Type 2B (MEN-2B)	Medullary thyroid carcinoma Pheochromocytoma Multiple neuromas Marfanoid habitus
Other Syndromes	
Neurofibromatosis type 1	Multiple fibromas on skin and mucosa Café-au-lait skin spots Pheochromocytomas
Paraganglioma syndromes	Head and neck tumors (carotid body tumors; vagal, jugular, and tympanic paragangliomas) Pheochromocytomas Abdominal or thoracic paragangliomas (or both)

Table 41-1 Primary clinical features of syndromes associated with pheochromocytoma. *CNS,* Central nervous system. *A third type of MEN type 2 consists of familial medullary thyroid carcinoma only (without pheochromocytoma).

Frequency of Symptoms in Pheochromocytoma

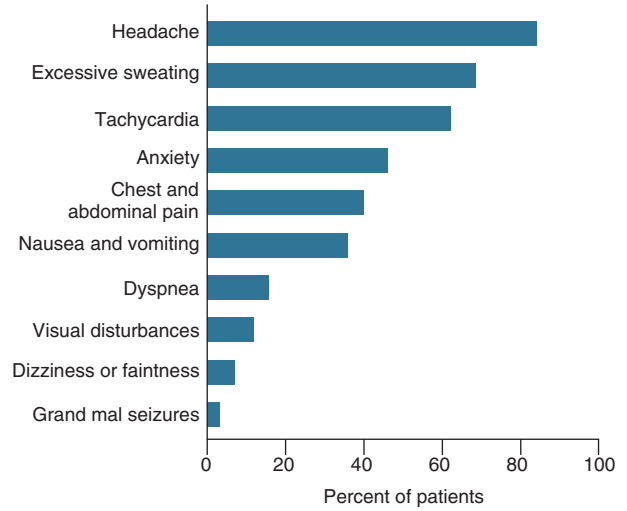

Figure 41-4 Frequency of symptoms in 324 patients with pheochromocytoma. *(Modified from reference 15.)*

levels. This can occur after minor or major trauma, at delivery, and apparently spontaneously from sudden release of catecholamines from the tumor or hemorrhage into it. Pheochromocytoma in pregnancy presents particular difficulties in diagnosis and management.[17]

Diagnosis

Diagnosis of pheochromocytoma is based on clinical suspicion but demands biochemical confirmation (Fig. 41-5). Current evidence is that plasma free metanephrines provide the best biochemical test for diagnosis or exclusion of pheochromocytoma, and the levels are relatively independent of renal function while also providing some guidance for tumor size and location.[18-20] When analysis of plasma free metanephrines is not available, plasma or urinary catecholamines or their other metabolites may be used and typically are 5- to 10-fold greater than normal. When catecholamine levels are at the upper limits of normal, a suppression test with clonidine is useful, which suppresses plasma norepinephrine into the normal range in health but fails to do so in patients harboring a pheochromocytoma.[21]

Once the biochemical diagnosis is secured, the lesion must be localized (Fig. 41-5). Imaging of a pheochromocytoma requires realization that the tumor, as with the clinical syndrome itself, may mimic other lesions.[22] MRI or CT scan of the abdomen and pelvis, concentrating first on the adrenals, is successful in most patients, but additional investigations may be required if no lesion is detected. These may include selective venous sampling to detect a step-up in catecholamine levels, metaiodobenzylguanidine (MIBG) scanning, indium (In-111)–labeled octreotide scanning, measurements of plasma free metanephrines coupled with vena caval sampling, and positron emission tomography (PET).[23] Removal of a pheochromocytoma-containing adrenal can result in compensatory medullary hyperplasia in the contralateral adrenal potentially, giving a false-positive MIBG scan on follow-up scanning, so the clinician must be cautious with interpretation.[24] Confirmation of the presence of a pheochromocytoma should trigger a review, with specialist consultation as needed to exclude associated syndromes, including von Hippel–Lindau syndrome, von Recklinghausen disease, and familial paraganglioma.

Treatment

Once the pheochromocytoma has been localized, the patient should be prepared for surgery with a collaborative team approach by the surgeon, anesthesiologist, and physician. Traditionally, several weeks of α-adrenoceptor blockade, usually with phenoxybenzamine, and the later addition of β-blockade, if necessary to control BP and tachycardia, have been implemented before surgery. β-Blocker monotherapy is contraindicated because of the risk of unopposed α-adrenergic stimulation leading to catastrophic hypertensive crisis. Alternative drugs that have been used successfully before surgery include prazosin (α-blocker) and labetalol (combined α- and β-blocker). However, the need for prolonged presurgical pharmacologic control is now debated, with an emerging view that improved anesthetic management, skilled use of short-acting vasoactive drugs,

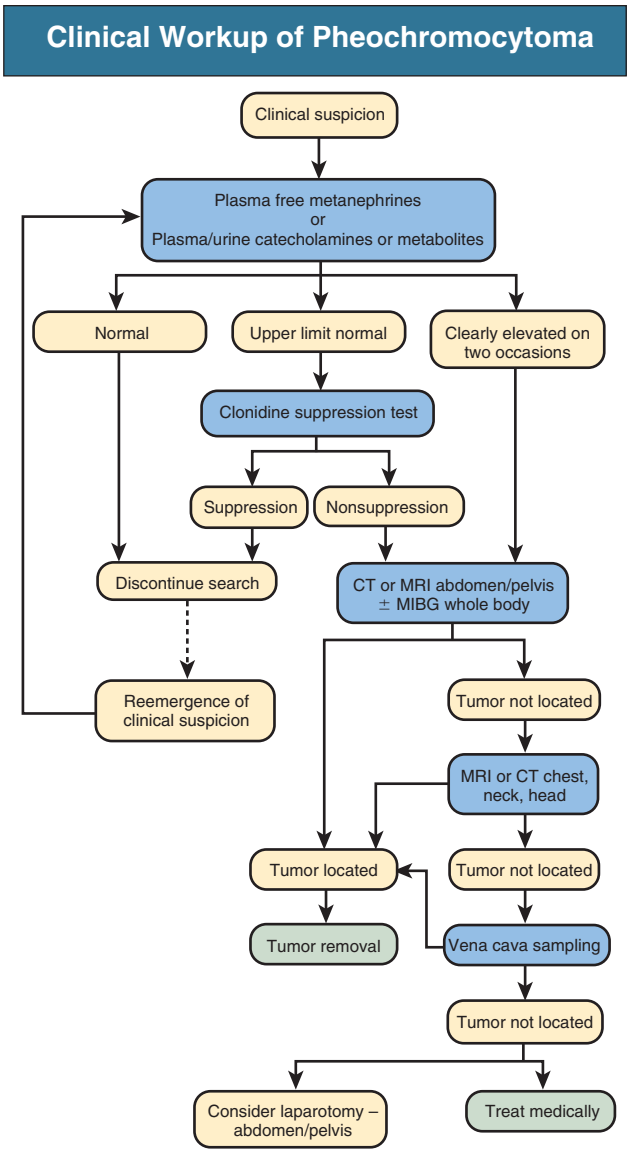

Figure 41-5 Clinical workup of pheochromocytoma. *CT,* Computed tomography; *MIBG,* metaiodobenzylguanidine; *MRI,* magnetic resonance imaging.

and careful intraoperative handling of the tumor may allow safe progression to early surgery, with perioperative mortality close to zero in recent series.[25]

A laparoscopic approach to surgical removal of adrenal pheochromocytomas and some extra-adrenal tumors has gained widespread acceptance, but the laparoscopic approach should be converted to open adrenalectomy for difficult dissection, invasion, adhesions, or surgical inexperience.[26] Laparoscopic surgery has also been used successfully for hereditary bilateral or recurrent pheochromocytoma. Agents used to achieve intraoperative BP control include phentolamine, sodium nitroprusside, and magnesium sulfate.

Hypotension and hypoglycemia are potential postoperative problems. In most patients, surgical removal of pheochromocytoma normalizes plasma catecholamine levels and previously suppressed central sympathetic outflow. BP usually improves with removal of a pheochromocytoma, but especially in those with persistent hypertension versus episodic, BP may remain elevated, necessitating long-term antihypertensive therapy.

For malignant pheochromocytoma, consideration should be given to aggressive surgical resection, particularly when there is a single metastatic lesion. Symptoms should be controlled with α- and β-blocking agents as needed, and irradiation can be useful for bone metastases. Chemotherapy, usually with cyclophosphamide, vincristine, and dacarbazine, should be considered for those with surgically inaccessible metastases producing symptoms that cannot be controlled by α- and β-blockade. Progression of malignant pheochromocytoma is extremely variable. Although median survival is approximately 5 years, survival for decades has been recorded in some cases.

ADRENAL INCIDENTALOMA

Definition and Epidemiology

"Incidentaloma" refers to the incidental discovery of an adrenal mass in the course of investigation for other conditions in the absence of any prior suspicion of adrenal disease.[27] The increasing use and sophistication of abdominal imaging for a wide range of indications frequently leads to the incidental discovery of an adrenal mass. Current prevalence of unsuspected adrenal masses is reported in 4% to 7% of adults undergoing high-resolution CT or MRI abdominal studies (<1% in those <30 years, rising to 7% in those >70 years).[27,28] Hypertension is more common in those with incidentalomas (40%) than in the general population. In a substantial series of more than 1000 incidentalomas, about 75% proved to be nonsecretory benign adenomas. However, an important minority show endocrine activity, including aldosteronoma (frequently normokalemic), pheochromocytoma (>4%, with half normotensive), and most often, cortisol-secreting tumors. Between 5% and 30% of patients with incidentalomas have subclinical hypercortisolism,[27,29] which may be complicated by hypertension, diabetes, obesity, and osteoporosis, as in full-blown Cushing syndrome.[29] The best diagnostic and therapeutic approaches to subclinical hypercortisolism remain to be defined.

Importantly, adrenal carcinoma, although rare at 0.6 to 2.0 cases per 1 million population, accounted for 4% of cases in a large, well-documented series of incidentalomas. Adrenal carcinoma is more likely with increasing size of the adrenal mass: 2% of masses up to 4 cm in diameter, 6% of masses 4 to 6 cm in diameter, and 25% of tumors larger than 6 cm. Adrenal carcinomas may or may not be functional. The prognosis is poor, with 5-year survival of less than 20%. The differential diagnosis of incidentalomas includes metastases, myelolipoma, ganglioneuromas, cysts, hemorrhage, and infections.

Management

Investigation and management should address two key issues: whether the tumor is malignant and whether it is hormonally active. Contrast and noncontrast CT attenuation values provide guidance in distinguishing malignant from benign tumors. CT appearances consistent with malignancy and tumors greater than 4 cm in diameter without benign imaging features should be surgically resected.[28] A careful history and examination should be directed at possible symptoms and signs of endocrine hypertension. Biochemical screening should be undertaken for pheochromocytoma (urine free metanephrines), glucocorticoid excess (urinary free cortisol to creatinine ratio and early-morning plasma cortisol concentration after 1 mg dexamethasone), or primary aldosteronism (plasma and 24-hour urinary potassium levels and plasma renin-aldosterone ratio), as outlined in relevant sections here and Chapter 40. It is reasonable to resect functional tumors. In nonfunctional tumors of benign

appearance, annual biochemical follow-up for 5 years has been recommended if the tumor is larger than 3 cm. Incidentalomas increasing in size by more than 0.8 cm per year should be considered for resection.[28]

RENIN-SECRETING TUMOR

Definition

Primary renin-secreting tumors are rare. Diagnostic criteria include an elevated plasma renin or prorenin level, which decreases on removal of the tumor, and demonstration of renin within the tumor. Most renin-secreting tumors are caused by benign renal juxtaglomerular cell tumors ranging from 5 mm to 6 cm in diameter, but these tumors occasionally occur with nephroblastomas, renal cell carcinomas, and extrarenal neoplasms (bronchial or pancreatic carcinoma, ovarian tumors, carcinoma of ileum or colon, soft tissue sarcomas, orbital hemangiopericytoma).

Etiology and Pathogenesis

Autonomous hypersecretion of renin results in high circulating levels of Ang II, which increase arterial pressure. Secondary hyperaldosteronism, giving rise to hypokalemia, results from stimulation of the adrenal glomerulosa by Ang II. High Ang II levels also induce hyponatremia in a minority of patients, by stimulation of thirst and antidiuretic hormone (ADH) secretion, together with a direct renal water-retaining action of the peptide, and may also cause proteinuria.[30]

Clinical Manifestations

Cases show slight female predominance; 75% of patients are younger than 30 years, presenting usually with severe, occasionally paroxysmal hypertension (average 206/131 mm Hg), hypokalemia (<3.0 mmol/l in ~70% of cases), proteinuria (>0.4 g/day in ~50% of patients), and in a minority, hyponatremia.[31] Glomerular filtration rate (GFR) is normal or high. BP may decrease substantially with the first dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).

Pathology

Renin-secreting tumors are encapsulated and tan or grayish yellow, with scattered hemorrhages. These masses consist largely of polygonal or spindle cells in close contact with capillary and sinusoidal vessels and contain cytoplasmic renin granules.[31]

Diagnosis and Differential Diagnosis

Patients presenting with hypertension and hypokalemia together with elevated renin (and prorenin) and aldosterone levels may harbor a renin-secreting tumor, most often a renal juxtaglomerular cell tumor. Renal artery stenosis or occlusion must first be ruled out by CT or MRI angiography or renal arteriography. These investigations also might reveal a radiolucent, relatively avascular, usually peripheral juxtaglomerular cell tumor (Fig. 41-6).[32] CT and MRI scans showing an isodense or hypodense lesion with little or no enhancement after injection of contrast material have proved helpful in the provisional localization of these tumors. Bilateral, simultaneous renal vein sampling may enable lateralization of the tumor. Because renal blood flow to the culprit kidney is not impaired, however, a renin ratio of more than 1.2:1 between the two renal veins may not be present, in contrast to the situation of unilateral renal artery stenosis, in which reduced blood flow to the stenosed kidney and renin oversecretion contribute to an often high renal vein renin ratio. Selective segmental renal vein renin sampling may help localize the tumor. When no renal lesion can be visualized and lateralization of renin secretion is not evident, an extrarenal renin-secreting lesion must be considered and sought by appropriate

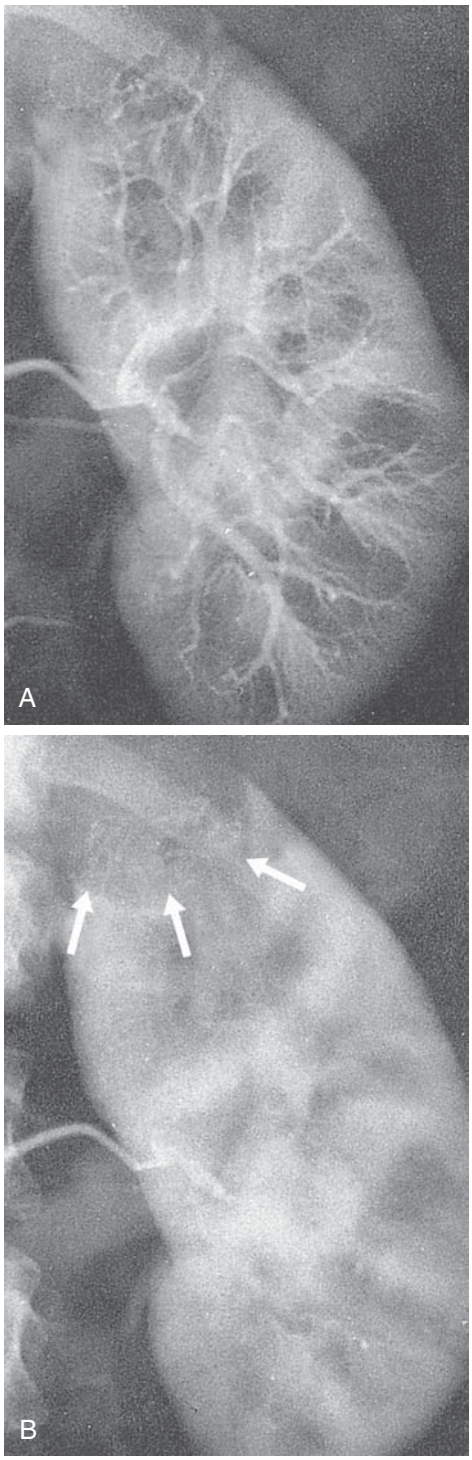

Figure 41-6 Renin-secreting tumor. Left renal angiography arterial **(A)** and nephrogram **(B)** phases revealing a 2.5-cm juxtaglomerular cell tumor with a circumscribed and relatively avascular appearance at the upper pole *(arrows). (Modified from reference 32.)*

radiographic investigations and venous sampling for renin measurements.

Apart from renal artery stenosis or occlusion, it may be necessary to exclude other renin-producing lesions, including Wilms tumor, renal carcinoma, neuroblastoma, hepatocellular carcinoma, and pheochromocytoma, which can either secrete renin or stimulate renal renin production. A careful clinical history and physical examination with selected radiography and occasionally venous sampling for measurements of renin should differentiate these disorders from a juxtaglomerular cell tumor in most patients.

Treatment

Preoperative control of arterial pressure is based on an ACE inhibitor or ARB, introduced with caution to avoid first-dose hypotension. For juxtaglomerular cell tumors, local excision, where possible, is advisable to preserve nephrons. When doubt exists, an intraoperative frozen section will differentiate a benign juxtaglomerular cell tumor from malignant lesions and guide surgery. Removal of a juxtaglomerular cell tumor results in the return of renin and aldosterone levels to normal. BP decreases rapidly, but not always to normal if there is a background of primary hypertension or hypertensive vascular damage.

ACROMEGALY

Definition and Epidemiology

Acromegaly is caused by excessive circulating growth hormone (GH), usually from a pituitary tumor. It is rare, with an incidence of 5 cases per 1 million population per year and a prevalence of 40 to 60 cases per million. Hypertension is more common in persons with acromegaly than in the general population, with an estimated 35% of acromegalic patients with diastolic BP above 100 mm Hg and a higher frequency in female and older patients. Uncertainty about the prevalence (17.5% to 57% in >20 different reports) reflects variation in definitions of hypertension and the stage of the disease.[33] Acromegalic patients who have additional hypopituitarism or advanced cardiomyopathy may have BP reduction masking prior hypertension.

The pathogenesis of hypertension in acromegaly is complex but reflects sodium retention and volume expansion associated with an inappropriate response of hormonal systems to counteract these effects. Total exchangeable sodium, total body water, and extracellular fluid volume are increased. Volume expansion should suppress plasma renin levels, but although levels are low, they are not consistent with the sodium status. Aldosterone levels are also normal or only slightly suppressed. Plasma ANP, which should be elevated in the volume-expanded state, remains normal in acromegaly. The kidneys are enlarged and GFR is increased, but sodium balance is not corrected unless the acromegaly is cured. Other mechanisms contributing to hypertension may include the presence of circulating endogenous Na^+,K^+-ATPase (digoxin-like substances), endothelial dysfunction and GH-induced vascular hypertrophy resulting in decreased vascular compliance, effects on SNS, and undefined genetic factors.

Clinical Manifestations

Acromegaly is characterized by enlargement of the skull (Fig. 41-7), hands (Fig. 41-8), and feet. Other symptoms result from local effects of an expanding pituitary tumor and include visual field defects and headache. Signs and symptoms include headache (40%), excessive sweating (50%), loss of libido (35%), amenorrhea (45%), carpal tunnel syndrome (25%), diabetes mellitus (19%), and visual field defects (5%).[34,35] Thyroid enlargement occurs in 50% of patients and thyrotoxicosis in 6%. Hirsutism occurs in 24% of women and galactorrhea in 10%. Other complications of acromegaly include cardiac hypertrophy, systolic and diastolic dysfunction, arrhythmia, sleep apnea, osteoarthritis and osteopenia, and disturbed calcium metabolism.[36]

Figure 41-7 Facial features of acromegaly with enlargement of brow, nose, and jaw.

Figure 41-8 Radiograph of the hand in acromegaly. "Arrowhead" distal phalanges, expanded joint spaces, and increased soft tissue can be seen.

Diagnosis

Clinical suspicion should be raised by symptoms and signs. Box 41-1 lists appropriate tests for acromegaly. Elevated plasma GH, especially in response to an oral glucose tolerance test, is strongly suggestive of the diagnosis. Visual field assessment and MRI of the pituitary fossa are necessary to define the tumor and to exclude supratentorial extension. Most patients with acromegaly have a GH-secreting

Tests for Acromegaly
Serum growth hormone
Serum growth hormone responses to glucose tolerance test
Serum insulin-like growth factor 1
Lateral skull x-ray film
Magnetic resonance imaging of the pituitary fossa
Visual field measurements
Assessment of other pituitary functions (e.g., thyroid function tests, thyroid-stimulating hormone, prolactin level, ACTH, and cortisol)

Box 41-1 **Diagnostic tests for acromegaly.**

pituitary adenoma. Rarely, pancreatic or hypothalamic tumors release GH-releasing hormone with secondary GH excess. Breast and bronchial tumors can also produce GH.

Treatment

Transsphenoidal adenomectomy is the treatment of choice for acromegalic patients. Irradiation and drug therapy are valuable when complete removal of tumor tissue is not possible (one third of patients) and when surgery is contraindicated. Dopaminergic agents, such as bromocriptine and cabergoline, and the somatostatin analogue octreotide reduce serum GH in acromegaly. Bromocriptine may induce tumor shrinkage and improve diabetes. The GH receptor antagonist pegvisomant has also been shown to be safe and effective.[37] Radiation therapy may not exert its full effect for months or years. Hypopituitarism may occur late after treatment and necessitate endocrine replacement for ACTH, thyroid-stimulating hormone (TSH), or gonadotropin deficiency. Therefore, regular monitoring of pituitary function is required after treatment.

Management of Hypertension in Acromegaly

Surgical removal of the pituitary adenoma with normalization of GH levels may reduce blood pressure to some extent, but the majority of acromegalic patients will continue to require antihypertensive therapy. Antihypertensive treatment requires a diuretic, given the volume-expanded state. Additional antihypertensive agents are frequently required, and both calcium channel blockers and ACE inhibitors may be effective. β-Blockers may also be used, although theoretically such agents may increase GH hormone concentration.

HYPOTHYROIDISM

Definition and Epidemiology

Hypothyroidism results from deficient production of thyroid hormones, whether through inadequate TSH secretion (from hypothalamic or pituitary lesions) or by impaired functioning of the thyroid itself (loss or atrophy of the gland, autoimmune destruction, iodine deficiency, antithyroid agents, or hereditary defects in hormone synthesis).[38] It is estimated that hypertension is 1.5 to 2 times more common in hypothyroid patients than in the general population.[39]

The pathogenesis of the hypertension is multifactorial and associated with both increased total body sodium and increased peripheral vascular resistance. Even in euthyroid patients, serum free thyroxine index (FTI) is lower and TSH is higher in hypertensive than in normotensive patients, and FTI also independently predicts BP response to increments in dietary sodium in both normotensive and hypertensive individuals.[40]

Figure 41-9 **Hypothyroid facies.**

Hypothyroidism is associated with increased aortic stiffness, loss of sensitivity to vasoconstrictors, and impaired endothelial function with loss of endothelial dependent vasodilation plus reduced vasodilatory responses to NO donors.[41] Observations of short-term hypothyroidism have confirmed increases in arterial pressure, plasma catecholamines, aldosterone, and cortisol, all reversible with thyroid hormone treatment.[42,43] The relationship between plasma catecholamine levels and BP is greater in hypothyroidism. The catecholamine levels of hypothyroid patients also show more variability associated with more variability in BP. This suggests underdamping of swings in sympathetic activity in the hypothyroid state.[44] Hypertension develops despite a low cardiac output.

Thyroid replacement therapy corrects the electrolyte, hemodynamic, and hormone changes and cures the hypertension in most patients.

Clinical Features

Any organ system can be affected in primary hypothyroidism. Symptoms and signs can be protean. The onset of clinical abnormalities is usually gradual, and diagnosis may not be made until gross hypothyroidism is established. Common clinical features include weakness, dry skin, lethargy, slow slurred speech, sensitivity to cold, thick tongue, facial puffiness (Fig. 41-9), coarse hair, failing memory, constipation, and weight gain with reduced appetite. Coronary heart disease is common, with contributions from dyslipidemia and hypertension accelerating the atherogenic process.

Diagnosis

Hypothyroidism should be considered in any patient with hypertension. Because the clinical manifestations of hypothyroidism are often difficult to elicit, especially in elderly patients, thyroid function tests, including TSH when FTI is equivocal, should be performed. In patients with primary hypothyroidism in whom normotension is not achieved by full thyroxine replacement therapy, primary

hypertension likely is a concomitant disorder. For those with gross or longstanding hypothyroidism, replacement thyroxine therapy should be cautious to minimize the chances of exacerbating latent myocardial ischemia.

HYPERTHYROIDISM

Definition and Epidemiology

Hyperthyroidism and thyrotoxicosis may result from Graves disease and less frequently toxic multinodular goiter, toxic adenoma, high iodine intake, trophoblastic tumor, and (rarely) excessive pituitary TSH secretion. Hypertension is common in hyperthyroidism, with a prevalence of 60% in toxic adenoma and approximately 30% in Graves disease.

Clinical Features

The clinical features depend on the underlying cause of the hyperthyroidism, severity of the disorder, rapidity of onset, age of the patient, and concomitant disease. Abnormalities may be evident in the cardiovascular system (tachyarrhythmias, heart failure), skin (increased sweating, increasing pigmentation with vitiligo), eyes (lid lag, exophthalmos), nervous system (hypertension, nervousness), alimentary system (increased appetite yet weight loss, diarrhea), and muscles (proximal weakness).

Hypertension in hyperthyroidism is associated with elevated systolic and normal or low diastolic BP. It may be observed in both postpartum thyrotoxicosis and neonatal thyrotoxicosis. Elevation of diastolic BP is unusual unless there is concomitant primary hypertension.

The hemodynamic characteristics in hypertension of thyrotoxicosis are an increased cardiac output, increased myocardial contractility, tachycardia, decreased peripheral vascular resistance, and expanded blood volume. These indices return to normal in most patients on achieving the euthyroid state. Interestingly, catecholamine levels tend to be low (inversely to hypothyroid hypertension), and there is no heightened activity of the sympathetic system. The RAS tends to be activated and the aldosterone levels increased in hyperthyroidism, which may contribute to the development of systolic hypertension. Experimental hyperthyroidism is characterized by enhanced endothelial responsiveness, perhaps reflecting increased sheer stresses from the hyperdynamic circulation. There is also a resetting of the pressure-natriuresis relationship, possibly attributable to increased renin-angiotensin activity.[41]

Suspicion of hyperthyroidism should be high in the elderly patient with hypertension and a high pulse pressure, particularly if there is also atrial fibrillation. Such patients are prone to developing cardiac failure, in which case the increased systolic arterial pressure will diminish, masking previous hypertension. Hypertension with a high pulse pressure, although typical of hyperthyroidism, is observed in many elderly patients with primary hypertension because of the loss of compliance of the aorta with aging.

Diagnosis and Treatment

Diagnosis of hyperthyroidism is confirmed by thyroid function tests, including measurement of TSH. β-Blockers are often effective first-line therapy for hyperthyroidism-associated hypertension. Treatment of hyperthyroidism, whether by antithyroid drugs, surgery, or radioiodine, will often normalize the increased systolic arterial pressure, although this is by no means invariable in the elderly patient, who may have concomitant primary hypertension.

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CHAPTER 42

Neurogenic Hypertension, Including Hypertension Associated with Stroke or Spinal Cord Injury

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The nervous system and blood pressure (BP) are closely interrelated.[1] It is well recognized that the elevated BP response to stressors is mediated by the sympathetic nervous system (SNS). However, the role of the SNS in the long-term regulation of BP and the initiation and maintenance of hypertension is also increasingly appreciated. Several studies of plasma catecholamine levels, renal norepinephrine spillover, microneurography, and heart rate variability support the hypothesis that sympathetic activation plays a major role in hypertensive patients.[2] The SNS also has an important role in hypertension after neurologic injury. This chapter describes the physiology and management of hypertension in such injury.

PHYSIOLOGY AND PATHOPHYSIOLOGY

Neural Control of Blood Pressure

The brainstem, especially the ventral medulla, has a key role in the maintenance of BP (Fig. 42-1). BP is controlled by the nucleus tractus solitarius (NTS), which receives inhibitory baroreceptor afferents, and by the rostral ventrolateral medulla and rostral ventromedial medulla, which are the source of excitatory descending bulbospinal pressor pathways. In addition, a depressor center in the caudal ventrolateral medulla composed of γ-aminobutyric acid (GABA)–containing neurons receives afferents from the NTS and projects to the rostral ventral medulla. These inhibitory GABA-containing neurons are tonically active, and reduced activity of these neurons leads to hypertension.[3-5]

The ultimate effector units are the sympathetic neurons located in the intermediolateral cell column of the spinal cord and the parasympathetic neurons found in the dorsal motor nucleus of the vagus and nucleus ambiguus located in the medulla. In addition, impulses from the limbic system, cerebral cortex, and hypothalamus also directly or indirectly project to the intermediolateral cell column of the spinal cord and influence BP regulation.

The factors that lead to increased sympathetic activation in hypertension are poorly understood. In recent years, however, the role of low-grade inflammation and reactive oxygen species (ROS) has been recognized. Some studies also suggest that activation of low-grade inflammation in the kidney may activate afferent sympathetic nerves that stimulate the central SNS. Hypertension is also associated with increased levels of circulating inflammatory markers such as tumor necrosis factor α, interleukin-6, C-reactive protein, monocyte chemoattractant protein 1, and adhesion molecules such as P-selectin and intercellular adhesion molecule 1. Angiotensin II (Ang II) and aldosterone also play a crucial role in vascular inflammation, and both candesartan and mineralocorticoid antagonists have been shown to decrease the levels of inflammatory markers. In addition, Ang II–mediated hypertension has been associated with brain microglial activation and increased brain levels of inflammatory cytokines and ROS. An increase in ROS may directly activate or sensitize sympathetic neurons and scavenge nitric oxide, which tonically inhibits sympathetic outflow. Thus, a dysfunction of the neural-immune-vascular triad leading to an increase in central oxidative stress may be the driving force behind sympathetic activation, which then increases Ang II and promotes further inflammation and vascular dysfunction.[6]

Cerebrovascular Autoregulation

Under normal conditions, cerebral blood flow (CBF) of the adult brain is 50 ml/100 g/min. CBF is regulated by the following relationship between cerebral perfusion pressure (CPP) and cerebrovascular resistance (CVR):

$$CBF = CPP/CVR$$

Cerebral perfusion pressure is defined as the difference between the mean arterial pressure (MAP) and the intracranial pressure (ICP). If ICP is increased, systemic BP needs to be higher to maintain CPP and CBF.

Cerebrovascular autoregulation maintains a constant blood flow over a wide range of CPP. Normally, changes in BP have little effect on CBF because of compensatory changes in cerebrovascular resistance. An increase in BP produces vasoconstriction, and a decrease in BP produces vasodilation, thus keeping CBF constant (Fig. 42-2). Autoregulation is effective over a range of CPP from about 60 to 150 mm Hg. In chronically hypertensive individuals, the cerebral arterioles develop medial hypertrophy and lose the ability to dilate effectively at lower pressures. This causes the autoregulatory curve to shift to the right.[7] In these individuals, a rapid reduction of BP may lead to a drop in CBF even though the BP might still be within the "normal" range. With effective control of hypertension for several months, the normal range for autoregulation can be reestablished.[8]

Above the upper limit of autoregulation, there is *breakthrough vasodilation* leading to damage of the blood-brain barrier and cerebral edema and possibly cerebral hemorrhage. Below the lower limit of autoregulation, decreases in CPP lead to a decrease in CBF. Under these circumstances, increased extraction of oxygen and glucose maintains normal cerebral metabolism and brain function. When CBF decreases to less than 20 ml/100 g/min, the increase in oxygen extraction is no longer able to supply the metabolic needs of the brain, leading to impaired brain function.

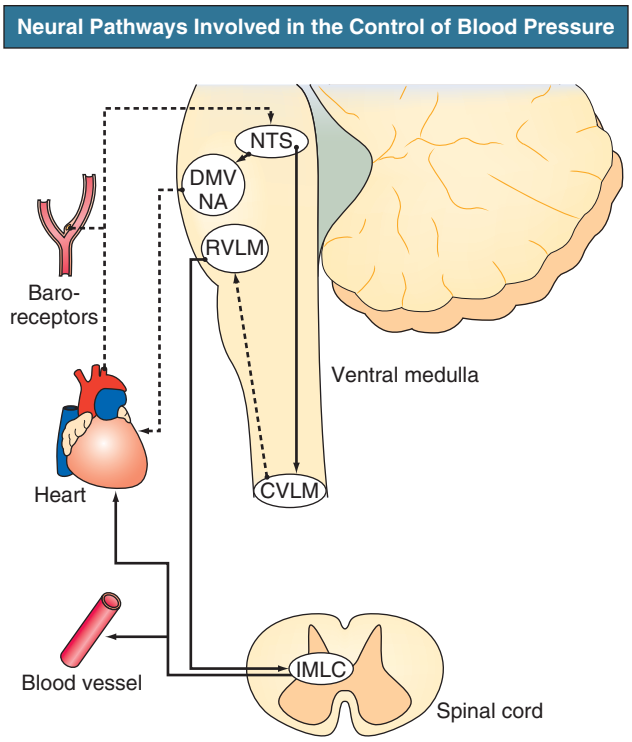

Figure 42-1 Neural pathways involved in the control of blood pressure. The ventral medulla has a key role in generating both excitatory *(solid line)* and inhibitory *(dotted line)* pathways, largely through the rostral ventrolateral medullary neurons *(RVLM)* and nucleus tractus solitarius *(NTS),* respectively. Ultimate effector control is provided by sympathetic activation originating in the intermediolateral cell column *(IMLC)* and parasympathetic action through the nucleus ambiguus *(NA)* and dorsal motor nucleus of the vagus nerve *(DMV)*. *CVLM,* Caudal ventrolateral medullary neurons.

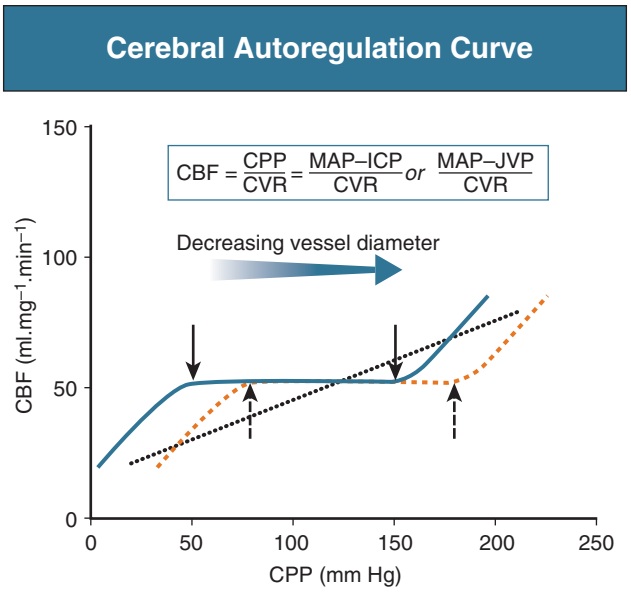

Figure 42-2 Cerebral autoregulation curve. In the normal state *(solid line),* cerebral blood flow *(CBF)* is held constant across a wide range of cerebral perfusion pressure (*CPP;* 60 to 150 mm Hg). In chronic hypertension *(dashed line),* the autoregulation curve shifts to the right. In the presence of acute cerebral ischemia *(dotted line),* cerebral autoregulation may be impaired, and CBF becomes dependent on CPP. *CVR,* Cerebral venous resistance; *ICP,* intracranial pressure; *JVP,* jugular venous pressure; *MAP,* mean arterial pressure. *(From reference 14.)*

HYPERTENSION AFTER STROKE

Epidemiology

Hypertension is the most important modifiable risk factor for cerebrovascular accident (stroke), and reduction in BP is effective in the primary prevention of stroke, improves outcomes in patients who have had an ischemic stroke, and may be especially beneficial for lowering risk of stroke among those with a history of intracerebral brain hemorrhage.[9] Combined data from 40 trials of antihypertensive agents have demonstrated that a 10% reduction in systolic BP lowers stroke risk by one third.[10] A 5-mm lower diastolic together with a 9-mm lower systolic BP confers a 33% lower risk of stroke, and a 10-mm lower diastolic together with an 18- to 19-mm lower systolic confers more than a 50% reduction in stroke risk.[11] In patients who had a stroke, the Perindopril Protection against Recurrent Stroke Study (PROGRESS) showed that a reduction in BP was associated with a significant reduction of total stroke recurrence by 28% and a reduction of major coronary and vascular events by 26%, even in patients with a normal initial BP.[12]

However, the management of BP in the immediate aftermath of a stroke is controversial.[13] A high proportion of patients have elevated BP immediately after a stroke, and BP has been shown to decrease spontaneously over 1 to 2 weeks to the prestroke baseline in most patients. Box 42-1 lists some postulated causes of elevated BP. Increased BP after stroke is associated with higher mortality. Nonetheless, it is uncertain whether the increased BP directly contributes to poor outcome, or whether immediate lowering of BP will lead to better outcomes.

Postulated Causes of Hypertension After Stroke

- Preexisting hypertension
- "White coat" effect
- Stress of hospitalization
- Cushing reflex*
- Catecholamine and cortisol release
- Lesion of brainstem or hypothalamus
- Nonspecific response to brain damage

Box 42-1 Postulated causes of hypertension after stroke. *A hypothalamic response to raised intracranial pressure or ischemia consisting of hypertension with bradycardia.

Pathophysiology

An understanding of cerebrovascular pathophysiology is essential to understand the pros and cons of treating hypertension in these patients (Table 42-1).

In patients with an ischemic stroke, vascular occlusion leads to a central region of irreversibly ischemic brain surrounded by an ischemic zone where blood flow is reduced but brain tissue is still viable. After 2 or 3 days, the ischemic areas either recover completely or undergo infarction. In the first few days, perfusion in this zone is marginal, and a further decrease in blood flow might lead to infarction. Because cerebral autoregulation is impaired with acute ischemic stroke, a fall in BP could lower blood flow and extend infarction, and a very high BP could lead to hemorrhagic transformation, especially if thrombolytic agents have been given.

At times, it can be difficult to distinguish between *hypertensive encephalopathy,* in which lowering of BP is clearly indicated, and

Acute Treatment of Hypertension in Stroke: Advantages and Disadvantages	
Advantages	**Disadvantages**
Acute Ischemic Stroke	
Might lower mortality Might decrease stroke progression Might decrease hemorrhagic transformation (especially after tPA) Might decrease cerebral edema formation Might be helpful for systemic reasons (e.g., associated myocardial ischemia) Patients likely to be more compliant with antihypertensive use if treatment initiated in hospital	BP decreases on its own No proven benefit Ongoing ischemia around infarct (ischemic penumbra) Altered autoregulation from chronic hypertension, ischemia Large-vessel stenosis might have resulted in reduction of perfusion. Chance of propagating thrombus Anecdotal case reports and trial results demonstrating deterioration with BP decrease Principle of "do no harm" *(primum non nocere)*
Acute Intracerebral Hemorrhage	
Might lower mortality Might decrease hematoma expansion Might decrease cerebral edema formation Might be helpful for systemic reasons (e.g., associated myocardial ischemia) Patients likely to be more compliant with antihypertensive use if treatment initiated in hospital	BP decreases on its own No proven benefit Possible zone of ischemia around intracerebral hematoma Chronically hypertensive patients require higher CPP, because of shift in autoregulatory curve. ICP may be elevated, and lowering BP reduces what could be marginal CPP. Principle of "do no harm" *(primum non nocere)*
Aneurysmal Subarachnoid Hemorrhage	
Might decrease rebleeding rate Might help if there is cardiac ischemia (stunned myocardium)	No proven benefit ICP may be elevated, and lowering BP reduces what could be marginal CPP. Might lead to cerebral ischemia in presence of vasopasm.

Table 42-1 Advantages and disadvantages (pros and cons) of acute treatment of hypertension in stroke. *BP,* Blood pressure; *CPP,* cerebral perfusion pressure; *ICP,* intracranial pressure; *tPA,* tissue plasminogen activator.

ischemic stroke with hypertension. The level of consciousness, the presence of focal neurologic deficits, and the ophthalmoscopic (funduscopic) examination can help make this distinction. Hypertensive encephalopathy is a syndrome of global neurologic dysfunction, usually with papilledema, and focal neurologic deficits are usually less prominent. In acute ischemic stroke, the focal neurologic deficit is more prominent, and alterations of consciousness are less common, except with brainstem strokes or "malignant" brain edema from massive hemispheric infarction.

In patients with intracerebral hemorrhage, the considerations are different.[14] Hematoma expansion occurs in one third of patients, with an intracerebral hemorrhage in the first 24 hours.[15] Therefore, BP is often lowered in these patients to decrease hematoma expansion. However, the evidence does not support a clear association between high BP and hematoma expansion.[16] On the other hand, some patients with intracerebral hemorrhage might have increased ICP from the hematoma volume or associated hydrocephalus. In these patients, lowering of BP is not warranted because it might critically lower CPP; monitoring of ICP and CPP may be helpful.

Patients with aneurysmal subarachnoid hemorrhage have significant risk of rebleeding; tight BP control is recommended to decrease the risk. Some patients with subarachnoid hemorrhage have associated myocardial dysfunction ("stunned myocardium"), in which case high BP might worsen myocardial function. Again, in patients with hydrocephalus or an associated intracerebral hemorrhage, monitoring ICP and CPP can help guide BP management. In the latter half of the first week and in the second week after subarachnoid hemorrhage, many patients develop vasospasm of the intracranial arteries. Reduction of BP may lead to worsening of cerebral ischemia in this situation. Therefore, once the aneurysmal rupture has been adequately treated with surgical clipping or coiling, BP is usually maintained at a normal or slightly elevated level in these patients.

Diagnosis and Treatment

Definitive studies adequately powered to assess the benefits and risks of BP lowering after ischemic and hemorrhagic stroke have not yet been performed. A Cochrane review concluded that evidence is insufficient to evaluate the effect of altering BP on outcome during the acute phase of stroke.[17] The following sections summarize the available evidence. Figure 42-3 outlines recommendations for treating BP in different clinical situations.

Acute Ischemic Stroke

The Acute Candesartan Cilexetil Evaluation in Stroke Survivors (ACCESS) trial studied early or late treatment with candesartan after a stroke in patients who were conscious, had a motor paresis, and were hypertensive. The combined end point of total mortality, cerebral complications, and cardiovascular complications at the end of 3 months was reduced by 48% for patients treated with candesartan (4 to 16 mg) initiated within 72 hours after stroke compared with those starting candesartan 7 days later. However, this difference in outcome was not associated with any difference in BP.[18]

The larger Scandinavian Candesartan Acute Stroke Trial (SCAST) was designed to confirm to benefit of candesartan in patients with acute stroke. Patients with a systolic BP of 140 mm Hg or more within 30 hours of an acute stroke (85% were ischemic) were randomized to treatment with candesartan or placebo for 7 days, with dose escalation from 4 mg on day 1 to 16 mg on days 3 to 7. The primary outcome of the composite of vascular death, myocardial infarction, or stroke at 6 months was not significantly different between the two groups. Functional outcome was slightly worse at 6 months in the candesartan group but did not meet statistical significance.[19]

In the Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS) trial, hypertensive patients with an ischemic or hemorrhagic stroke were randomized within the first 36 hours to labetalol, lisinopril, or placebo, titrated to a systolic BP goal of 145

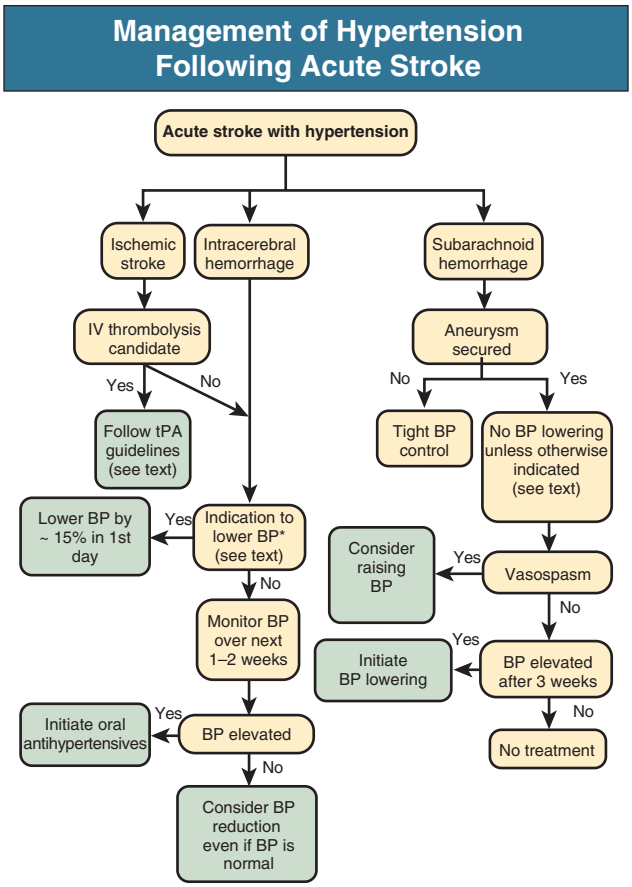

Figure 42-3 Management of hypertension after acute stroke. *BP,* Blood pressure; *IV,* intravenous; *tPA,* tissue plasminogen activator. *Indication for treatment includes systolic BP above 220 or diastolic BP above 120 mm Hg for ischemic stroke, the presence of associated conditions such as aortic dissection or myocardial infarction, and in patients with cerebral hemorrhage, systolic BP above 180 or mean arterial pressure above 130 mm Hg.

Guidelines for Blood Pressure Management After Acute Ischemic Stroke

AHA/ASA	ESO
Patients Eligible for Thrombolytic Therapy	Routine BP lowering is not recommended.
Before Thrombolytic Therapy	Cautious BP lowering is recommended in patients with extremely high BP (>220/120 mm Hg) on repeated measurements, or with severe cardiac failure, aortic dissection, or hypertensive encephalopathy.
Lower BP if SBP >185 or DBP >110 mm Hg.	Abrupt BP lowering should be avoided.
After Thrombolytic Therapy	BP must be below 185/110 mm Hg before, and for the first 24 hours after, thrombolysis.
Lower BP if SBP >180 or DBP >105 mm Hg.	
Patients Not Eligible for Thrombolytic Therapy	
Patients with markedly elevated BP may have their BP lowered. Lowering BP by ~15% in these patients is reasonable. Antihypertensive drugs should be withheld unless SBP >220 or DBP >120 mm Hg.	

Table 42-2 Guidelines for blood pressure (BP) management after acute ischemic stroke. *AHA,* American Heart Association, *ASA,* American Stroke Association; *ESO,* European Stroke Organisation; *SBP,* systolic blood pressure; *DBP,* diastolic blood pressure.

to 155 mm Hg or a systolic BP reduction of 15 mm Hg from the BP at randomization. The primary outcome of death or dependency at 2 weeks in the treated group was not significantly different from that of the placebo group; however, mortality was halved at 3 months in the treatment groups compared with placebo.[20]

The Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS) was a prospective randomized trial to determine the efficacy and safety of continuing or stopping preexistent antihypertensive drugs in patients with a recent stroke. The trial was prematurely stopped because it lacked research support and was underpowered. At the end of 2 weeks, however, there was no difference in mortality or dependency between the group continuing antihypertensives and the group stopping the drugs.[21]

Early decrease in BP had no effect on outcome in the Glycine Antagonist in Neuroprotection (GAIN Americas) trial. In the Intravenous Nimodipine West European Stroke Trial (INWEST), a more than 20% reduction of diastolic BP on day 2 was associated with a worse outcome.[22,23]

The Chinese Antihypertensive Trial in Acute Ischemic Stroke (CATIS) studied 4071 hypertensive patients with nonthrombolyzed ischemic stroke within 48 hours of onset. Patients were randomized to receive antihypertensive treatment (aimed at lowering systolic blood pressure by 10% to 25% within the first 24 hours after randomization, achieving blood pressure less than 140/90 mm Hg within 7 days, and maintaining this level during hospitalization) or to discontinue all antihypertensive medications during hospitalization. There was no difference in the combined outcome of death and major disability at 14 days, at hospital discharge, or at 3 months between the two groups.[23a]

Table 42-2 summarizes the currently recommended guidelines of the American Heart Association and American Stroke Association (AHA/ASA) and the European Stroke Organisation (ESO) for BP management in acute ischemic stroke.[24,25]

Intracerebral Hemorrhage

A small, controlled study of 14 hypertensive patients with a small to moderate-sized cerebral hemorrhage within 24 hours showed that treatment with nicardipine or labetalol to reduce MAP by 15% to a lower MAP limit of about 120 mm Hg produced no change in CBF.[26] In contrast, a decrease in MAP by more than 20% or a systolic BP below 110 mm Hg in patients with cerebral hemorrhage has been shown to decrease CBF.[27]

The Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) study used intravenous (IV) nicardipine infusion for 18 to 24 hours in patients with cerebral hemorrhage with a systolic BP above 200 mm Hg presenting within 6 hours of symptoms. Patients with small hematomas (mean volume <20 ml) were treated to three different systolic BP goals (170 to 200, 140 to 170, and 110 to 140 mm Hg) with no difference in 3-month mortality among the groups.[28]

The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) randomized hypertensive patients within 6 hours of symptom onset to achieve a target of 140 or 180 mm Hg. Treatment was for 7 days or until hospital discharge. The lower BP target resulted in less hematoma expansion at 24 hours, but this difference was not significant after adjustment for initial hematoma volume and time from onset of symptoms to computed tomography (CT) scan. There was no significant difference in adverse event rate or outcome at 90 days.[29]

Although neither ATACH nor INTERACT was powered to detect a difference in clinical outcome, the results indicate that acute BP

Guidelines for Blood Pressure Management After Acute Cerebral Hemorrhage

AHA/ASA	EUSI
If SBP >200 mm Hg or MAP >150 mm Hg, consider aggressive BP reduction. If SBP >180 mm Hg or MAP >130 mm Hg and there is evidence of or suspicion of elevated ICP, consider monitoring ICP and reducing BP to keep CPP >60 to 80 mm Hg. If SBP >180 mm Hg or MAP >130 mm Hg and there is no evidence or suspicion of elevated ICP, consider modest BP reduction (e.g., MAP of 110 mm Hg, target BP of 160/90 mm Hg)	Routine BP lowering is not recommended. Treatment is recommended in patients *with* known history of hypertension or signs (ECG, retina) of chronic hypertension: SBP >180 or DBP >105 mm Hg. If treated, target BP should be 170/100 mm Hg (or MAP 125 mm Hg). Treatment is recommended in patients *without* known hypertension: SBP >160 and/or DBP >95 mm Hg. If treated, target BP should be 150/90 mm Hg (or MAP 110 mm Hg). Reduction of MAP by >20% should be avoided. These limits and targets should be adapted to higher values in patients undergoing monitoring of increased ICP, to guarantee sufficient CPP >70 mm Hg.

Table 42-3 Guidelines for blood pressure (BP) management after acute cerebral hemorrhage. *AHA,* American Heart Association; *ASA,* American Stroke Association; *EUSI,* European Stroke Initiative; *SBP,* systolic blood pressure; *DBP,* diastolic blood pressure; *ECG,* electrocardiogram; *MAP,* mean arterial pressure; *ICP,* intracranial pressure; *CPP,* cerebral perfusion pressure.

reduction in intracerebral hemorrhage may be safe. Based on the results of INTERACT, the main-phase study, INTERACT2 randomized 2839 hypertensive patients with acute cerebral hemorrhage within 6 hours to blood pressure targets of <140 mm Hg or <180 mm Hg. There was no significant difference in the rate of the primary outcome of death or severe disability between the two groups. However, the group randomized to the lower blood pressure target had significantly lower modified Rankin scores. There was no significant difference in hematoma growth between the two groups.[29a] ATACH-II, a similar follow-up trial to ATACH, is currently under way.

Table 42-3 summarizes the currently recommended guidelines of the AHA/ASA and the European Stroke Initiative (ESI) for BP management in acute cerebral hemorrhage.[30,31]

Subarachnoid Hemorrhage

Before definitive treatment of the ruptured aneurysm, systolic BP is usually kept below 140 to 160 mm Hg, although there is no conclusive evidence that higher BPs increase rebleeding rate. In patients with suspected elevation of ICP, it is important to monitor ICP and to keep CPP above 70 mm Hg. The AHA/ASA guidelines recommend monitoring and control of BP to balance the risk of stroke, hypertension-related bleeding, and maintenance of CPP. A systolic BP goal of below 160 mm Hg is considered reasonable.[32] The ESO recommends keeping the systolic BP below 180 mm Hg but keeping MAP above 90 mm Hg.[33] After the ruptured aneurysm has been secured, aggressive treatment of BP should be avoided, and in the patient with cerebral vasospasm, BP is usually elevated until the neurologic deficits resolve, generally up to a systolic BP of 200 to 220 mm Hg.

HYPERTENSION AFTER CAROTID ENDARTERECTOMY AND ENDOVASCULAR PROCEDURES

Definition, Incidence, and Clinical Features

Hemodynamic disturbances such as hypotension, bradycardia, and hypertension are common (10% to 40%) after carotid endarterectomy and endovascular procedures such as angioplasty and stenting. A small percentage of these patients develop the *carotid hyperperfusion* (or reperfusion) *syndrome*. This syndrome occurs in the first week after surgery or angioplasty-stenting and manifests as transient or permanent contralateral neurologic signs, ipsilateral pulsatile headache, seizures, cerebral hemorrhage, or reversible cerebral edema.[34-36] Some patients with cerebral hyperperfusion after revascularization may not manifest clinical signs acutely but may later develop cortical neuronal loss and cognitive impairment.[37]

In a recent review of hypertension and hyperperfusion syndrome after carotid endarterectomy, the incidence of postoperative severe hypertension was 19% and that of carotid hyperperfusion syndrome was 1%. Most cases occurred in the first week, and the average time to symptoms was the fifth postoperative day. Seizures (36%), hemiparesis (31%), or both (33%) were the common presenting features, and 59% of patients had headache.[38]

Pathophysiology

Preexisting hypertension, baroreceptor impairment after surgical manipulation, and elevated catecholamine levels after cerebral hypoperfusion during intraoperative cross-clamping may contribute to postoperative hypertension that contributes to cerebral hyperperfusion. The hyperperfusion syndrome may be caused in part by impaired autoregulation from chronic vasodilation of the distal vascular bed ipsilateral to a hemodynamically significant internal carotid artery stenosis.[39] Other postulated mechanisms include activation of the trigeminovascular axon reflex and derangement of the carotid baroreceptors.[40] Patients at risk for development of hyperperfusion syndrome are those with extensive microvascular disease, preoperative hypoperfusion and impaired autoregulation, or postoperative hyperperfusion.

Diagnosis and Treatment

Cerebral hyperperfusion has been defined as a postoperative increase in cerebral blood flow of more than 100% compared with preoperative flow. However, this CBF increase may be only approximately 20% compared with the contralateral side.[41] Bouri and colleagues[38] believe that making a diagnosis of cerebral hyperperfusion syndrome based on CBF doubling alone leads to a significant overestimation of the incidence and suggest the following four criteria:

1. Onset within 30 days after carotid endarterectomy
2. Evidence of hyperperfusion (on transcranial Doppler, single-photon emission computed tomography [SPECT], or CT/magnetic resonance [MR] perfusion imaging), *or* systolic BP above 180 mm Hg
3. Clinical features such as new headache, seizures, or hemiparesis (Glasgow coma scale <15) *or* radiologic features such as cerebral edema or intracerebral hemorrhage
4. No evidence of new cerebral ischemia, postoperative carotid occlusion, or metabolic or pharmacologic cause

Because of the risk for development of carotid hyperperfusion syndrome after carotid endarterectomy or stenting, all patients should have continuous intraoperative and postoperative BP

monitoring. Most authors advocate strict BP control (systolic BP <120 mm Hg) from the time of intraoperative internal carotid artery unclamping or angioplasty, particularly in high-risk patients.[42] Others suggest aiming for a systolic BP of 140 to 160 mm Hg or preoperative systolic BP if lower. Elevated BP should be treated with IV labetalol or clonidine. Vasodilators such as nitroglycerin and sodium nitroprusside should be avoided.

HYPERTENSION AFTER SPINAL CORD INJURY

Definition and Epidemiology

Autonomic dysreflexia occurs in up to 70% of patients after spinal injury, most often during the first 2 to 4 months after injury. Autonomic dysreflexia is defined as an increase in systolic BP by at least 20%, associated with a change in heart rate and accompanied by at least one sign (sweating, piloerection, facial flushing) or symptom (headache, blurred vision, stuffy nose).[43] If unrecognized, dysreflexia can result in serious sequelae, such as posterior leukoencephalopathy, cerebral hemorrhage, subarachnoid hemorrhage, seizures, arrhythmia, pulmonary edema, retinal hemorrhage, and rarely coma or death.[44]

Pathophysiology and Diagnosis

Autonomic dysreflexia is most often seen in patients with complete injuries. The spinal cord lesion is typically at or above the sixth thoracic spinal nerve level. Immediately after the injury, the patient has initial loss of supraspinal sympathetic control similar to the initial period of muscle flaccidity. This often leads to hypotension and bradycardia (spinal shock). After a few weeks to months, there is extrajunctional sprouting of the α-receptors, denervation hypersensitivity, and impaired presynaptic uptake of norepinephrine. In addition, derangement of spinal glutaminergic interneurons may occur. Noxious stimuli below the neurologic level of the lesion trigger a spinal reflex arc that results in increased sympathetic tone and hypertension.[45] The most common inciting events are an overdistended urinary bladder and fecal impaction. However, autonomic dysreflexia may be secondary to other precipitants, including infections, pressure ulcers, urologic and endoscopic procedures, sympathomimetic medications, and sildenafil citrate used for sperm retrieval.[46]

Clinical symptoms of spinal cord injury include pulsatile headache, blurred vision, anxiety, nasal congestion, nausea, and sweating above the spinal nerve level. The flushed sweaty skin above the lesion level is caused by brainstem parasympathetic activation. At and below the lesion, the skin remains pale, cool, and dry. Heart rate can vary from bradycardia to tachycardia. The hallmark physical finding is elevated BP. However, because BP may normally be quite low after spinal cord injury, baseline BP readings may be within the normal range but elevated for a given individual, making clinical suspicion and reliance on other clinical signs and symptoms paramount in the diagnosis if baseline BP is not known.[45]

Treatment

Vigilant preventive measures for autonomic dysreflexia include proper bowel, bladder, and skin care. However, expeditious treatment of elevated BP is critical to avoid the potentially life-threatening consequences. Placement of the patient upright with the legs lowered, to precipitate orthostatic BP lowering, and removal of any possible noxious stimuli, such as binding clothing and devices, are the initial treatment steps. Checking for urinary overdistention and changing, flushing, or insertion of a new catheter if the patient receives intermittent catheterization are important.

Pharmacologic treatment with rapid-acting, short-lived agents may be indicated for systolic BP elevation of 150 mm Hg or more that persists after the preceding interventions. Nitroglycerin is often used to treat hypertension associated with autonomic dysreflexia. However, to avoid precipitating hypotension, nitrate-containing agents should not be given for 24 hours before use of sildenafil or similar agents. Calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors have also been reported to be effective.[47] If the bladder is empty and BP below 150 mm Hg, fecal disimpaction with a topical anesthetic should be attempted. If dysreflexia is refractory or associated with severe clinical presentation, other precipitants should be sought, and hospitalization may be indicated.[48]

Up to 90% of pregnant women with upper spinal cord injury experience autonomic dysreflexia during labor and delivery. Appropriate epidural or spinal anesthesia techniques can ameliorate the risk.[49]

CEREBROVASCULAR EFFECTS OF ANTIHYPERTENSIVE AGENTS

Different classes of antihypertensive agents have different direct effects on cerebral blood flow, intracranial pressure, and autoregulation. The ideal drug would not increase ICP or decrease CBF to ischemic regions. In addition, in treatment of hypertension in the acute setting, drugs that can be given intravenously, have a short half-life, and do not cause sedation are preferable. In the chronic phase after a stroke, there is no clear evidence favoring one class of antihypertensive agent over another. Table 42-4 summarizes the advantages and disadvantages of various classes of antihypertensive agents in the acute stroke setting

β-Adrenergic antagonists (e.g., esmolol) and combined α- and β-adrenoceptor antagonists (e.g., labetalol) do not increase ICP or affect cerebral autoregulation. They are suitable for treatment of hypertension in the patient with cerebral ischemia or increased ICP. However, bradycardia secondary to increased ICP is a relative contraindication.

Vasodilators (e.g., hydralazine, sodium nitroprusside, nitroglycerin) cause cerebral arterial dilation and venodilation and can theoretically increase ICP and cause a "cerebral steal" phenomenon in patients with cerebral ischemia. Other disadvantages of sodium nitroprusside are tachyphylaxis, the need for shielding from light because of its photosensitivity, and the danger of cyanide and thiocyanate toxicity, which may be difficult to detect in patients with brain injury. However, vasodilators may be used in patients with small and moderate-sized intracerebral hemorrhage and in those with subarachnoid hemorrhage if increased ICP is not a concern.

Calcium channel blockers have varying effects on cerebral autoregulation. Nifedipine can lead to severe reduction in BP and is not recommended. Nimodipine is used routinely in patients with subarachnoid hemorrhage because it has been shown to improve outcome, possibly because of a neuroprotective effect. Nicardipine has been used in patients with acute intracerebral hemorrhage without any change in CBF and is often used in patients with subarachnoid hemorrhage. Nicardipine is becoming popular in neurologic critical care units because of its efficacy, ease of titration, predictable response, and favorable cerebral hemodynamic effects.

The ACE inhibitors and the angiotensin receptor blocker (ARB) candesartan have been used in patients with cerebral ischemia and

Preferred Antihypertensives in Treatment of Stroke-Associated Hypertension				
Drug	**Mechanism of Action**	**Intravenous Dose**	**Advantages**	**Disadvantages**
Labetalol	α_1-, β_1-, and β_2-Receptor antagonist	Test dose 5 mg, then 20- to 80-mg bolus every 10 min up to 300 mg; IV infusion 0.5-2 mg/min	Does not lower CBF Does not increase ICP	May exacerbate bradycardia
Esmolol	β_1-Receptor antagonist	500-μg/kg bolus, then 50-300 mg/kg/min	Does not lower CBF Does not increase ICP	May exacerbate bradycardia
Sodium nitroprusside	Vasodilator	0.25-10 μg/kg/min	Potent antihypertensive	May increase ICP Can cause cerebral steal Potential for cyanide toxicity
Nitroglycerin	Vasodilator	5-100 μg/kg/min	Can be helpful for concomitant cardiac ischemia	May increase ICP Can cause cerebral steal
Hydralazine	Vasodilator	2.5- to 10-mg bolus	Can be given as IV bolus when labetalol is contraindicated due to bradycardia	May increase ICP Can cause cerebral steal
Nicardipine	L-type CCB	5-15 mg/h	Does not decrease CBF	May increase ICP Long duration of action
Enalaprilat	ACE inhibitor	0.625-1.25 mg every 6 hours	Does not decrease CBF	Variable response Long duration of action

Table 42-4 Preferred antihypertensive agents in the treatment of stroke-associated hypertension. *ACE,* Angiotensin-converting enzyme; *CBF,* cerebral blood flow; *CCB,* calcium channel blocker; *ICP,* intracranial pressure; *IV,* intravenous.

have no effect on CBF. However, short-acting parenteral forms of these drugs are not available. ACE inhibitors and ARBs shift the lower limit of cerebral autoregulation toward lower BP in rats and humans. However, these agents have a long half-life, which is not desirable in treatment of hypertension in the acute phase.

Similarly, because of its long half-life and sedative effect, the α_2-adrenergic agonist clonidine is not preferred.

The cerebrovascular effects of the newer parenteral antihypertensives, such as fenoldopam, a peripheral dopamine-1 receptor agonist, and the calcium channel blocker clevidipine, have not been extensively studied. However, in small studies, fenoldopam has been shown to decrease global CBF and increase ICP in patients with impaired intracranial compliance.[50] In a single-center study, clevidipine was found to be safe and effective in perioperative neurosurgical patients with hypertension.[51]

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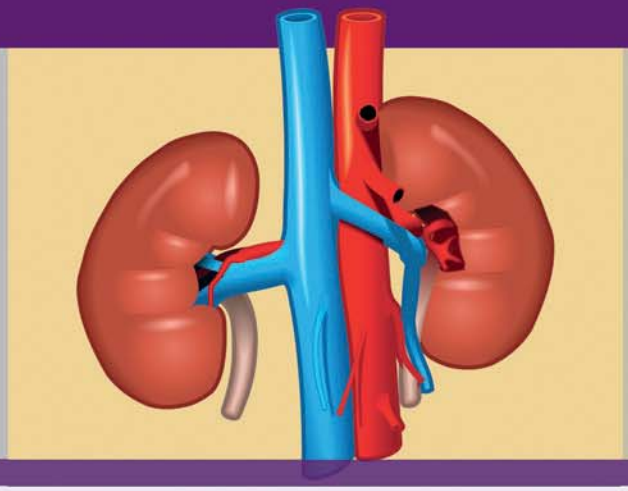

SECTION VII

Pregnancy and Renal Disease

CHAPTER 43

Renal Physiology in Normal Pregnancy

Chris Baylis and John M. Davison

There are profound changes in renal function in normal pregnancy that lead to marked alterations from the nonpregnant physiologic norm. An appreciation and understanding of these alterations are essential to recognize both normal and compromised pregnancies.

ANATOMY

In normal pregnancy, there is a progressive increase in renal bipolar diameter, maximally 1 to 2 cm by 26 weeks' gestation, and kidney volume enlarges by about 70% because of increments in both vascular and interstitial fluid compartments.[1] The most striking anatomic change is dilation of the calyces, renal pelvis, and ureter (more prominent on right side), and by the third trimester, about 80% of women show evidence of hydronephrosis[2] (Fig. 43-1). A consequence of the ureteral dilation is urinary stasis, which predisposes pregnant women with asymptomatic bacteriuria to development of symptomatic ascending infection (acute pyelonephritis). Rarely, the anatomic changes may be extreme and precipitate the overdistention syndrome, with massive dilation, recurrent severe flank pain, increasing serum creatinine, hypertension, or even reversible acute kidney injury.[3]

SYSTEMIC HEMODYNAMICS

There are significant alterations in systemic hemodynamics in normal pregnancy. A plasma (and extracellular fluid) volume expansion occurs while red blood cell volume also increases, leading to a large increase in blood volume that correlates with clinical outcome and birth weight. Interestingly, subsequent pregnancies tend to be more successful than the first, with larger babies and greater plasma volume increases. Women with twins and triplets have proportionately greater increments, and those with poorly growing fetuses, as in preeclampsia or with a history of poor reproductive performance, have correspondingly poor plasma volume responses. The increase in plasma volume (maximum increase ~1.25 liters) takes place progressively up to 32 to 34 weeks, after which there is little further change. The plasma volume expansion has a hemodilutional effect, causing decreases in hematocrit: the physiologic anemia of normal pregnancy.[4]

Cardiac output is significantly increased by the fifth gestational week, initially caused by a 10% to 20% increase in heart rate, with stroke volume increased by more than 20% the eighth week. Left atrial and left ventricular end-diastolic dimensions increase, suggesting an associated increase in venous return. Cardiac output increases of 40% to 50% are greatest by the 26th week, despite which systemic blood pressure (BP) substantially decreases in normal pregnancy (representative values are shown in Fig. 43-2 and Table 43-1).[5] The physiologic decrease in BP results from a profound reduction in systemic vascular resistance (SVR) of unknown cause (maximal at 26 weeks), although the loss of responsiveness to vasoconstrictor agents (e.g., angiotensin II, arginine vasopressin) certainly contributes.[6] Inhibition of angiogenic factors in preeclampsia causes vasoconstriction, suggesting that these factors, such as vascular endothelial growth factor (VEGF), may contribute importantly to normal gestational vasodilation through stimulation of endothelial nitric oxide and prostaglandins.[7] The combination of increased cardiac output and peripheral vasodilation means that organ blood flow increases in pregnancy, with the most dramatic changes occurring in the kidney and skin circulation throughout gestation and in the uterus in the second part of the pregnancy.[1] Left ventricular mass continues to increase up to 36 weeks, but thereafter, perhaps related to the increasing SVR toward term, systolic and diastolic cardiac function decrease, with increased ventricular wall stress, as evidenced by decrements in both myocardial contraction and relaxation capacity.[8]

In the third trimester, the enlarged uterus compresses surrounding tissues and can influence hemodynamic measurements, so that attention should be paid to maternal posture during hemodynamic monitoring. In the supine position, there is partial obstruction of the inferior vena cava and decreased venous return, reducing cardiac output and causing a decrease in BP, the supine hypotensive syndrome of pregnancy. It is important to be aware of these postural effects in measuring BP in late pregnancy.[1]

RENAL HEMODYNAMICS

There are striking changes in renal hemodynamics in normal pregnancy, with an increase in glomerular filtration rate (GFR) and consequent decrease in serum creatinine detectable very early.[1,9] The GFR increases about 25% by 4 weeks after the last menstrual period, and a robust early increase in GFR (see Fig. 43-2) is associated with a good obstetric outcome. Longitudinal studies in normal pregnant women show that GFR (measured by inulin or 24-hour creatinine clearance) increases by a maximum of about 50% by midpregnancy, which is maintained until the last few weeks of the pregnancy, when values begin to decrease, but remain above the nonpregnant level (Fig. 43-3).[10] These marked increases in GFR mean that serum creatinine decreases to 0.4 to 0.5 mg/dl (36 to 45 µmol/l),[11] and values considered normal for nonpregnant conditions, at 0.7 to 0.8 mg/dl (63 to 72 µmol/l), can be a cause for concern in normal pregnancy (see Table 43-1). In small women, however, whose total muscle mass may be quite low, significantly elevated serum creatinine levels may be absent, even in the presence of renal dysfunction. The increase in renal plasma flow (RPF) of about 60% is slightly more pronounced than the increase in GFR (see Fig. 43-2), so that the filtration fraction (FF) decreases (see later discussion). At the end of pregnancy, the RPF decreases proportionally more than the GFR, so that FF returns to the nonpregnant value.[10,12]

A similar pattern of renal hemodynamic change occurs during pregnancy in some animals, including the rat, in which GFR increases to a maximum of 30% to 40% above the "virgin" value by midterm,

Figure 43-1 Hydronephrosis in normal pregnancy. Intravenous urogram at 36 weeks' gestation. Note bilateral hydronephrosis, more marked on the right side.

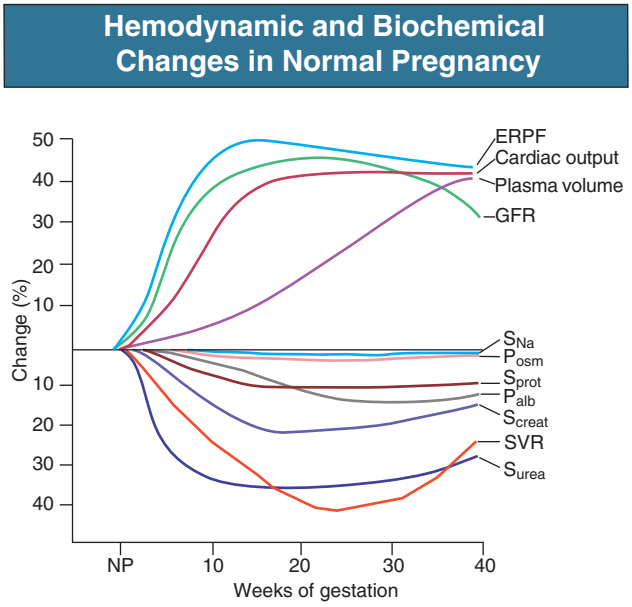

Figure 43-2 Hemodynamic alterations induced by normal pregnancy. Increments and decrements in hemodynamic and biochemical parameters shown as percentage of change from nonpregnant baseline. *ERPF,* Effective renal plasma flow; *GFR,* glomerular filtration rate; *S,* serum; *SVR,* systemic vascular resistance.

with a late return toward the nonpregnant value close to term (22 days). Glomerular micropuncture studies have shown that the increase in GFR is paralleled by increases in single-nephron GFR secondary to increased glomerular plasma flow.[13] Because the preglomerular and postglomerular resistance vessels dilate in parallel, glomerular plasma flow increases without a change in glomerular BP. As shown in Figure 43-4, the glomerular capillary blood pressure

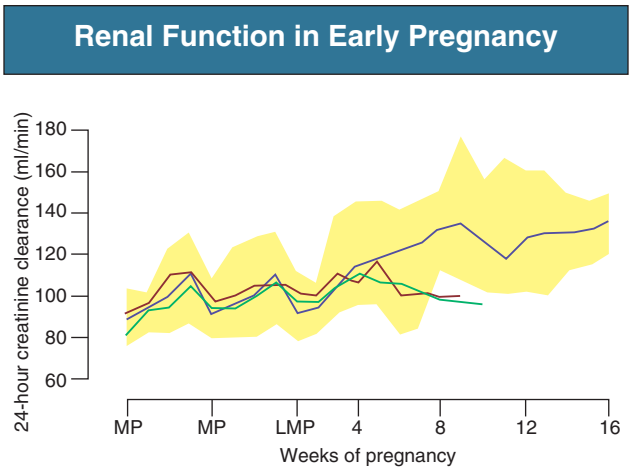

Figure 43-3 Renal function in early pregnancy. Changes in 24-hour creatinine clearance measured weekly before conception and through pregnancy. There was uncomplicated spontaneous abortion in two women *(red and green lines)*. The *blue line* represents the mean, and the *yellow area* shows the range for nine women with successful obstetric outcome. *LMP,* Last menstrual period; *MP,* menstrual period. *(Modified from references 9, 10, and 19.)*

Changes in Some Common Indices During Pregnancy

	Nonpregnant	Pregnant
Hematocrit (%)	41	33
Serum protein (g/dl)	7.0	6.0
Plasma osmolality (mOsm/kg)	285	275
Serum sodium (mmol/l)	140	135
Serum creatinine (mg/dl, μmol/l)	0.8 (73)	0.5 (45)
Blood urea nitrogen (mg/dl)	12.7	9.3
Serum urea (mmol/l)	4.5	3.3
pH units	7.40	7.44
Arterial P_{CO_2} (mm Hg)	40	30
Serum bicarbonate (mmol/l)	25	20
Serum uric acid (mg/dl, μmol/l)	4.0 (240)	3.2 (190) early 4.3 (260) late
Systolic BP (mm Hg)	115	105
Diastolic BP (mm Hg)	70	60

Table 43-1 Changes in some common indices during pregnancy. *BP,* Blood pressure; P_{CO_2}, carbon dioxide partial pressure. *(Mean values compiled from references 9-11, 19, and 36.)*

(P_{GC}) remains unchanged throughout the pregnancy despite marked alterations in preglomerular vascular resistance. Similar conclusions have been reached by an indirect modeling approach in normal pregnant women measuring whole-kidney GFR, RPF, and serum protein concentrations; in addition, polydisperse neutral dextran was infused for determination of dextran sieving curves.[9,12] This approach allows (with certain reasonable assumptions) modeling of glomerular hemodynamics. In pregnant women, there is a decrease in serum protein concentration that contributes slightly to the increased GFR. As in the rat, the majority of the gestational increase in GFR in normal women is caused by increased RPF with no change in glomerular BP. The constancy of glomerular BP during sustained renal vasodilation has important implications for the long-term effects of pregnancy on renal function, as discussed later.

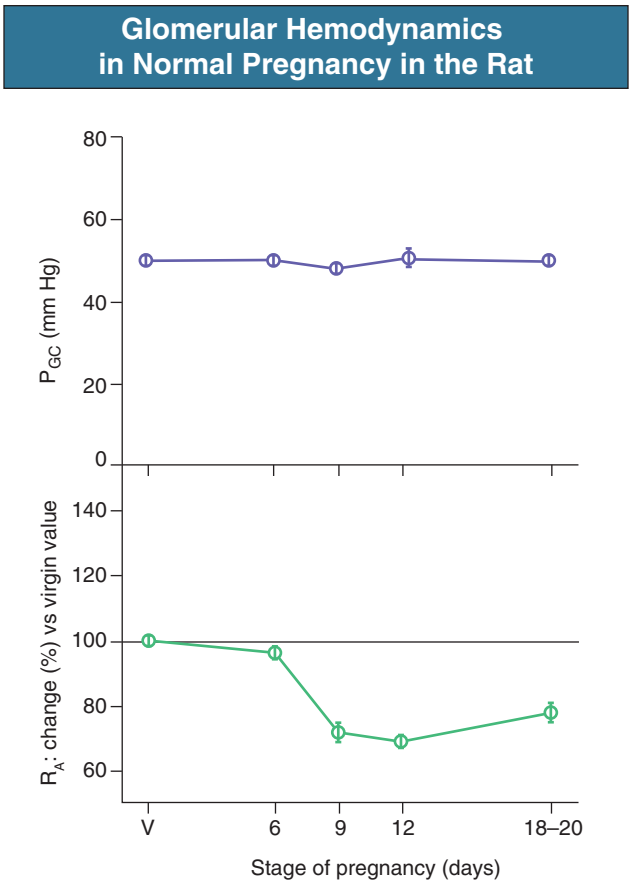

Figure 43-4 Glomerular hemodynamics in normal pregnancy in the rat. Summary of mean glomerular capillary blood pressure *(P_{GC}, upper panel)* and preglomerular arteriolar resistance *(R_A, lower panel)* in Munich Wistar rats in the virgin state (V) and throughout normal pregnancy.[13,14]

It is often assumed that a change in FF reflects a change in glomerular BP, but this is not always the case because FF is also determined by K_f, the product of water permeability of the glomerular wall and total glomerular capillary surface area.[10] Both glomerular wall water permeability and filtration pressure are very high, and thus filtration proceeds rapidly. In some situations, not all the available filtration surface area is used, so that filtration ceases (because the driving pressure is exhausted) before the end of the glomerulus. This state is known as *filtration pressure equilibrium.* When plasma flow increases during filtration pressure equilibrium, a proportional increase in GFR occurs with no change in FF. This is seen in the normal pregnant rat.[13] In contrast, FF decreases during normal pregnancy in women as RPF is increasing.[10] This most likely reflects that humans are closer than rats to filtration pressure disequilibrium, a situation in which the entire glomerular capillary surface area available for filtration is used, leaving a positive driving pressure at the end of the glomerulus. At filtration pressure disequilibrium, GFR becomes less dependent on plasma flow; thus an increase in plasma flow (with no change in other determinants of filtration) leads to a disproportionately smaller increase in GFR, with a decrease in FF.[14]

Despite the prolonged renal vasodilation, the renal vasculature remains fully responsive to various stimuli during pregnancy. For example, in the rat, the intrinsic renal autoregulatory ability remains intact,[15] although the myogenic response of the interlobular artery is blunted in normal rat pregnancy.[16] The tubuloglomerular feedback component of renal autoregulation is reset to recognize the elevated GFR as normal in the pregnant rat,[17] and a recent clinical study reports increased an increased renal artery resistive index during normal pregnancy, suggestive of maintained renal autoregulatory ability.[1] Both pregnant rats and women exhibit a marked additional renal vasodilation in response to amino acid infusion,[18,19] demonstrating substantial renal vasodilatory reserve in normal pregnancy. The cause of the gestational increase in GFR remains uncertain, although studies in the pseudopregnant rat have shown that the fetoplacental unit is not necessary,[20] indicating that a maternal stimulus must initiate the gestational renal hemodynamic changes.

A number of vasoactive factors have been evaluated as possible mediators of the renal vasodilation,[13] and although there are no clinical data, animal studies have implicated a role for nitric oxide (NO).[21-23] A novel splice variant of the neuronal NO synthase is induced in the kidney cortex of the pregnant rat, which parallels the increased renal plasma flow and GFR.[24] Increases in renal cortical antioxidant capacity may also contribute to enhanced renal NO levels in the normal pregnant rat.[25] Studies have suggested a key role for the ovarian hormone relaxin, which may signal increased renal NO production in pregnancy, possibly through an endothelin type B receptor mechanism.[26,27] The renal vasodilatory signal of pregnancy is remarkably robust because women with single kidneys (organ donors) and renal transplant recipients who have already undergone significant compensatory renal hypertrophy and vasodilation can produce further increases in RPF and GFR in pregnancy.[9,10] In the human, the signal is not solely relaxin as there is still a gestational increase in GFR, although blunted, in infertile women who lack corpus luteum function and who conceive from ovum donation and assisted conception techniques.[28]

Furthermore, although relaxin levels do increase steeply early in pregnancy (peaking at 6 weeks, declining thereafter to 36 weeks, but still much higher than pre-pregnancy),[1] there is no correlation between the levels and any hemodynamic parameter and no differences in levels between normal and preeclamptic pregnancies, despite substantial and persistent GFR abnormalities in the latter.[29] Also, although relaxin may be one important renal vasodilator in pregnancy, complementary factors and changes likely permit concomitant GFR increments because to attain levels akin to early pregnancy, women infused with recombinant human relaxin significantly augment RPF but not GFR.[30]

Glomerular hypertension associated with renal vasodilation is considered a primary pathogenic stimulus to progressive renal injury in chronic kidney disease.[31] As discussed, normal pregnancy is also a state of chronic renal vasodilation; however, glomerular BP remains normal. This may account for the findings that repetitive pregnancies in women and rats with normal renal function have no long-term adverse effects on glomerular function or structure.[32] Pregnancy will increase the rate of loss of renal function in some women with underlying renal disease (see Chapter 45), but evidence suggests that this is not by a hemodynamically mediated action.[9,32]

Formulas that use serum creatinine in relation to age, height, and weight to calculate GFR (e.g., Cockcroft-Gault formula) should not be used in pregnancy because body weight or size does not reflect kidney size. The use of estimated GFR (eGFR) from the Modification of Diet in Renal Disease (MDRD) study equation, or the refined Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, which adjusts serum creatinine for age, gender, and race, cannot be recommended in pregnancy, because both significantly underestimate true GFR measured by inulin clearance.[33,34] Similarly, cystatin C is not a useful marker for GFR changes in pregnancy because it also does not correlate with inulin clearance.[35] This unexpected lack of correlation in pregnancy between cystatin C and GFR may be explained by evidence that the placenta may release cystatin C in response to placental ischemia.

Abnormal Renal Hemodynamics

A woman may lose up to 50% of her renal function and still maintain serum creatinine concentration below 1.5 mg/dl (130 µmol/l) because of hyperfiltration in remaining nephrons. If there is more severe compromise, however, further glomerular damage will cause serum creatinine to increase.[9,33,36] Pregnancy in the presence of impaired renal function can have a marked adverse effect on obstetric outcome, as well as increased risk of an accelerated decline in renal function, as previously mentioned[37] (see Chapter 45).

In preeclampsia, both RPF and GFR decrease, although absolute values may remain above the nonpregnant range. A decrease in ultrafiltration coefficient (K_f) of about 50% in combination with reduced RPF is the most likely mechanism for the hypofiltration.[36,38] The endothelium is targeted at an early stage in preeclampsia, and the glomerulus is not spared. The vascular endothelial cell dysfunction (glomerular endotheliosis) results in swollen bloodless glomeruli, associated with glomerular filtration barrier damage, This may involve loss of both glomerular size and charge selectivities, although the exact role of the endothelium and its surface glycocalyx coat is not well defined (see Chapter 44). Most consider glomerular endotheliosis to be merely "characteristic," not pathognomonic, of preeclampsia, although one study reports this lesion in healthy controls.[39] This study has been challenged both regarding concerns about qualitative histologic grading as well as ethical issues.[40]

RENAL TUBULAR FUNCTION IN PREGNANCY

Enormous plasma volume expansion occurs in normal pregnancy, with resultant small decrements in plasma concentration of many solutes (see Fig. 43-2). Nevertheless, the large increase in GFR means that the filtered load of most plasma constituents will increase during pregnancy.[9,10] Increments in excretion are seen for some substances, but this is limited by increases in tubular reabsorption, preventing depletion. Intake also often increases, with net retention leading to positive balance for many of the key constituents. The renal handling of a number of solutes is altered in normal pregnancy.

Uric Acid

Uric acid, an end point of purine metabolism, is freely filtered at the glomerulus and extensively reabsorbed in the proximal tubule, with further downstream reabsorption and possibly some active secretion, such that only about 10% of filtered load is excreted. Serum uric acid concentration decreases during early pregnancy by about 25% (see Table 43-1), which may reflect a decrease in net tubular reabsorption.[10] As the pregnancy advances, fractional excretion of uric acid decreases, leading to an increasing serum uric acid concentration, attaining levels close to the nonpregnant mean. Serum uric acid concentrations are significantly higher in preeclamptic pregnancy, and above a critical level of 6 mg/dl (350 µmol/l), perinatal mortality increases in hypertensive patients (see Chapter 44). However, physiologic variability is such that some healthy women have high serum uric acid levels without problems, so that uric acid values must be interpreted in the clinical context.

Glucose

Excretion of glucose increases soon after conception to approximately 10 times the nonpregnant value and remains high throughout pregnancy, although glycosuria is variable.[10] The glycosuria is not related to changes in serum glucose concentration and reflects decreased tubular reabsorption. In the nonpregnant state, there is usually complete renal reabsorption of glucose, mostly in the proximal tubule, where high capacity exists for glucose transport. This maximum transport capacity (T_{max}) is not usually reached until serum glucose increases to values in excess of about 200 mg/dl (11 mmol/l). The glycosuria of pregnancy is caused by a decrease in T_{max} and the inability of the renal tubules to cope with the increased filtered glucose load, and does not reflect a metabolic disturbance.

Water-Soluble Vitamins and Amino Acids

Nicotinic acid, ascorbic acid, and folic acid are all excreted in increased amounts during pregnancy,[9] which emphasizes the need for adequate vitamin supplementation.

Urinary excretion of most amino acids increases in pregnancy, probably as a result of decreased tubular reabsorption.[41] There are distinct patterns. Glycine, histidine, threonine, serine, and alanine excretion increases early, and values remain elevated throughout pregnancy. Excretion of lysine, cystine, taurine, phenylalanine, valine, leucine, and tyrosine also increases in early pregnancy but later declines. Glutamic acid, methionine, and ornithine are excreted in slightly greater amounts than before pregnancy, isoleucine excretion is unchanged, and arginine excretion decreases.

Acid-Base Balance

The generation of hydrogen ions (H^+) increases in pregnancy because of an increased basal metabolism and greater food intake, but despite this, the blood H^+ concentration decreases; thus plasma pH increases slightly (see Table 43-1). This mild alkalemia is respiratory in origin because pregnant women normally hyperventilate, leading to a primary decrease in arterial carbon dioxide tension ($Paco_2$) and secondary compensatory decreases in serum bicarbonate concentration. A mild chronic respiratory alkalosis is a feature of normal pregnancy.

Potassium

Potassium excretion decreases, and a slow cumulative net potassium retention in pregnancy is distributed between the enlarging maternal tissues and the developing fetus. The decrease in potassium excretion occurs despite the mild alkalosis and high aldosterone values of normal pregnancy and is at least partly caused by the potent antimineralocorticoid action of progesterone[42] (see later discussion).

Calcium

Calcium excretion increases two to three times during pregnancy because of the increased filtered load and despite some increase in tubular reabsorption. This could predispose to the formation of calcium stones, but increased magnesium and citrate, acidic glycoproteins, and nephrocalcin serve to inhibit calcium oxalate stone formation so that the incidence of stone formation is not increased in normal pregnancy.[43]

Protein

Some proposed that increased urinary total protein excretion in pregnancy should not be considered abnormal until it exceeds 500 mg in 24 hours,[9,10,19,22] although many classifications and definitions of the hypertensive disorders of pregnancy still define more than 300 mg/24 h as abnormal.[44] A small increment in albumin excretion usually occurs during the third trimester, which with total

protein excretion may continue into the puerperium, with nonpregnant levels not restored until 5 to 6 months after delivery.[45] The gestational changes may be related to alterations in glomerular size and charge selectivity as well as in proximal tubular function, plus the possibility of the appearance of other proteinaceous material in the urine of pregnant women.[36,38,45] In clinical practice, urine protein above 300 mg/24 h roughly correlates with 30 mg/dl in a random urine sample, but given the problems with dipstick tests, many still prefer a 24-hour or some timed quantitative determination. Use of a random urine protein-creatinine (PC) ratio, however, is a clinically useful alternative, with a threshold value of 30 mg/mmol creatinine (0.3 mg/mg) a reasonable cutoff for defining significant proteinuria.[10,44-46] In preeclampsia, urinary shedding of podocytes (podocyturia), cells with a limited regenerative capacity, may precede and accompany proteinuria, as part of the disruption of the glomerular filtration barrier.[47] Evaluation of proteinuria in pregnancy is discussed further in Chapter 44.

Sodium

A massive, cumulative volume expansion occurs during pregnancy with an associated gradual retention of sodium of about 900 mmol, distributed between the products of conception and the maternal extracellular space. This positive sodium balance develops despite about a 30% increase in filtered load and reflects an increase in tubular reabsorption that allows net additional sodium retention of about 2 to 3 mmol/day.[4] Nevertheless, it is normal for sodium excretion to increase in pregnancy, reflecting the marked increase in sodium intake. Lithium clearance studies in women have indicated enhanced sodium reabsorption in the proximal tubule and distal nephron segments in late pregnancy, whereas animal studies have been contradictory.[48] The reason for the net renal sodium retention in pregnancy is not known. As shown in Table 43-2, there are many factors operating both to increase and to decrease sodium excretion, and exactly how the normal balance of net retention is achieved remains a mystery.

Several antinatriuretic systems are activated in normal pregnancy.[49] Renin, angiotensin, and aldosterone levels are all greatly increased, and the renin-angiotensin-aldosterone system (RAAS) can be appropriately regulated around these new set points when changes occur in extracellular fluid volume. In addition to stimulating aldosterone release, physiologic levels of angiotensin II (Ang II) act directly on the proximal tubule to increase sodium reabsorption. However, a marked refractoriness develops to the vascular actions of Ang II in normal pregnancy,[49] which may blunt Ang II–dependent net sodium retention. The high aldosterone levels of pregnancy will certainly promote renal sodium retention in the distal tubule and collecting duct. Indeed, an increase occurs in the abundance of the regulatory, α subunit of the epithelial sodium channel (ENaC) as well as ENaC activity, which is controlled by aldosterone.[50] The very high levels of deoxycorticosterone (from 21-hydroxylation of progesterone) may also exert mineralocorticoid actions to promote sodium retention.[51] Estrogens increase greatly during human pregnancy and may directly induce renal sodium retention or act indirectly by enhancing the conversion of progesterone to deoxycorticosterone.[51] In addition to hormonal factors, the increased ureteral pressure and the decrease in systemic BP both decrease sodium excretion.[52]

The concentrations of several natriuretic agents also increase in pregnancy. Progesterone increases by 10 to 100 times, and these levels exert a marked anti-mineralocorticoid action by competing with aldosterone for the mineralocorticoid receptor.[51] Plasma atrial natriuretic peptide (ANP) levels are also moderately elevated,[53] as is NO.[23] In addition to natriuretic factors, the large increase in GFR leads to increased filtration of sodium (despite the small decrease in serum sodium concentration), which will also increase sodium excretion. Decreases in serum albumin concentration and the increment in effective renal plasma flow during pregnancy will also enhance sodium excretion by inhibiting sodium reabsorption.[12] Animal studies have suggested that there is a generalized loss in pregnancy of natriuretic responsiveness to cyclic guanosine monophosphate (cGMP)–dependent signals,[23] resulting from increased inner medullary phosphodiesterase-5 activity.

Despite the many conflicting stimuli, net sodium retention and marked plasma volume expansion are normal in pregnancy. In the normal nonpregnant steady state, plasma volume expansion and renal sodium retention cannot coexist. However, pregnancy is not a steady state, and the volume sensing and regulatory systems are dramatically readjusted throughout pregnancy to accommodate and to maintain the volume expansion (see later discussion).

Factors Influencing Sodium Excretion During Pregnancy

Antinatriuretic	Natriuretic
Aldosterone	↑ Glomerular filtration rate
Angiotensin II	Progesterone
Estrogen	Atrial natriuretic peptide
Deoxycorticosterone	Nitric oxide
Supine posture	Prostaglandins
Upright posture	
Decreased blood pressure	
Increased ureteral pressure	
Placental shunting	

Table 43-2 Antinatriuretic and natriuretic factors influencing sodium excretion during pregnancy.

OSMOREGULATION

Early in pregnancy, plasma osmolality (P_{osm}) decreases by about 10 mOsm/kg below the nonpregnant norm because of a reduction in serum sodium and associated anions (see Table 43-1). Whereas a decrease in P_{osm} of this magnitude would completely suppress release of the antidiuretic hormone arginine vasopressin (AVP) in nonpregnant women, in pregnancy the osmotic thresholds for AVP release as well as for thirst are reduced to recognize the reduced plasma osmolality as normal.[54] Figure 43-5 demonstrates the resetting of the relationship between plasma AVP and P_{osm} during normal pregnancy. The placental hormone human chorionic gonadotropin (which stimulates the release of ovarian relaxin)[55] may have a role in this reduction in the osmotic threshold for AVP release.[54] Plasma volume status is a separate, nonosmotic determinant of AVP release, and this system is also reset to recognize the massively expanded plasma volume as normal. The metabolic clearance rate of AVP has increased four times by midpregnancy because of the release of cystine aminopeptidase (vasopressinase) from the placenta,[54] so the rate of AVP production must also be accelerated. Despite these marked alterations, the urinary concentrating and diluting capacity remain good, although there is a slight reduction in the maximum urine concentration in the second part of pregnancy.[54]

VOLUME REGULATION

As discussed previously, continual sodium retention and cumulative volume expansion in pregnancy reflect complex readjustments of the

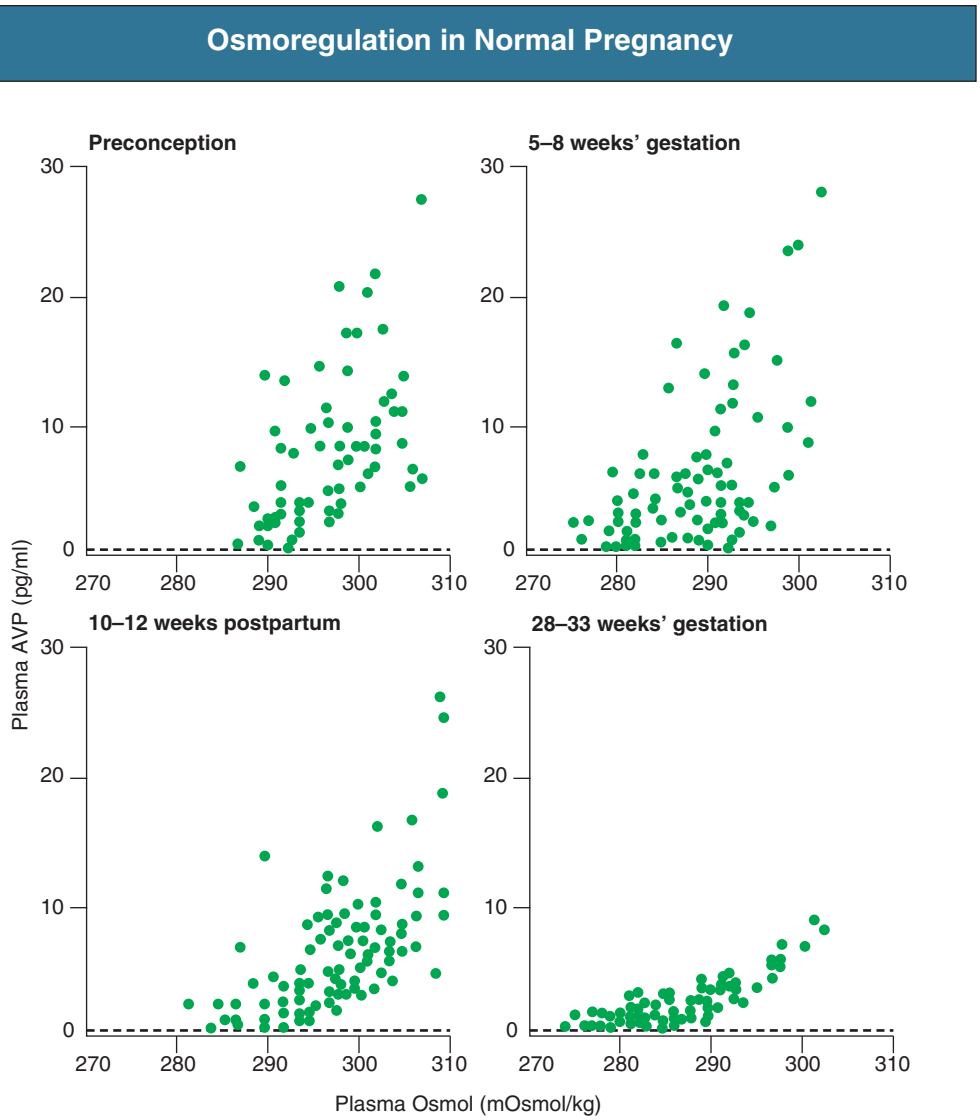

Figure 43-5 Osmoregulation in normal pregnancy. Relationship between plasma arginine vasopressin concentration *(AVP)* and plasma osmolarity *(Osmol)* during several 5% saline infusions in eight women before and during pregnancy. Each point represents an individual plasma measurement. There is a marked decrease in osmotic threshold for AVP release during pregnancy. Values for the osmotic threshold for thirst (not shown) were always 2 to 5 mOsmol/kg above AVP release thresholds and 10 mOsmol/kg lower in pregnancy.[9,54]

various volume regulatory systems. These readjustments also permit volume expansion without increases in blood pressure; in fact, BP decreases substantially as pregnancy proceeds (see Table 43-1).

What happens to volume perception and regulatory systems in pregnancy can be considered in terms of the effective circulating volume.[56,57] The RAAS is an antinatriuretic system activated by volume depletion, and the increase in plasma renin activity and angiotensin and aldosterone concentrations of normal pregnancy suggests an *underfill* signal, despite the absolute increase in plasma volume. The primary event in pregnancy may be *peripheral vasodilation* that generates an underfill signal and leads to renal sodium retention.[56] In contrast to the RAAS, both osmotic and nonosmotic control of AVP release is reset in a manner indicating that the expanded volume of pregnancy is sensed as normal.[54] The tubuloglomerular feedback system is suppressed by volume expansion in the nonpregnant state but is reset in pregnant rats to recognize the expanded volume and increased GFR as normal.[17] Plasma ANP increases slightly in late pregnancy, but this is unlikely to reflect a physiologic response to volume expansion, because even greater increases in ANP are seen in volume-contracted, preeclamptic pregnancies.[53] Whatever the stimulus, increased ANP and intrarenal NO are predicted to exert powerful, cGMP-dependent natriuretic influences, which the increased medullary phosphodiesterase-5 activity of pregnancy will antagonize. In support of the underfill hypothesis, chronic vasodilation of nonpregnant female rats also activates medullary phosphodiesterase-5 and causes renal sodium retention and plasma volume expansion.[58] However, volume regulation in pregnancy remains an enigma.

IMPACT OF MATERNAL HEMODYNAMIC CHANGES ON FETAL PROGRAMMING

Strong evidence indicates that women with normal pregnancy who have suboptimal increases in plasma volume are more likely to deliver babies small for gestational age. Fetal growth restriction and preterm delivery pose serious neonatal risks[59] and are often seen in preeclamptic pregnancies, in which there is usually volume

contraction.[60] Reduction in uterine blood flow, as occurs in preeclampsia or when volume expansion is inadequate, and maternal (and thus fetal) malnutrition have been implicated in the pathogenesis of fetal growth restriction. Considerable epidemiologic as well as animal evidence suggests that adverse events *in utero* leading to fetal growth restriction and preterm delivery[61] can program the offspring for increased risk in adult life for the development of hypertension, other cardiovascular events, diabetes, hypercholesterolemia, and chronic kidney disease, the last at least partly caused by reduction in nephron number.[62,63] Thus, optimal maternal systemic and renal hemodynamic changes have a huge impact not only on fetal well-being but also on the long-term health of the offspring.

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CHAPTER 44

Renal Complications in Normal Pregnancy

Annabel C. Martin and Mark A. Brown

Most women have normal pregnancies. The most common renal problem that arises in pregnancy in an otherwise well woman is urinary tract infection (UTI). Also, by far the most common *de novo* "renal disease" in the second half of pregnancy is preeclampsia, usually presenting with hypertension and proteinuria. Fortunately, acute kidney injury in pregnancy is rare in developed countries, but still carries a poor prognosis for this young age group.

URINALYSIS AND MICROSCOPY

Many young women have their first urinalysis and urine microscopy performed during pregnancy, leading to the detection of hematuria, proteinuria, and pyuria, either related to or coincidental to the pregnancy.

Hematuria

Definition and Epidemiology

Microscopic hematuria is detected at some time during pregnancy in about 20% of women.[1] Clinically significant *microhematuria* is defined as three or more red blood cells (RBCs) per high-power field on microscopic evaluation of urinary sediment from two of three properly collected (clean-catch, midstream) urine specimens,[2] or as greater than 2500 RBCs/ml.[3] Microhematuria disappears in about 75% of women after delivery, but secondary to glomerulonephritis, it persists throughout the pregnancy, and can be further investigated postpartum.

Etiology and Outcome

Dysmorphic microhematuria (defined by phase contrast microscopy) during pregnancy is most frequently caused by glomerulonephritis but is occasionally associated with preeclampsia. *Isomorphic* hematuria is more likely to be caused by bladder infection or bladder compression by the fetal head. Pregnant women with microhematuria showed no significant difference in gestational age at delivery, birth weight, gestational hypertension, or preeclampsia compared with controls.[4]

Macrohematuria (gross hematuria) in pregnancy is most often the result of vaginal bleeding or hemorrhagic bacterial cystitis. Other, less common causes include renal calculi, renal arteriovenous malformations, polycystic kidneys, and rarely, bladder or kidney neoplasms.

Differential Diagnosis

When microhematuria is found in the pregnant patient, a urine culture is required to exclude infection. If there is no proteinuria, and blood pressure (BP) and serum creatinine are normal, further investigations can be delayed until postpartum review, usually about 3 months, when microscopy to determine RBC morphology, antinuclear antibody testing, and renal ultrasound can be performed.

When significant numbers of dysmorphic urinary RBCs are present during pregnancy and BP is normal, the most likely cause is glomerular disease, either thin basement membrane nephropathy or IgA nephropathy. If microhematuria is associated with renal angle pain or renal colic, ultrasound will exclude the presence of stone in only two thirds of pregnant women with calculi and may demonstrate other abnormalities such as polycystic kidneys and in rare cases neoplasms. For persistent isomorphic microhematuria, we do not recommend cystoscopy during pregnancy. This often disappears spontaneously after pregnancy, and the likelihood of uroepithelial tumors is very low in this age group.

Treatment

For the pregnant patient with microhematuria, the treatment of associated UTI and calculi is discussed later. There is no specific treatment for glomerulonephritis during the pregnancy, provided renal function is normal and nephrotic syndrome is absent.

Proteinuria

The development of proteinuria during pregnancy warrants investigation and will most often be associated with preeclampsia. A condition known as *gestational proteinuria* may also develop, which has no adverse effects for fetus or mother.

Definition

Normal pregnancy is associated with an increase in protein excretion compared with the nonpregnant state. Some studies suggest this results from a combination of increased glomerular filtration rate and increased permeability of the glomerular basement membrane in normal pregnancy.[5] Others have found 24-hour urinary albumin excretion similar in nonpregnant and normal pregnant women, with more than 20 mg/day considered abnormal; in such patients, increased total proteinuria must be caused by tubular proteinuria.

In contrast to abnormal total protein excretion defined as greater than 150 mg daily in nonpregnant women, proteinuria in pregnancy is generally defined as the excretion of more than 300 mg of total protein per 24 hours. However, more than 95% of pregnant women excrete less than 200 mg/day.[6]

Proteinuria is most frequently detected in pregnancy by dipstick urinalysis, but this method is notoriously unreliable, with a significant proportion of false-positive and false-negative results. Dipstick is generally reliable for confirming either the absence of proteinuria or the presence of true proteinuria, when dipstick readings are 3+ (>3 g/L) or 4+ (>20 g/L). At intermediate levels, false-positive rates are as high as 50%. Detection may be improved using an automated urinalysis device, thereby reducing observer error.[7]

The 24-hour urine collection remains the gold standard for quantitation but is often impractical when a quick assessment of proteinuria is required, as in preeclampsia. A reliable alternative is the protein-creatinine ratio; a ratio greater than 30 mg protein/mmol

creatinine (~0.3 mg/mg) correlates reasonably well with protein excretion of more than 300 mg/24 h.[8]

Although use of the albumin-creatinine ratio may gain a greater role in pregnancy in the future, clinicians currently should continue to use the protein-creatinine ratio until further data are available.[9]

Differential Diagnosis

Proteinuria arising *de novo* in pregnancy should be quantitated and further investigated according to the clinical situation. The course of pregnancy in women with proteinuria present before pregnancy is discussed in Chapter 45.

Persistent proteinuria associated with preeclampsia usually arises in the second half of pregnancy, and generally but not always after the development of hypertension. Occasionally, proteinuria predates all other signs of preeclampsia. The severity of the proteinuria is not indicative of the severity of preeclampsia and should not be used to guide management. Furthermore, proteinuria may be absent in 10% of women with clinical and histologic manifestations of preeclampsia.[10] In the absence of UTI or preeclampsia, isolated proteinuria in an otherwise asymptomatic pregnant woman usually reflects new-onset renal disease such as a primary glomerulonephritis. Alternatively, proteinuria may appear because pregnancy has unmasked renal disease secondary to systemic disorders, such as diabetes mellitus, systemic lupus erythematosus, or essential hypertension. In addition, superimposed preeclampsia occurs in 20% to 25% of women with chronic hypertension.[11] In these patients, it often occurs earlier in gestation and may be severe.

We limit investigation of *de novo* non-preeclamptic, non-nephrotic proteinuria during pregnancy to a renal ultrasound and the measurement of serum creatinine, electrolytes, albumin, and antinuclear antibodies. Renal biopsy is not indicated. When underlying renal disease has been unmasked by pregnancy, appropriate investigations can usually be delayed until the postpartum period. The exceptions to this are women with nephrotic syndrome or renal impairment in whom fetal viability is not yet ensured and whose pregnancy needs to be continued (i.e., <24 weeks' gestation). In these patients, full investigation should be undertaken quickly, usually including renal biopsy, to determine whether specific treatment (e.g., corticosteroids) may be of benefit.

Natural History

Proteinuria occurring as a complication of preeclampsia invariably resolves in the postpartum period, although this may take several months. Proteinuria in women with gestational proteinuria, an entity that describes new-onset proteinuria without features of preeclampsia but with intermediate changes in angiogenic factors (see later), also resolves postpartum. Tradition holds that in both cases, proteinuria disappears within 3 months postpartum, but that many cases take longer.[12] In the absence of renal function or impaired function, we do not investigate non-nephrotic proteinuria until it persists after 12 months postpartum.

Treatment

For women with nephrotic syndrome, an inverse correlation exists between serum albumin and birth weight, although no studies have examined whether reduced fetal growth can be reversed by reducing proteinuria. Antiproteinuric therapy with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are contraindicated in pregnancy because of their unwanted effects on the fetus.

Intravenous (IV) albumin has little role in managing nephrotic syndrome during pregnancy unless there is progressive deterioration in renal function. We recommend IV albumin infusion when serum creatinine rises above 100 µmol/l (1.2 mg/dl) with no other explanation, acknowledging that this may only provide a temporary benefit to allow the pregnancy to be prolonged. Diuretics and sodium restriction should be avoided unless the woman has severe, intractable edema; the concern is that diuretics will lead to a further reduction in plasma volume and reduced uteroplacental perfusion. The pregnant woman with nephrotic syndrome is at high risk of venous thromboembolism and should receive prophylactic heparin during pregnancy and until the nephrotic syndrome has resolved postpartum.

Pyuria

Isolated pyuria, in the absence of UTI, is common in normal pregnancy, usually from contamination by vaginal secretions. There is also an increased white blood cell excretion rate in normal pregnancy. It requires no further follow-up other than ensuring it disappears, usually by 3 months postpartum.

URINARY TRACT INFECTION

Definitions

In *asymptomatic bacteriuria* (ASB), the urinary tract is colonized by a single species of bacteria in the absence of specific symptoms. Outside of pregnancy, ASB usually should not be treated with antibiotics. However, ASB can lead to serious complications in pregnancy, and there is a cost benefit from its screening and treatment.[13] Although the gold standard for diagnosis is detection of more than 10^5 organisms per milliliter, without epithelial cells, in a midstream urine specimen on two or more occasions, or from a single suprapubic aspiration,[14] in practice such bacteriuria is usually detected by a single routine bacterial culture early in pregnancy. As many as 1% to 2% of pregnancies are complicated by *acute bacterial cystitis*, defined as an acute bacterial UTI accompanied by symptoms such as frequency, dysuria, or strangury. Although more than 10^5 organisms/ml defines ASB, as few as10^2 organisms/ml is sufficient to diagnose cystitis if accompanied by pyuria and characteristic symptoms.[15] In *acute pyelonephritis* there is UTI, generally with more than 10^5 organisms/ml, in association with parenchymal renal infection, usually diagnosed clinically by fever and loin pain and sometimes features of systemic sepsis.

Epidemiology

Asymptomatic bacteriuria affects 2% to 10% of all pregnant women. The prevalence is higher in women from lower socioeconomic groups and increases with age, parity, coexistent genital tract infection, and sickle cell trait. ASB is also more common in women with urinary tract abnormalities such as reflux nephropathy and neurogenic bladder, in diabetic patients, and in women with several previous UTIs. The highest risk of infection is thought to be from the 9th to the 17th week of gestation, although this may simply reflect the stage at which routine screening usually takes place.

The overall incidence of acute pyelonephritis in pregnancy is approximately 1%, but it may occur in up to 30% among women with ASB. It is thought that about 70% of women who develop acute pyelonephritis have preceding covert bacteriuria, but this is difficult to prove. With treatment of ASB, it has been estimated that the incidence of pyelonephritis would be reduced by more than 80%.[15] When possible, urethral catheters should be avoided, even in women having cesarean section, because the incidence of UTI in these women is twice that of those not catheterized.

Organisms Typically Causing Urinary Tract Infection in Pregnancy

- *Escherichia coli* (>70% of infections)
- *Klebsiella* spp.
- *Proteus* spp. (particularly in diabetic women or urinary tract obstruction)
- Enterococci
- Staphylococci, especially *Staphylococcus saprophyticus*
- *Pseudomonas*

Box 44-1 Organisms most often responsible for UTI in pregnant women.

Pathogenesis

Certain host characteristics may increase the risk for UTI or pyelonephritis (see Chapter 53). Women, such as those who do not express the antibody to the O antigen of *Escherichia coli*, may have ASB that predates pregnancy (i.e., are chronically colonized). Pregnancy is a state of relative urinary tract stasis; the calyces, pelves, and ureters dilate, particularly on the right, and this contributes to ASB developing into ascending acute pyelonephritis in pregnant women.

The most common mechanism of infection is through the urethra from perineal bacteria. Box 44-1 lists common organisms causing UTI in pregnancy. Some strains of *E. coli* are particularly virulent and are associated with both ASB and pyelonephritis. They possess P fimbriae, which enable the bacteria to attach themselves to the uroepithelial cells with pili, allowing them to ascend the urinary tract from the perineum.

Clinical Manifestations

Asymptomatic Bacteruria

A meta-analysis indicated that untreated ASB during pregnancy significantly increases rates of low birth weight (LBW) and preterm delivery.[16] However, it is still unclear whether ASB is an independent risk factor for LBW or whether its association with low socioeconomic status is the predictor for LBW. The mechanism by which UTI may cause premature labor is not yet fully understood, but proinflammatory cytokines secreted in response to bacterial endotoxins likely initiate labor in these patients.

Most maternity units operate a policy of screening all pregnant women on at least one occasion, whether by dipstick urinalysis for leukocytes/nitrites or by direct urine culture. Both dipstick and urine culture appear cost-effective compared with no screening when the prevalence of ASB is 2% to 6%. As stated, isolated pyuria on dipstick testing is very common in normal pregnancy, and we recommend screening by primary urine culture rather than the dipstick method.

Women who have threatened premature labor should have further urine cultures even without symptoms suggestive of UTI.

Pyelonephritis

Pyelonephritis most often presents between 20 and 28 weeks of gestation with malaise, fever, loin pain, and rigors. Not all women will have had lower urinary tract symptoms, and pyelonephritis can also manifest in pregnancy as acute abdominal pain, or may be detected only after presentation with premature labor. Pyelonephritis is more common in pregnant women with urologic abnormalities or diabetes and more often affects the right kidney, probably because the ureter is generally more dilated on that side.

The diagnosis of pyelonephritis is usually made on clinical grounds. Definitive diagnosis requires positive urine culture, but this may take about 2 days, and treatment should not be delayed. *E. coli* is the most common infecting organism (>85% of cultures).

Bacteremia is a common and usually transient complication of pyelonephritis. Occasionally, however, women become septicemic and may develop endotoxemia with shock, with sequelae including respiratory failure, disseminated intravascular coagulation, and acute kidney injury. Pyonephrosis and perinephric abscess are rare complications but should be suspected when treatment fails.

Without treatment, the complications of acute pyelonephritis during pregnancy can be severe, probably more so than in nonpregnant women. In the preantibiotic era, maternal mortality was 3% to 4%. Currently, death from pyelonephritis is rare in developed countries but still occurs.

Treatment

Asymptomatic Bacteruria

Antibiotic treatment of ASB significantly reduces the incidence of pyelonephritis in pregnancy. A systematic review also suggests treatment results in a significant reduction in the risk of preterm delivery.[18]

In choosing treatment, the clinician must consider the safety of the antibiotic in pregnancy. In most women, treatment with cephalexin, amoxicillin–clavulanic acid, or nitrofurantoin is first-line therapy. Overall, trials demonstrate that longer duration of treatment is likely to be more effective than single-dose therapy, although data are limited.[18] Until evidence from new trials is available, a 4- to 7-day treatment regimen is recommended, although some authorities allow for a 3-day rather than 7-day course of antibiotics.[17]

Without treatment, ASB will persist in 80% of women, and even with treatment, 20% will still have ASB. Those with persistent colonization are difficult to treat, with eradication achieved in only 40% after a second course of antibiotics. Where eradication is not achieved, we recommend prophylactic antibiotics, usually cephalexin (250 mg at night), throughout pregnancy to prevent pyelonephritis and its consequences; however, no studies specifically address this situation. The incidence of pyelonephritis after effective treatment of ASB is reduced from about 30% to 3%, comparing favorably with a 1% prevalence of pyelonephritis for the overall pregnant population.

Cystitis

Treatment of cystitis at the first presentation should be for 5 days with an appropriate antibiotic. As for ASB, it is important to obtain a follow-up urine culture to be certain infection has been eradicated.

Pyelonephritis

It is usual practice to admit pregnant women with pyelonephritis to the hospital, although a trial has reported successful outpatient management for milder cases.[18] Treatment may occasionally require resuscitation with IV fluids, but usually a short course of IV antibiotics followed by oral antibiotics, once the woman is afebrile, is adequate therapy.

It is desirable to choose an antibiotic that produces a high blood level that will concentrate in the renal parenchyma, usually a cephalosporin as first-line treatment. An aminoglycoside is a useful adjunct in more severe cases, used for 24 to 48 hours while awaiting urine cultures, provided maternal renal function is satisfactory. The risk of irreversible fetal ototoxicity precludes prolonged use, and aminoglycosides are not recommended in the first trimester. The full

duration of treatment is generally at least 2 weeks, and it is imperative to repeat urine culture 1 week after treatment to ensure eradication.

Renal ultrasound is generally not indicated during an initial infection, because urinary tract dilation is still likely to be present, and it is impossible to distinguish this from significant urinary tract obstruction. However, if infection persists, ultrasound is indicated to help exclude pyonephrosis, perinephric abscess, and renal calculi. If pyelonephritis persists despite adequate antibiotic therapy and urinary tract dilation is confirmed, percutaneous nephrostomy should be performed under ultrasound guidance. In our experience, this is rarely necessary and should be a last resort in management of these cases, but nephrostomy is the only way to be certain urinary tract obstruction and pyonephrosis have been properly treated.

Clinicians also should remain alert for premature labor in the presence of pyelonephritis and institute appropriate treatment while aggressively treating the infection. When more than two UTIs have occurred in pregnancy, prophylaxis is indicated until delivery with either nitrofurantoin (50 mg) or cephalexin (250 mg) at night. Table 44-1 outlines some antibiotic regimens suitable for use in pregnancy.

RENAL CALCULI

Epidemiology

Despite the physiologic state of pregnancy being an ideal environment for renal stone formation, the incidence of renal calculi remains similar in pregnant and nonpregnant women, in the range of 0.03% to 1%.

Antibiotic Regimens for Treatment of Urinary Tract Infections in Pregnancy

Antibiotic	Dose	Duration
Acute Cystitis		
Amoxicillin	500 mg three times daily	3-7 days
Nitrofurantoin	100 mg twice daily	3-7 days
Cephalexin	500 mg two or three times daily	3-7 days
Asymptomatic Bacteriuria		
Cephalexin	500 mg three times daily	3 days
Amoxicillin	500 mg three times daily	3 days
Amoxicillin–clavulanic acid	500 mg three times daily	3 days
Nitrofurantoin	50 mg four times daily	3 days
Fosfomycin	3 g single dose	
Recurrent Bacteriuria or Cystitis		
Cephalexin	250 mg nighttime (or postcoital)	
Nitrofurantoin	50 mg nighttime (or postcoital)	
Amoxicillin	250 mg nighttime (or postcoital)	
Pyelonephritis (Initial IV Therapy)		
Ceftriaxone	1 g daily	
Ampicillin (with gentamicin)	1 g every 6 hours	
Gentamicin	3 mg/kg daily	
Ticarcillin	3.2 g every 8 hours	
Piperacillin	4 g every 8 hours	

Table 44-1 Antibiotic regimens for treatment for urinary tract infections in pregnancy.

Pathogenesis

The majority of stones are formed from calcium oxalate and calcium phosphate. Struvite stones are the next most common, usually when the urinary tract is infected with organisms such as *Proteus* spp. Small proportions of renal stones are formed from uric acid or cystine. As discussed, pregnancy is a physiologic state of relative urinary stasis, as well as of increased calcium and uric acid excretion. The incidence of renal calculi is not increased during pregnancy probably because of the enhanced excretion of inhibitors of stone formation, such as magnesium, citrate, and the glycoprotein nephrocalcin.

Clinical Manifestations

Symptomatic stones during pregnancy are rare, usually presenting in the second or third trimester with acute flank pain radiating to the groin or lower abdomen and hematuria. However, clinical features of renal calculi may be more difficult to interpret in pregnancy because frequent episodes of diffuse, poorly localized abdominal pain and lower urinary tract symptoms are relatively common in normal pregnancy.

From 75% to 85% of stones will pass spontaneously during pregnancy,[19] and some women with calculi will have a concomitant UTI. Pregnant women with renal calculi are at greater risk of superimposed pyelonephritis.

The diagnosis of renal calculi in pregnancy is made more difficult because of the accompanying physiologic hydronephrosis and the risks of radiation to the fetus if investigating the urinary tract with computed tomography (CT). Ultrasound will detect hydronephrosis (usually as part of normal pregnancy) and will often detect calculi within the kidney, but ultrasound rarely finds ureteral stones and is less accurate than CT for these purposes. Transvaginal ultrasound should be performed when transabdominal ultrasound is uninformative, to detect distal ureteral stones if pain persists.[20] If this remains negative, the woman can be treated symptomatically, with pain relief, hydration, and lying on her side, with the symptomatic side up, enabling relief of pressure on the ureter from the gravid uterus. If symptoms persist and further diagnosis is required, magnetic resonance (MR) urography or low-dose CT (in second or third trimester) can be used, although in our experience, this is rarely needed.

Treatment

Initial management of renal calculi is conservative, with appropriate hydration, antiemetics, and analgesia. Stones pass spontaneously (75% to 85%) in part because of the normally dilated urinary tract in pregnant women. Calcium intake should not be limited in pregnancy. However, women in whom calcium oxalate stones form persistently can limit foods high in oxalate, such as spinach, rhubarb, and chocolate. Urine should always be cultured and appropriate antibiotics administered when a UTI is suspected.

Quantitation of urine calcium, uric acid, or other mineral excretion is not necessary in pregnancy, because specific pharmacologic agents to modify excretion (including thiazides and allopurinol) are contraindicated. Investigations can be completed postpartum.

Urine output should be monitored and renal function assessed. Surgical intervention is considered only when stones cause persistent obstruction, deteriorating renal function, intractable pain or infection, or premature labor unresponsive to other treatment.

Cystoscopy with ureteral stenting may be required in pregnancy, and ureteroscopic removal of stones has been reported.[21] Lithotripsy is generally contraindicated during pregnancy because of the presumed adverse effect of the shock waves on the fetus; however, some centers have used ureteroscopic laser lithotripsy in pregnant women.[22] Extracorporeal shock wave lithotripsy has been reported as an inadvertent procedure in six women in the first month of pregnancy, all of whom subsequently delivered normal infants.[23]

Postpartum follow-up is important. In the absence of ongoing symptoms, we perform a CT scan of kidney, ureters, and bladder 3 months later. This delay is necessary to eliminate confusion in interpreting the findings; calyceal and ureteral dilation may persist that long after delivery. Women planning a further pregnancy should be assessed for idiopathic hypercalciuria or other causes of renal calculi after a minimum of 3 months postpartum.

HYPERTENSION IN PREGNANCY

Definitions

There are four major hypertensive disorders related to pregnancy (Fig. 44-1), as follows:

1. Gestational hypertension
2. Preeclampsia-eclampsia
3. Chronic/preexisting hypertension
   - Primary
   - Secondary
   - White coat hypertension
4. Preeclampsia superimposed on chronic/preexisting hypertension

Hypertension in pregnancy is defined as blood pressure of 140/90 mm Hg or higher. Normal pregnancy is characterized by a fall in BP, beginning in the first trimester and reaching a nadir in the second trimester. BP rises toward preconception levels near the end of the third trimester. A BP increment of 30 mm Hg or greater systolic and/or 15 mm Hg diastolic to levels still below 140/90 mm Hg warrants increased frequency of follow-up. By itself, this BP increase does not diagnose gestational hypertension or preeclampsia, but in the presence of proteinuria, this may signify early preeclampsia in some women.

The development of newly elevated BP after 20 weeks' gestation without evidence of maternal organ dysfunction is known as *gestational hypertension.* This should usually resolve by 12 weeks postpartum. If hypertension persists beyond 12 weeks postpartum, the diagnosis is likely chronic/preexisting hypertension that has been masked by the physiologic decrease in BP that occurs in early pregnancy. It is important to note, however, that some women with preeclampsia or gestational hypertension may take longer for their high BP to resolve.

Preeclampsia is also hypertension developing in the second half of pregnancy, but this more serious disorder includes accompanying evidence of maternal renal, cerebral, hepatic, or clotting abnormalities and fetal growth restriction (see later discussion).

Chronic/preexisting hypertension is BP of 140/90 mm Hg or higher that antedates pregnancy or is present before the 20th week of pregnancy (on at least two occasions) or persists beyond 12 weeks postpartum. This should ideally be confirmed by 24-hour ambulatory BP monitoring or home self-initiated BP monitoring, to exclude *white coat hypertension,* which is common in pregnancy.[24]

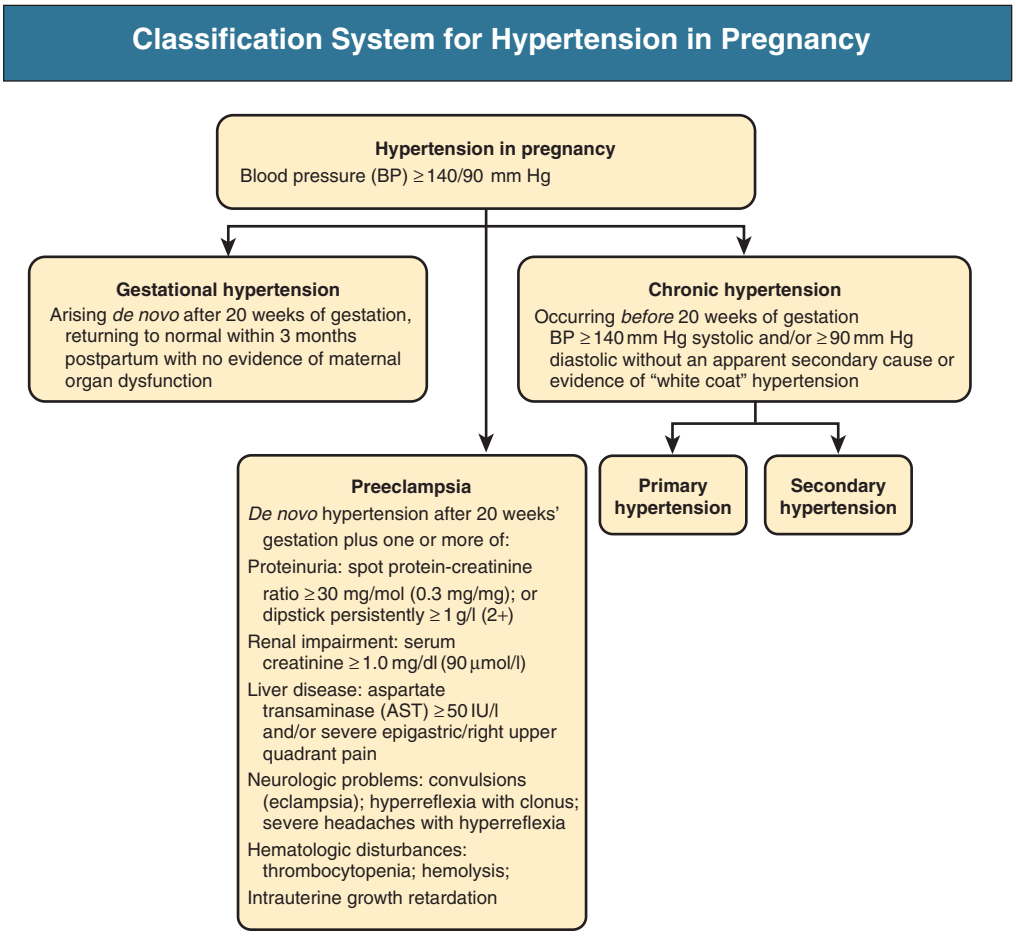

Figure 44-1 Classification of hypertension in pregnancy.

Superimposed preeclampsia is the development of proteinuria or new renal dysfunction, thrombocytopenia, neurologic features, or abnormal liver function after 20 weeks' gestation in a woman with chronic/preexisting hypertension.

The traditional definition of *preeclampsia* has been hypertension with proteinuria and edema developing after 20 weeks' gestation. However, edema accompanies two thirds of both normal and preeclamptic pregnancies and is not a particularly useful sign. The detection of proteinuria in the past has also been quite unreliable, and insisting on the finding of proteinuria for this diagnosis ignores the protean manifestations of preeclampsia, as discussed later. In practice, however, the majority of women with multisystem features of preeclampsia also have proteinuria.

Eclampsia (convulsions) is now uncommon in developed countries, with a prevalence of about 0.3% of hypertensive pregnancies. In underdeveloped countries, eclampsia is much more common, with greater risks of maternal mortality and morbidity as well as perinatal mortality.

Epidemiology

Hypertensive disorders of pregnancy are the second most common cause for maternal death worldwide, after hemorrhage.[25] Hypertension affects 10% to 12% of all pregnancies,[26] and the distribution of causes in a population depends largely on the nature of the obstetric unit assessing that population; tertiary referral units tend to have a higher proportion of severe preeclamptic cases. In general, primary hypertension accounts for about 20%, secondary causes 4%, preeclampsia 35%, and gestational hypertension the remainder of hypertensive disorders in pregnancy. About one in four women with apparent primary hypertension early in pregnancy has white coat hypertension. They present early in pregnancy with apparent chronic hypertension, but their outcomes are better than those with true chronic hypertension. Women with white coat hypertension may be managed without medication through regular home BP monitoring. A small proportion will go on to develop preeclampsia.[27]

PREECLAMPSIA

Epidemiology

Preeclampsia follows no recognized racial patterns, and no specific genotype-phenotype relation has been associated with this disorder.[27] Preeclampsia occurs in 2% to 8% of pregnancies and is a major contributor to maternal mortality worldwide.[31] Box 44-2 lists risk factors for preeclampsia. The risk is highest in those with a past history of preeclampsia, with rates ranging from15% to 65% depending on the gestation at onset of the preeclampsia.[28,29] Risk of preeclampsia is also high in the first pregnancy, possibly because of limited recent exposure to paternal (sperm) antigens, which may play a role in disease pathogenesis.

An intriguing observation is the reduced risk of preeclampsia in subsequent pregnancies, but a return to the risks of the first pregnancy in women who have a new partner for subsequent pregnancies. This observation, combined with an increased likelihood of preeclampsia in women who have used barrier methods of contraception, raised the possibility of an impaired immunologic response to paternal antigens in such pregnancies. However, this may simply be explained by a longer interpregnancy interval rather than a change of partners, with the incidence increasing after about 7 years between pregnancies.[30]

Smoking reduces the risk of preeclampsia by a third, but increases the risk of preterm labor, intrauterine growth restriction (IUGR) and placental abruption.[31] Obesity increases the likelihood of preeclampsia.

Risk Factors for Preeclampsia

Maternal Obstetric Factors
Nulliparity
Multiple-gestation pregnancy
History of previous preeclampsia
Molar pregnancy
Trisomy 13 or fetal hydrops
Gestational diabetes

Obstetric Paternal Factors
Father born from preeclamptic pregnancy

Maternal Comorbid Conditions
Chronic hypertension
Chronic kidney disease
Pregestational diabetes mellitus
Obesity
Antiphospholipid antibody
Systemic lupus erythematosus

Maternal Genetic Factors
Thrombophilias
Preeclampsia in pregnancy of first-degree relative

Other Maternal Factors
Age over 40 years

Box 44-2 Risk factors for the development of preeclampsia. *(Modified from reference 73.)*

Pathogenesis

The pathogenesis of preeclampsia is complex. The placenta likely causes preeclampsia, with other maternal organs (e.g., kidney) amplifying the disease process (Fig. 44-2). This is supported by the observation that preeclampsia can occur in hydatidiform mole, where the fetus is absent, with the condition resolving when the placenta is removed. The following key mechanisms are involved in the progression to the clinical preeclamptic syndrome:

- *The immune response at the placental-maternal interface.* An imbalance in the immunologic milieu can lead to placental failure. The fetal-maternal immunologic interaction at placentation involves maternal killer, immunoglobulin-like receptors and fetal human leukocyte antigen (HLA-C) molecules. This interaction fails in preeclampsia, leading to an abnormal interaction among uterine natural killer cells, trophoblastic cells, and macrophage-derived tumor necrosis factor α (TNF-α).
- *Superficial placentation with insufficient remodeling of spiral arteries and imbalance of angiogenic factors.* Invasive cytotrophoblasts penetrate the walls of the spiral arteries, where they replace maternal endothelium, converting them to capacitance vessels capable of carrying greater blood flow through the placenta and reducing their capacity for vasoconstriction.[32] Factors implicated in the pathogenesis of preeclampsia include placental growth factor (PlGF), vascular endothelial growth factor (VEGF-A), the VEGF receptor soluble fms-like tyrosine kinase 1 (sFlt-1), transforming growth factor β (TGF-β), and soluble endoglin (sEng).[33] In particular, there is an excess of syncytiotrophoblast-derived antiangiogenic factors, such as sEng and sFlt-1. Although still not fully understood, this excess is thought to be triggered by placental

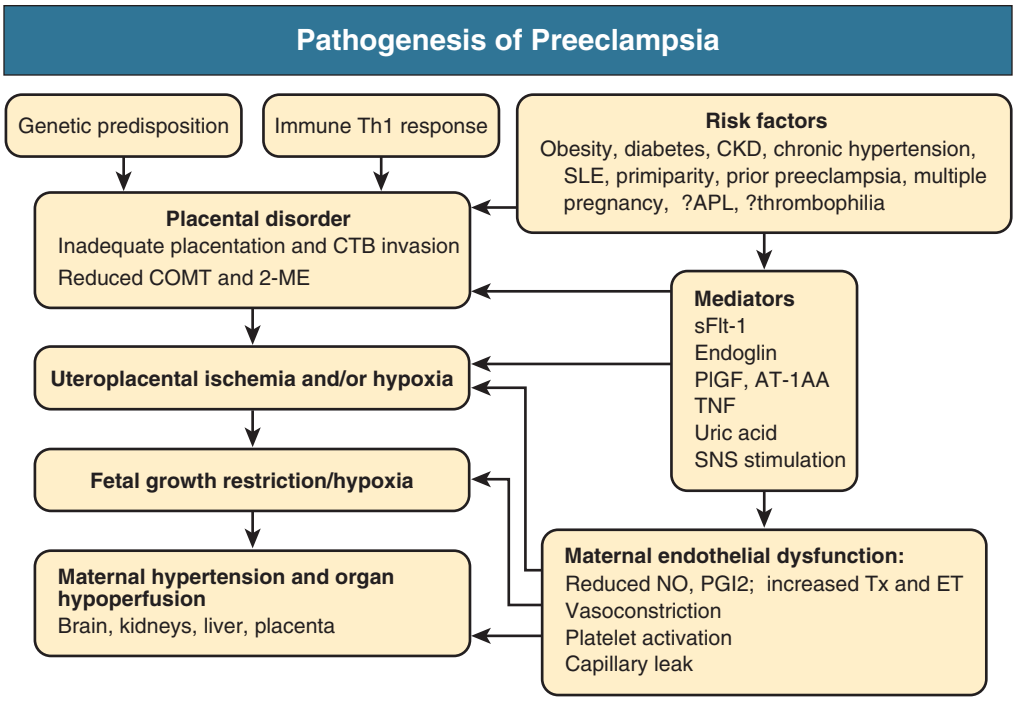

Figure 44-2 Pathogenesis of preeclampsia. *Th1,* T helper cell type 1; *CKD,* chronic kidney disease; *SLE,* systemic lupus erythematosus; *APL,* antiphospholipid syndrome; *CTB,* cytotrophoblast; *COMT,* catechol-*O*-methyltransferase; *2-ME,* 2-methoxyestradiol; *sFlt-1,* soluble fms-like tyrosine kinase 1; *PlGF,* placental growth factor; *AT-1AA,* angiotensin-II type 1 receptor autoantibodies; *TNF,* tumor necrosis factor; *SNS,* sympathetic nervous system; *NO,* nitric oxide; *PGI2,* prostacyclin; *Tx,* thromboxane; *ET,* endothelin.

ischemia or hypoxia. sFlt-1 binds to VEGF and PlGF, preventing its interaction with endothelial receptors on the cell surface, inducing endothelial dysfunction (Fig. 44-3).

- *Oxidative stress that triggers inflammation.* Maternal blood enters into the intervillous space at higher pressure and faster rate because of the impaired arterial remodeling of the spiral arteries. This exposes the placental villi to fluctuating oxygen concentrations, leading to oxidative stress and activation of nuclear factor-κB, a transcription factor central to the inflammatory response.[34] Increase in necrotic trophoblast shedding occurs and may be important in the pathogenesis of preeclampsia through systemic endothelial cell activation by secretion of interleukin-6 (IL-6).[35] Microparticles derived from placental syncytiotrophoblasts in maternal plasma interact with leukocytes and monocytes and stimulate production of proinflammatory cytokines.[36]

In summary, the impaired placentation leads to an imbalance in angiogenic factors and oxidative stress that triggers inflammation. The resulting insufficient placental function, release of placental factors into the maternal circulation, and exaggerated maternal inflammatory response cause a generalized endothelial dysfunction with leukocyte and clotting activation.

Regardless of etiology, preeclampsia is characterized by the following pathophysiologic triad:

1. Vasoconstriction
2. Platelet activation with intravascular coagulation (usually local but occasionally disseminated)
3. Maternal plasma volume contraction

This triad leads to further impairment of blood flow through the placenta as well as through the maternal kidneys, liver, and brain. It is unknown why these organs are most often affected in preeclampsia or why other vascular beds (e.g., gut) are unaffected, even in severe cases.

The clinical presentation of preeclampsia will depend on the extent to which maternal organ systems and the placenta have been affected by this process, but once begun, preeclampsia runs a progressive course until delivery, the only definitive cure.

Renal Abnormalities in Preeclampsia

Several abnormalities of renal function and structure occur in preeclampsia (Fig. 44-4). The kidneys in preeclampsia undergo a series of unique pathologic changes, including diffuse *glomerular endotheliosis,* characterized by swelling and vacuolization of endothelial cells, capillary lumen occlusion, and enlarged glomeruli. The swollen endothelial cytoplasm encroaches upon the lumen of the glomerular capillaries, contributing to the tuft ischemia[37] (Fig. 44-5). Immunofluorescence may reveal fibrin deposits. These changes are infrequently seen in clinical practice because renal biopsy is rarely performed in preeclamptic women.

Proteinuria

The urine sediment is usually bland. Both *tubular* and *glomerular* patterns of proteinuria have been reported in preeclampsia. Glomerular proteinuria is nonselective and may range from a few hundred milligrams per day up to the nephrotic range. In many studies, levels of proteinuria in women with preeclampsia do not seem to correlate with maternal and fetal outcomes.[38] However, there is some evidence for increased risk of adverse maternal and fetal outcomes with a very high level of proteinuria (spot urine protein-creatinine ratio >900 mg/mmol at any age or >500 mg/mmol in women over 35).[39] Preeclamptic women with mild or no proteinuria should be managed with the same caution as those with nephrotic-range proteinuria. Measuring microalbuminuria has not yet proved useful in clinical management of preeclamptic women, or

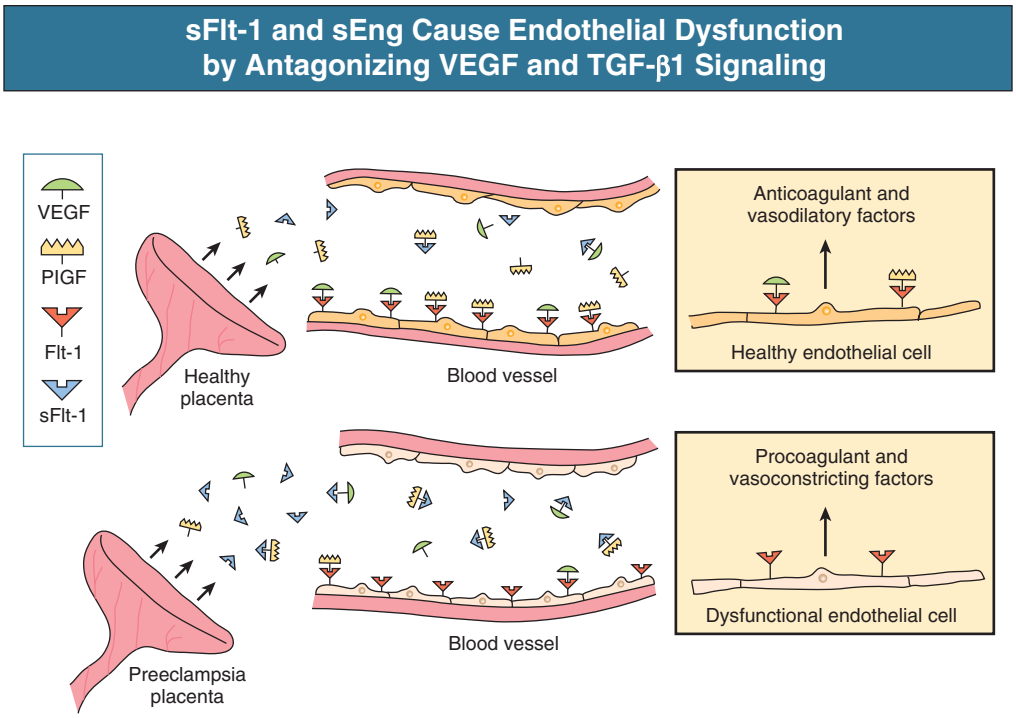

Figure 44-3 Proteins sFlt-1 and sEng cause endothelial dysfunction by antagonizing VEGF and TGF-β1 signaling. There is mounting evidence that vascular endothelial growth factor *(VEGF)* and transforming growth factor β1 *(TGF-β1)* are required to maintain endothelial health in several tissues, including the kidney and perhaps the placenta. During normal pregnancy, vascular homeostasis is maintained by physiologic levels of VEGF and TGF-β1 signaling in the vasculature. In preeclampsia, excess placental secretion of sFlt-1 and sEng (two endogenous circulating antiangiogenic proteins) inhibits VEGF and TGF-β1 signaling, respectively, in the vasculature. This results in endothelial cell dysfunction, including decreased prostacyclin, nitric oxide production, and release of procoagulant proteins. *PlGF,* Placental growth factor; *sFlt-1,* soluble fms-like tyrosine kinase 1; *sEng,* soluble endoglin. *(From reference 74.)*

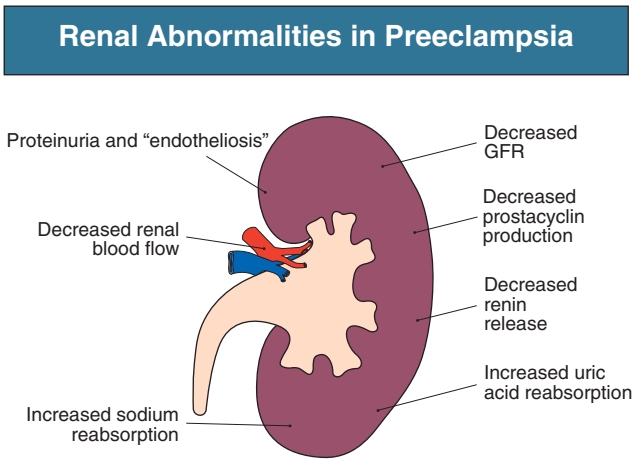

Figure 44-4 Renal abnormalities in preeclampsia. *GFR,* Glomerular filtration rate.

in predicting which women with gestational hypertension will develop preeclampsia.

Proteinuria may be part of the general capillary leak of preeclampsia or may, in part, be a consequence of glomerular endotheliosis.

Decreased Glomerular Filtration Rate

A fall in the glomerular filtration rate (GFR) may be partly caused by the decrease in renal blood flow (in turn caused by vasoconstriction, plasma volume loss, and decreased cardiac output). Other factors may also be involved, however, such as impaired placental production of the vasodilator relaxin, impaired renal prostacyclin or nitric oxide production, or the glomerular morphologic changes themselves.

Acute Tubular Necrosis

Acute tubular necrosis is the most common cause of acute kidney injury (AKI) in preeclampsia. If impaired GFR (serum creatinine >88 μmol/l; >1 mg/dl) is not corrected by BP control and plasma volume restoration, delivery is indicated if renal function continues to deteriorate.

Sodium Retention

Avid sodium retention occurs in preeclampsia, as a renal tubular response to perceived reduction in renal perfusion and perhaps also to increased sympathetic nervous system activity or alterations in expression of epithelial sodium channels. This is a normal renal response to these changes and the resultant oliguria; in the absence of an elevated serum creatinine, oliguria should not itself be an indication for delivery.

Renin

Plasma renin and aldosterone concentrations are reduced in preeclampsia, correlating inversely with the severity of the disorder. This has little direct clinical relevance; however, it may be explained by the recent discovery of a mineralocorticoid receptor mutation, *MRL810,* which allows factors normally antagonistic to aldosterone, such as progesterone, to bind and activate this receptor leading to inappropriate sodium retention, hypertension, and subsequent suppression of renin and aldosterone release.[40] There is a general upregulation of the renin-angiotensin system (RAS) in normal pregnancy and activation of the placental RAS in preeclampsia.[41] However, this

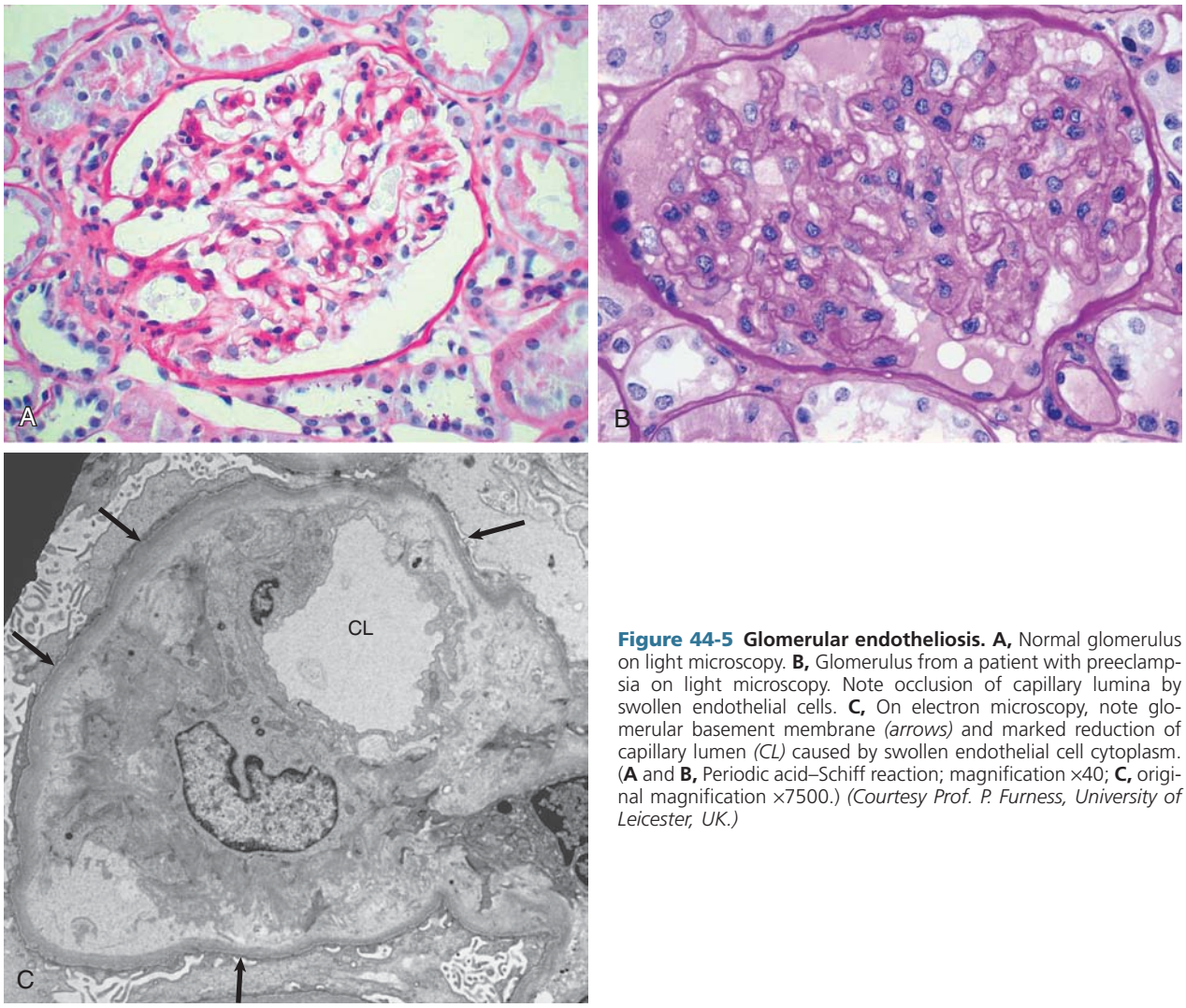

Figure 44-5 Glomerular endotheliosis. A, Normal glomerulus on light microscopy. **B,** Glomerulus from a patient with preeclampsia on light microscopy. Note occlusion of capillary lumina by swollen endothelial cells. **C,** On electron microscopy, note glomerular basement membrane *(arrows)* and marked reduction of capillary lumen *(CL)* caused by swollen endothelial cell cytoplasm. (**A** and **B,** Periodic acid–Schiff reaction; magnification ×40; **C,** original magnification ×7500.) *(Courtesy Prof. P. Furness, University of Leicester, UK.)*

delicate balance is lost in preeclampsia, possibly because of development of AT_1 receptor autoantibodies.[42]

Increased Uric Acid Reabsorption

Hyperuricemia in preeclampsia results largely from renal uric acid retention, although there may be some component of increased uric acid production, perhaps by the placenta.[43] Serum uric acid is a useful test in hypertensive pregnant patients because it is generally, but not always, elevated in preeclampsia, and values below 350 µmol/l (5.9 mg/dl) suggest an alternative cause for explanation for hypertension, such as primary hypertension. The degree of hyperuricemia correlates with fetal risk, even in women with gestational hypertension alone, when it should alert clinicians to seek evidence of fetal growth restriction (Table 44-2).[44]

Gestation-Corrected Serum Uric Acid During Pregnancy

Gestational Age	Serum Uric Acid (µmol/l)	Serum Uric Acid (mg/dl)
<32 weeks	>240	>4.0
32-35 weeks	>270	>4.5
36-37 weeks	>290	>4.9
≥38 weeks	>330	>5.6

Table 44-2 Gestation-corrected serum uric acid during pregnancy. Concentrations above these levels should prompt review for associated adverse pregnancy outcomes, even in patients with gestational hypertension alone. Data are from 1610 hypertensive pregnant women. *(From reference 44.)*

Clinical Manifestations

Preeclampsia is initially detected in most women by the onset of hypertension after the 20th week of pregnancy (Box 44-3). It rarely occurs before the 20th week, and such cases are occasionally caused by hydatidiform mole. Symptoms are not always present, but may include severe headaches, convulsions, stroke, repeated visual scotomata (all manifestations of cerebral involvement), severe epigastric or right upper quadrant pain (reflecting hepatic ischemia with possible subcapsular hematoma of the liver or even liver rupture), oliguria, bleeding caused by disseminated intravascular coagulation (DIC), lower abdominal pain caused by placental abruption, or reduced fetal movements.

Routine physical examination should include assessment of fetal growth, fetal heart rate patterns measured by cardiotocography (CTG), and assessment of the maternal reflexes because clonus is a warning sign of impending eclampsia. The following investigations should be performed in all patients:

Clinical Features of Preeclampsia

Primary Manifestation

Hypertension

Renal Involvement

Significant proteinuria: dipstick positive confirmed by spot urine protein-creatinine ratio >30 mg/mmol

Acute kidney injury: serum or plasma creatinine >90 mmol/L

Oliguria

Hematologic Involvement

Thrombocytopenia

Hemolysis

Disseminated intravascular coagulation

Liver Involvement

Raised serum transaminases

Severe epigastric or right upper quadrant pain

Neurologic Involvement

Convulsions (eclampsia)

Hyperreflexia with sustained clonus

Severe headache with hyperreflexia

Persistent visual disturbances (photopsia, scotomata, cortical blindness, retinal vasospasm)

Cerebrovascular accident (stroke)

Other Major Features

Pulmonary edema

Fetal growth restriction

Placental abruption

Box 44-3 Clinical manifestations of preeclampsia.

- Urine dipstick testing for proteinuria, with quantitation by measuring the urinary protein-creatinine ratio if the dipstick is 1+ (30 mg/dl) or higher
- Hemoglobin, platelet count
- Serum creatinine, electrolytes, uric acid
- Liver function tests
- Ultrasound assessment of fetal growth, amniotic fluid volume, and umbilical artery flow

Eclampsia

Eclampsia is defined as the occurrence of tonic-clonic seizures in a woman who is pregnant or has recently delivered that cannot be attributed to other causes. Of these women, 79% have premonitory signs and symptoms present during the week before the first eclamptic seizure: headache (56%), visual disturbances (23%), epigastric pain (17%), hypertension (48%), proteinuria (46%), and concurrent hypertension and proteinuria (38%).[45] Risk of eclampsia is not directly related to BP level. Although some view this as a form of "hypertensive posterior reversible encephalopathy syndrome" (hypertension with headache, confusion or decreased consciousness, visual changes, or seizures, accompanied by MR findings of cerebral white matter edema), eclampsia may occur at relatively low BP levels and has been reported in the absence of proteinuria. Importantly, about half the cases of eclampsia occur after delivery, although rarely more than 5 days postpartum.

HELLP Syndrome

The HELLP syndrome—hemolysis, elevated liver enzymes, and low platelet count—is a variant of preeclampsia. Although sometimes regarded as a separate entity, HELLP simply refers to a severe form of preeclampsia in which the hepatic and platelet abnormalities dominate, with thrombotic microangiopathy. The diagnosis of HELLP syndrome is based on the following laboratory criteria:

- Microangiopathic hemolytic anemia: schistocytes in blood smear, elevated serum bilirubin or lactate dehydrogenase, low haptoglobin
- Increased liver transaminases: aspartate transaminase (AST) greater than 70 U/l
- Platelet count: less than $100 \times 10^3/mm^3$

Maternal mortality from severe HELLP syndrome is about 1% and perinatal mortality between 7% to 34%, largely depending on gestational age.[46] It is best to consider this as a subtype of preeclampsia and continue to seek and manage all the features of preeclampsia as these arise.

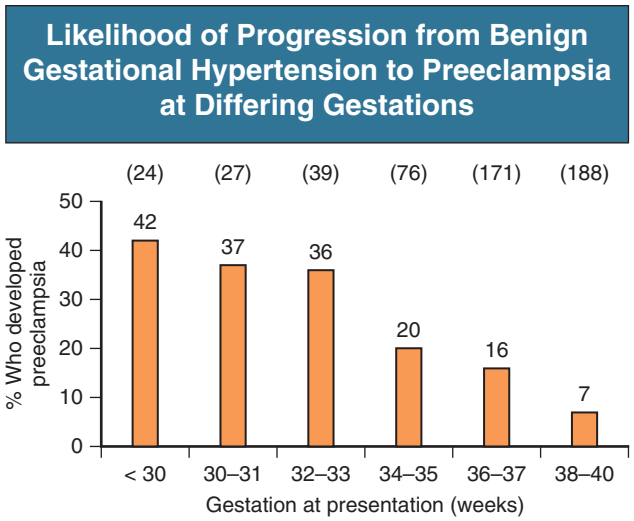

Figure 44-6 Likelihood of hypertension progressing to preeclampsia at various weeks of gestation. The earlier the presentation with gestational hypertension, the greater is the likelihood of progression to preeclampsia. *(Modified from reference 75.)*

Natural History

Women with gestational hypertension have a 10% risk of progressing to develop preeclampsia if they present after 36 weeks of gestation, but a greater than one third risk if they present before 32 weeks (Fig. 44-6).

In general, the prognosis is favorable for women with preeclampsia. Severe preeclampsia is associated with maternal, fetal, or neonatal complications, including abnormal liver function or thrombocytopenia (10% to 20%), pulmonary edema (2% to 5%), AKI (1% to 5%), placental abruption (1% to 4%), fetal growth restriction (10% to 25%), neurologic damage (<1%), and perinatal death.[47] After delivery, all clinical and laboratory derangements of preeclampsia resolve but may be delayed by several days; thus it is critical to remain vigilant until the patient's clinical picture improves. Some patients require antihypertensives for the first time in the postnatal period, which should be commenced when BP exceeds 150/100 mm Hg, although some recommend treatment at 140/90 mm Hg. Hypertension may persist for days, weeks, or months. If there is no underlying medical disorder, resolution will occur.

Prediction and Prevention

Unfortunately, despite numerous studies, no test has been found that can reliably predict the development of preeclampsia. Multiple risk

factors for development of preeclampsia have been described, although most are not highly predictive of the disorder or modifiable. Measurement of angiogenic factors (VEGF, PlGF, sFlt-1, sEng) in blood or urine seems a promising approach, particularly the ratio of sFlt-1/PlGF.[48] However, these tests require further study and are not part of usual clinical practice at present.

The observation that preeclampsia is associated with increased platelet turnover and increased platelet-derived thromboxane levels led to trials investigating the effect of aspirin in prevention of preeclampsia. It has been shown to reduce the risk of developing preeclampsia, with 19 high-risk women (one or more of previous severe preeclampsia, diabetes, chronic hypertension, renal disease, or autoimmune disease) and 119 moderate-risk women being treated to prevent one case of preeclampsia.[49] Treatment with aspirin should begin at 12 to 14 weeks' gestation because the pathophysiologic features of preeclampsia develop at this time, weeks before clinical disease is apparent. Aspirin is ideally discontinued 10 days before expected delivery, but bleeding is not significantly increased, even for women in labor while taking aspirin.[50] Women who have already developed preeclampsia do not benefit from aspirin in preventing progression to more severe disease.[51]

Oral calcium supplementation appears to halve the risk of preeclampsia in women at high risk and in communities with low dietary calcium levels.[52] Nutritional supplements, including magnesium, folic acid, fish oils, antioxidants, and garlic, have been extensively studied and do not seem to be effective in preventing preeclampsia.[53] In particular, combined use of vitamins C and E has been associated with worse maternal and fetal outcomes. Currently, anticoagulation is not recommended for reducing the risk of preeclampsia. Maternal obesity is associated with an increased risk of preeclampsia and weight loss has been shown to reduce the risk of preeclampsia.[54]

Antihypertensive drugs do not reduce the risk of preeclampsia, but do reduce the incidence of severe hypertension with its associated maternal risks.

Treatment

The only definitive treatment for preeclampsia is delivery of the placenta. Because the disorder may occur in the absence of the fetus (e.g., hydatidiform mole), it is removal of the placenta that is important. Therefore, preeclampsia that continues to worsen several days postpartum should prompt consideration of retained placental products.

Indications for delivery are generally as follows:

- Progressive evidence of maternal organ dysfunction: worsening renal or hepatic function, worsening thrombocytopenia, and development of neurologic symptoms or signs
- Inability to control blood pressure
- Inadequate fetal growth or nonreassuring fetal status
- Gestational age beyond 37 weeks

Timing of delivery should be based on optimizing perinatal outcomes while avoiding maternal risks. This requires assessment of fetal well-being with ultrasound and CTG, and an assessment of the likely gains to be made with further intrauterine time. Antenatal corticosteroids for fetal lung maturation should be given to all women at risk of delivery at less than 34 weeks' gestation; many obstetricians will also give steroids at later gestation if cesarean birth is likely.

There is consensus after the HYPITAT trial that women with preeclampsia at later than 37 weeks' gestation should be delivered.[55] The optimum management for women with preeclampsia between 34 to 37 weeks' gestation is uncertain because no randomized trials have been performed. These patients are usually managed expectantly to enable further fetal growth and maturation, with delivery if any of the previously listed indications arise. At earlier than 34 weeks' gestation, expectant management of preeclampsia is recommended, testing repeatedly for one of the indications for delivery.

General Management

All women with preeclampsia should be admitted at the initial diagnosis. If the condition appears stable, outpatient care is reasonable provided appropriate resources and expertise are available. Reviews should include once- or twice-weekly laboratory evaluation of platelet count, serum creatinine, and AST as well as CTG. Repeated quantification of proteinuria is not required once protein-creatinine ratio has risen to 30 mg/mmol, because the amount or rate of increase of proteinuria is not associated with maternal or perinatal outcome. Ultrasound estimation of fetal weight, looking for growth restriction and oligohydramnios, along with umbilical artery Doppler flow should be done at diagnosis and every 2 to 3 weeks if initially normal.

Blood Pressure Management

The major indication for antihypertensive therapy in preeclampsia is prevention of maternal cerebrovascular accident (stroke) and other sequelae of severe hypertension. Treatment does not affect the course of preeclampsia because the primary pathogenic process is related to the maternal response to abnormal placental vasculature. However, lowering BP removes one maternal indication for delivery and therefore allows pregnancy to be prolonged, with further fetal maturation and possibly fetal growth.

Antihypertensive medications are always recommended if systolic BP is 160 and/or diastolic is 100 mm Hg or higher, although the BP level at which treatment is required remains controversial. Treatment of hypertension in the range 140 to 160 systolic and 90 to 100 diastolic is a reasonable approach and will reflect local practice. For such chronic treatment, the first-line agents oxprenolol, labetalol, and methyldopa are used (Table 44-3). When additional treatment is required, hydralazine, nifedipine, or prazosin may be added. ACE inhibitors and ARBs should be avoided, because they cause fetal renal abnormalities in the latter half of pregnancy and fetal cardiac or other abnormalities with first-trimester exposure. Diuretics should be avoided because they reduce an already-impaired maternal blood volume, although there are no convincing data about harm of diuretics in pregnancy.

Target blood pressure is controversial, with a lack of clinical trial data; our practice is to target BP between 110 to 140/80 to 90 mm Hg, balancing between reducing maternal stroke risk, and ensuring adequate pressure to support placental perfusion.

Blood pressure of 170/110 mm Hg or higher always requires acute treatment, to prevent maternal stroke and eclampsia. In this patient, oral nifedipine (short-acting tablets), IV hydralazine, or labetalol is typically used.

Magnesium sulfate (4 g over 10 to 15 minutes) followed by an infusion (1 to 2 g/h) is used as seizure prophylaxis, and after a seizure, it should be continued for at least 24 hours. Magnesium sulfate is renally excreted, so particular caution is required in women with oliguria or renal failure. Serum magnesium concentrations can be monitored in conjunction with electrocardiogram (ECG), respiratory rate, and reflexes. The recurrence rate of seizures despite appropriate magnesium therapy is 10% to 15%.[56] In our view, convulsion prophylaxis should usually be reserved for preeclamptic women with clinical evidence of cerebral involvement, such as hyperreflexia with clonus, severe headaches, or visual scotomata. Withholding convulsion prophylaxis in the remainder is associated with an extremely

Medications in Treatment of Hypertension in Preeclampsia	
Drug	**Treatment Regimen**
Acute Hypertension	
Hydralazine	5-mg IV bolus every 20-30 minutes, to maximum of 20 mg, then infusion at 5-10 mg/h
Labetalol	50 mg IV every 20 minutes, to maximum 300 mg
Nifedipine	10 mg oral (tablets, not capsules)
Chronic Hypertension	
First-Line Choice	
Methyldopa	500-2000 mg/day PO
Clonidine	0.2-0.8 mg/day PO
Oxprenolol	80-480 mg/day PO
Labetalol	200-1200 mg/day PO
Second-Line Choice	
Hydralazine	25-200 mg/day PO
Prazosin	1-15 mg/day PO
Nifedipine SR	40-120 mg/day PO

Table 44-3 Medications typically used in the treatment of hypertension in women with preeclampsia. Diuretics and propranolol are not recommended. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are contraindicated. *PO,* Orally; *SR,* sustained release.

Management of Preeclampsia	
Clinical Problem	**Management**
Assess indications for delivery	Always review whether an indication for delivery is present by clinical and laboratory monitoring
Control blood pressure (BP)	Acute treatment if BP ≥170/110 mm Hg Chronic treatment if BP ≥140/90 mm Hg
Eclampsia prophylaxis or treatment	Magnesium sulfate for eclampsia or persistent neurologic signs (also indication for delivery): 4 g intravenously over 20 minutes, then 1.5 g/h for 48 hours
Supportive therapies (sometimes required)	Platelet infusion if count <20-40 × 10^9/l Fresh-frozen plasma for microangiopathy or for reduced clotting factors Dialysis for established acute kidney injury
Progressive decline in renal, hepatic, or clotting function or fetal growth	Delivery

Table 44-4 Summary of management of preeclampsia.

Long-term Consequences of Preeclampsia
Following preeclampsia, there is long-term increased likelihood of:
Fatal and nonfatal coronary heart disease
Cerebrovascular accident (stroke)
Hypertension
Thromboembolism
End-stage renal disease (ESRD)
Diabetes
Cognitive dysfunction and white matter lesions on cerebral CT scan
Death from any cause

Box 44-4 Long-term consequences of preeclampsia. *CT,* Computed tomography.

low likelihood of fits and avoids the potential for drug toxicity in a large number of pregnant women.[57] However, in developing countries, we recommend routine magnesium prophylaxis because the rate of eclampsia is higher and the cost benefit much greater.[58]

Although preeclampsia is a volume-contracted state, the increased capillary permeability makes IV volume expansion a potentially harmful procedure, with the ever-present risk of pulmonary edema. Therefore, volume expansion should be used only in select patients, such as before parenteral treatment of acute severe hypertension (when rapid vasodilation may occur) and as initial treatment in the persistently oliguric woman. No more than 1 liter of crystalloid or colloid should be given in such women, usually over 4 to 6 hours. This will restore the average plasma volume deficit in most preeclamptic women, but careful clinical observation is required for the possibility of pulmonary edema, particularly if oliguria persists.

Platelet transfusion is generally given when the platelet count falls below 20 × 10^9/l, but in some cases at higher levels (e.g., 20 to 40 × 10^9/l) if hypertension is difficult to control and the risk of intracerebral hemorrhage is therefore high. Fresh-frozen plasma is only indicated if there is accompanying microangiopathy and thrombocytopenia, when it may be difficult to differentiate preeclampsia from hemolytic uremic syndrome (HUS), or when hepatic disease leads to impaired coagulation in preeclamptic women. We do not recommend plasma exchange or corticosteroids for HELLP syndrome. Adsorption of sFlt-1 by dextran column pheresis has been in trials and will be the subject of ongoing study, although it is not part of standard practice at present.[59] Table 44-4 summarizes management of preeclampsia.

Postpartum Management

Recovery should be anticipated over 5 to 7 days in most women after delivery. In many women, the condition may worsen in the first 3 days after delivery, and they should be monitored and treated just as aggressively then as antepartum. Some patients may require up to 3 months for all the features to resolve, and a few patients will have proteinuria that takes up to 1 year to disappear completely.

Assessment of the preeclamptic woman several months postpartum is mandatory. BP should have returned to normal within 3 months in most women, and if not, this should prompt a search for underlying primary or secondary hypertension. Urinalysis and urine microscopy should be normal, certainly by 12 months postpartum, and if not, a primary underlying renal disease should be sought.

Women with recurrent preeclampsia, or severe early-onset disease (in whom recurrence is more likely) warrant special consideration and should be tested for underlying connective tissue, renal, thrombophilic and antiphospholipid disorders.

As a general rule, preeclampsia and the more benign gestational hypertension will recur in only about 15% of women in a subsequent pregnancy. Women who have presented at or before 28 weeks of gestation have at least a 25% risk of recurrence.

There are now well-recognized long-term implications of preeclampsia, particularly if it occurs before 37 weeks, including an increased risk of primary hypertension, coronary heart disease, stroke, venous thromboembolism, and end-stage renal disease (ESRD) (Box 44-4). The mechanism behind these increased risks appears to be a tendency to metabolic syndrome.[60] It is appropriate

to counsel women who develop hypertension in pregnancy on cardiovascular risk factor lifestyle modifications, along with periodic BP, serum lipid, and blood glucose checks. All such women should also receive counseling before embarking on another pregnancy.

ACUTE FATTY LIVER OF PREGNANCY

Acute fatty liver of pregnancy (AFLP) presents in the third trimester with fever, malaise, epigastric pain, nausea, vomiting, and jaundice. The incidence of AFLP is 1 per 7000 to 20,000 pregnancies,[61] but many milder cases may go undiagnosed. AKI is a common complication of AFLP, although the exact incidence is unclear, with a small case series describing rates that vary from 20% to 100%.[62]

Pathogenesis and Pathology

The disease is frequently associated with an autosomal recessive genetic error that causes a defect on long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), an enzyme involved in mitochondrial fatty acid β-oxidation. This causes excessive fetal fatty acid accumulation to be released into the maternal circulation, which deposits in liver tissue and leads to maternal hepatic dysfunction. The hallmark of the hepatic pathology is lipid microvesicle infiltration of the hepatocytes without inflammation or necrosis.

The renal lesion in AFLP is nonspecific, and the pathophysiology is unclear. It may be caused by hemodynamic changes similar to those seen in the hepatorenal syndrome or by a thrombotic microangiopathy. Coexisting preeclampsia may also contribute to the renal injury. Renal biopsy and autopsy studies have shown mild glomerular hypercellularity with thick, narrow capillary loops and tubular free fatty acid accumulation, suggesting that abnormal fatty acid oxidation may also contribute to renal dysfunction.

Clinical Manifestations

The severity of liver involvement in women with AFLP is highly variable, ranging from a moderate isolated increase in transaminases to fulminant hepatic failure with encephalopathy and coagulopathy. Characteristic laboratory abnormalities include hyperbilirubinemia, increased transaminases, hypoglycemia, leukocytosis, and evidence of coagulopathy (hypofibrinogenemia, prolonged prothrombin time, depressed antithrombin III levels) with thrombocytopenia.

Differential Diagnosis

Viral hepatitis and biliary obstruction should be excluded before confirming the diagnosis of AFLP. Distinguishing AFLP from severe preeclampsia can be challenging; up to 50% of women with AFLP have concomitant preeclampsia with hypertension and proteinuria. Because the two disorders share many pathophysiologic and clinical features, some suspect that these are part of the same spectrum of disease. Nevertheless, distinguishing between preeclampsia and AFLP is important to guide whether offspring should be assessed for LCHAD mutation.

Treatment and Outcome

Early diagnosis, supportive care, and prompt delivery are critical in the management of AFLP. In most women, there is complete liver and kidney recovery after delivery. However, AFLP is associated with maternal and perinatal mortality of 10% to 20%. Renal recovery typically follows delivery, but dialysis may be needed.

THROMBOTIC MICROANGIOPATHY

Pregnancy-associated thrombotic microangiopathy (TMA) is defined by the presence of fibrin and platelet thrombi in the microcirculation of multiple organs, microangiopathic hemolysis, and thrombocytopenia. Manifestations of pregnancy-associated TMA include the HELLP syndrome, HUS, and thrombotic thrombocytopenic purpura (TTP). Pregnancy-associated TMA is also discussed in Chapter 29.

Clinical Manifestations and Differential Diagnosis

Women with HUS typically present with AKI (often with hypertension) in the postpartum period, although injury can occur at any time during pregnancy, even as early as the first trimester. TTP presents antepartum, usually before 28 weeks' gestation. Coagulation studies and liver function tests are usually normal in HUS and TTP, unlike cases of severe preeclampsia or AFLP. One study suggests that a high lactate dehydrogenase (LDH)–AST ratio (25:1) indicates that HUS is a more likely diagnosis than preeclampsia/HELLP in the third trimester.

In practice, it may be difficult to distinguish HUS and TTP from preeclampsia without renal biopsy, which often must be delayed until thrombocytopenia is resolving. If renal failure is progressive, biopsy becomes more important to guide ongoing therapy, including plasma exchange.

Natural History

The maternal mortality in pregnancy-associated TMA has declined in recent years and is now between 10% and 20%. However, perinatal mortality is high (30% to 80%), mainly from growth restriction and placental infarction caused by thrombosis of decidua arterioles.[63] The long-term renal outcome is poor, with 76% of patients with AKI from HUS developing ESRD.[64]

ACUTE KIDNEY INJURY

Definition

The diagnosis of AKI in pregnancy is based on the serum creatinine increase. The usual formulas for estimating GFR are not validated in pregnancy, nor are systems for defining AKI (e.g., AKIN; see Chapter 71). Creatinine clearance by 24-hour urine collection remains the gold standard method for estimating GFR in pregnancy, but this is impractical in most women with AKI. Unfortunately, there is still no agreed definition of AKI in pregnancy, but in general, a serum creatinine greater than 88 μmol/l (>1 mg/dl), or an increase within 48 hours of 44 μmol/l (0.5 mg/dl) above baseline, should be investigated.

Epidemiology

Acute kidney injury necessitating dialysis now occurs in developed countries in only about 1 of 20,000 pregnancies, so a typical obstetric unit (with 2000 to 3000 unselected deliveries per year) will only see one case every 6 to 10 years; the incidence will be greater in tertiary referral centers but is still very low. The development of AKI in pregnancy follows a bimodal distribution with two incidence peaks: the first and third trimesters. Pre-renal causes are more common in the first trimester because of hyperemesis gravidarum or acute

tubular necrosis in the context of septic abortion. Common causes in the later stages of pregnancy are preeclampsia, HUS, or AFLP. Obstructive uropathy is an uncommon cause of AKI in pregnancy.

Pathogenesis

Common to many of the disorders causing AKI in pregnancy are the pre-renal elements of volume contraction and vasoconstriction, as well as intravascular coagulation, each abnormality tending to reduce renal perfusion and setting the scene for renal ischemia (Table 44-5). It is generally believed that a pregnant woman is more likely to develop AKI than a nonpregnant woman exposed to the same set of conditions that threaten renal perfusion, although there are no confirmatory data for this view. The best explanation for this would be that many of the renal "protective" mechanisms (e.g., increased prostacyclin production to enhance renal blood flow) are already activated maximally in normal pregnancy and may not be augmented in the setting of a pre-renal problem.

It is also a common view that subsequent bilateral renal cortical necrosis is more likely than if AKI had developed outside of pregnancy. The risk of cortical necrosis is estimated at 20% when AKI follows septic abortion. This contrasts with a lower incidence of cortical necrosis (~2%) after other causes of AKI in pregnancy.[65] Irreversible renal damage follows 10% to 25% of such cases of cortical necrosis, mostly after preeclampsia or antepartum hemorrhage.[66] Since septic abortion is now an uncommon problem in developed countries, cortical necrosis is a less common complication of obstetric AKI than in the past, although this risk remains higher in developing countries where opportunities to prevent AKI are fewer.

Antepartum Hemorrhage, Prolonged Intrauterine Fetal Death, or Amniotic Fluid Embolism

In these conditions, primary DIC and severe renal ischemia (leading to endothelial damage and secondary fibrin deposition) are the initiating events. Local release of nitric oxide (NO) normally minimizes the degree of thrombus formation by diminishing platelet aggregation, but if endothelial injury is too great, NO release is impaired, accelerating the tendency to thrombosis. Renal cortical necrosis or acute tubular necrosis (in less severe cases) may then occur, manifesting as abrupt onset oliguria or anuria with gross hematuria, flank pain, and often hypotension caused by the initiating disorder.

Causes of Acute Kidney Injury in Pregnancy

Category	Specific Causes*
Pre-renal	Antepartum or postpartum hemorrhage Hyperemesis gravidarum Sepsis Congestive heart failure (rare)
Renal	Acute tubular necrosis Pyelonephritis Renal cortical necrosis Thrombotic microangiopathy Preeclampsia/HELLP syndrome Acute fatty liver of pregnancy glomerulonephritis Medication toxicity
Post-renal	Urinary tract obstruction Gravid uterus (rare) Calculi

Table 44-5 Causes of acute kidney injury (AKI) in pregnancy. *Although all the usual causes of AKI apply, these causes are more specific to pregnancy.

Sepsis

In septic conditions in pregnancy, AKI is probably the result of cytokine-induced changes in vascular permeability and a loss of effective renal plasma flow, sometimes with accompanying hemolysis or DIC or acute pyelonephritis.

Clinical Manifestations and Differential Diagnosis

Most cases of AKI in pregnancy are associated with oliguria, and the clinical manifestations in the mother are the same as for AKI in general (see Chapter 71). However, there is the added concern of fetal death; the fetus does not survive in an environment of prolonged uremia. Clinical features that should be considered in the differential diagnosis of AKI in pregnancy include preeclampsia and obstructive uropathy.

Preeclampsia

Oliguria in the context of preeclampsia is a worrying sign but of itself may represent a normal renal response to volume contraction. The rise in serum creatinine can sometimes be prevented by good BP control and judicious volume expansion in these patients. AKI is more likely to develop in the HELLP syndrome. Table 44-6 outlines the differential clinical features of preeclampsia/HELLP syndrome, HUS, and AFLP.

Obstructive Uropathy

Obstructive uropathy is uncommon in pregnancy. Usually, there are no specific clinical features; renal failure is discovered when serum creatinine is measured because a pregnant woman is progressively unwell or she is oliguric. Ureteral dilation, more common on the right, may reach up to 8 cm of renal pelvic dilation as part of normal pregnancy. Therefore, ultrasound diagnosis of obstructive uropathy is difficult. If urinary tract obstruction is the suspected cause of AKI

Differential Clinical Features of Syndromes Causing Acute Kidney Injury

Clinical Feature	HUS/TTP	HELLP	AFLP
Hemolytic anemia	+++	++	+/–
Thrombocytopenia	+++	++	+/–
Coagulopathy	–	+/–	+
CNS symptoms	+/– (HUS)/ ++ (TTP)	+/–	+/–
Renal failure	+++	+	++
Hypertension	+/–	+++	+/–
Proteinuria	+/–	++	+/–
Elevated AST	+/–	++	+++
Elevated bilirubin	++	+	+++
Anemia	++	+	+/–
Blood ammonia	Normal	Normal	High
Effect of delivery on disease	None	Recovery	Recovery
Management	Plasma exchange	Supportive care, delivery	Supportive care, delivery

Table 44-6 Comparison of clinical and laboratory characteristics of syndromes causing AKI in pregnancy. *HUS,* Hemolytic uremic syndrome; *TTP,* thrombotic thrombocytopenic purpura; *HELLP,* syndrome of hemolysis, elevated liver enzymes, and low platelet count; *AFLP,* acute fatty liver of pregnancy; *CNS,* central nervous system; *AST,* aspartate transaminase.

in pregnancy, a thorough search should be made first for other disorders causing the AKI. If no other cause is found, if renal failure is progressive, and if delivery cannot be initiated immediately, percutaneous nephrostomy may rarely be required. The diagnosis is confirmed if serum creatinine falls.

Natural History

The likelihood of AKI in pregnancy progressing to a dialysis-dependent patient has not been studied systematically. Recovery from dialysis-dependent AKI is much more likely in preeclamptic women or those with AFLP or antepartum hemorrhage, because the pathophysiologic changes of these disorders resolve quickly after delivery. Recovery is much slower after HUS, and CKD is more likely.

Maternal and Fetal Mortality

Maternal mortality varies between 6% and 30% depending on the study.[67] Fetal mortality rates are much higher but vary enormously depending on the availability of perinatal care.[68]

Treatment

The key issue in treatment of AKI in the pregnant patient is restoration of fluid volume deficits, and in later pregnancy, delivery of the baby and placenta, because this is likely to remove the stimulus for AKI as quickly as possible. This is relatively easy when AKI develops late in pregnancy, but when fetal viability is uncertain and the maternal condition stable, dialysis and specific treatment of the underlying condition are begun.

Dialysis

The indications for dialysis are the same as for the general population with severe AKI: uremic symptoms (encephalopathy or pericarditis), volume overload, hyperkalemia, and metabolic acidosis unresponsive to initial medical treatment. However, it is generally recommended to start dialysis earlier, when the urea rises above 15 mmol/l (equivalent to BUN of 42 mg/dl) despite volume restoration, because the uremic environment has a negative effect on fetal survival. Both peritoneal dialysis and hemodialysis have been used in pregnancy with success. Peritoneal dialysis requires dialysis catheter insertion under direct vision and has the potential advantage of maintaining fairly constant maternal hemodynamics without threatening uteroplacental blood flow, but it does carry the risk of peritonitis. Hemodialysis is required more frequently than usual and has the risk of impairing uteroplacental perfusion if sudden fluid shifts occur. Neither method is superior, and there is only limited experience with continuous renal replacement therapy in pregnancy. Dialysis in pregnancy is discussed in more detail in Chapter 45.

OVARIAN HYPERSTIMULATION SYNDROME

Definition and Epidemiology

Ovarian hyperstimulation syndrome (OHSS) is an exaggerated response to ovulation induction associated with *in vitro* fertilization (IVF) therapy. OHSS manifests as increased capillary permeability and fluid retention, with inflammatory mediators (e.g., VEGF). Fortunately, it is self-limiting. Severe OHSS is reported to occur in 0.5% to 5% of stimulated ovarian cycles.[69] Risk factors include polycystic ovarian syndrome, retrieval of more than 200 oocytes, relative youth (<35 years), atopy, previous OHSS, and pregnancy. Mortality rates may be as high as 1 in 50,000 patients, usually from multiorgan failure caused by volume depletion and hemoconcentration.[70]

Pathogenesis

In spontaneous ovulatory cycles, hypothalamic-pituitary-ovarian negative feedback mechanisms usually limit recruitment and development to a single follicle. Ovulation induction generally involves administration of a pharmacologic dose of exogenous gonadotropin that overrides normal feedback mechanisms. This results in recruitment of a large number of follicles. When human chrorionic gonadotropin (hCG) or a gonadotropin-releasing hormone (GnRH) agonist is administered to trigger ovulation in the setting of multiple follicles, or if pregnancy ensues, massive follicular luteinization occurs, which can lead to excessive release of factors, including VEGF, cytokines, prostaglandins, histamine, and angiotensin. These factors increase vascular permeability, causing massive fluid shifts and abdominal ascites, pleural and pericardial effusions, and edema. The hemoconcentration, hypovolemia, and elevated estrogen increase susceptibility to thromboembolic events. Hypovolemia and hypotension decrease renal perfusion and stimulate the RAS and sympathetic nervous system, along with antidiuretic hormone release, which then leads to oliguria, hyperkalemia, hyponatremia, and acidosis. A state of relative immunodeficiency results from loss of serum immunoglobulins into the peritoneal cavity, leading to greater infection risk. Eighty-three percent of patients with severe OHSS will have at least one febrile episode over 24 hours, with only one third of these associated with infection, usually UTI.[71]

Prevention

Modifications to the IVF protocol, such as delaying the administration of hCG until estradiol levels plateau or decrease, using a lower dose of hCG in high-risk patients, or using GnRH antagonists without hCG, have all been used to minimize the risk of OHSS. A meta-analysis of five randomized controlled trials (RCTs) demonstrated that prophylactic albumin significantly reduced the risk of developing OHSS, with albumin infusion preventing one case of severe OHSS for every 18 women at risk who are treated.[72]

Clinical Manifestations and Investigations

The clinical presentation of OHSS can be categorized into mild or severe (Table 44-7). OHSS has also been classified by time of onset.

Clinical Features of Ovarian Hyperstimulation Syndrome

Severity	Symptoms and Signs
Mild to moderate	Ovaries enlarged up to 12 × 12 cm with: Abdominal discomfort Nausea, vomiting, diarrhea Sudden increase in weight of >3 kg
Severe	Ovaries enlarged, abdominal pain, and one or more of following: Rapid weight gain Ascites, pleural or pericardial effusion Hypovolemia, hemoconcentration Oliguria, acute kidney injury Abnormal liver function Hypoalbuminemia Hyponatremia or hyperkalemia

Table 44-7 Clinical features of ovarian hyperstimulation syndrome (OHSS). OHSS is a cause of acute kidney injury.

Early-onset OHSS occurs 3 to 7 days after the administration of the ovulatory dose of hCG and is caused by excessive preovulatory ovarian response to stimulation. Late-onset OHSS occurs later than 1 week after hCG administration and is thought to be caused by pregnancy-related increase in hCG level. Pregnancy-related OHSS is usually clinically severe and more prolonged. Patients should be investigated with full blood count and hematocrit, serum creatinine, electrolytes, liver function tests (albumin), β-hCG, and coagulation studies. An abdominal ultrasound will help confirm the diagnosis. Abdominal pain must be investigated thoroughly because the enlarged, fragile ovaries are prone to torsion and rupture. Intra-abdominal infection and ectopic pregnancy must also be considered.

Management

Ovarian hyperstimulation syndrome is self-limiting, on average 7 days in nonpregnant patients and 10 to 20 days in pregnant patients. Treatment is mainly supportive. In the woman with moderate to severe OHSS, hospital admission is required for correcting volume depletion, monitoring and correcting electrolyte abnormalities (particularly hyperkalemia), providing analgesia, offering nutrition and psychological support, preventing deep vein thrombosis, and supporting respiratory function. The ideal fluid replacement is not clear. Our practice is to give only 2 liters of crystalloid over 24 hours to correct intravascular volume depletion, recognizing that some of this will be lost into third-space fluid. Paracentesis may be necessary to improve symptoms and respiratory function in the short term. It can also improve hemodynamic status, renal blood flow, creatinine clearance, and urinary output by decreasing intra-abdominal pressure. Simultaneous albumin infusion is given to avoid protein depletion, hypotension, and rapid reaccumulation of fluid within the pleural and peritoneal spaces. Diuretics are contraindicated because these will not reduce third-space fluid and may worsen hypovolemia and hemoconcentration and precipitate AKI. Prophylactic anticoagulation with heparin is required due to the risk of thromboembolism.

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CHAPTER 45

Pregnancy with Preexisting Kidney Disease

Mark A. Brown

Historically, renal disease was considered a contraindication to pregnancy, but now many pregnant women with chronic kidney disease (CKD) have successful outcomes. Accordingly, nephrologists and obstetricians need to be skilled in the management and counseling of such women. This chapter details the outcomes and management of such pregnancies. More recently, information indicates that even women with the earliest stages of CKD and those with previously treated lupus nephritis carry increased pregnancy risks, and that fetal survival continues to improve in well-dialyzed pregnant women.

CHRONIC KIDNEY DISEASE: ADVERSE EFFECTS ON PREGNANCY

Up to 3% to 10% of women of childbearing age have CKD stages 3 to 5.[1] Available data on pregnancy outcomes are mainly from studies published 10 to 20 years ago and probably overestimate risk compared to outcomes achieved with modern care, particularly with improvements in neonatal intensive care. This is changing, with more recent emphasis on assessing pregnancy outcome according to pre-pregnancy estimated glomerular filtration rate (eGFR) when possible, but there are still fewer data for pregnancy outcomes assessed by this method than by pre-pregnancy serum creatinine alone. The key pre-pregnancy factors predicting outcome include the following:

- Degree of renal impairment
- Control of hypertension
- Degree of proteinuria

In most circumstances, these features are more important in predicting outcome than the mother's specific renal disease.

The traditional view was that most women with mild renal impairment (serum creatinine <1.5 mg/dl; 130 µmol/l) and controlled hypertension have a successful pregnancy outcome, with preexisting hypertension the main predictor of pregnancy outcome in women with mild renal impairment. However, more recent studies challenge this. Perinatal mortality, preterm delivery, small-for-gestational age rates, and development of superimposed preeclampsia appear high even in women with creatinine less than 125 µmol/l before conception, but more than 100 µmol/l in early pregnancy, and indeed, even in women with normal GFR but dipstick proteinuria and one or more other risk factors for preeclampsia.[2] Those with moderate (serum creatinine 1.5 to 2.5 mg/dl; 130 to 220 µmol/l) to severe (>2.5 mg/dl; 220 µmol/l) renal impairment, particularly when accompanied by hypertension and heavy proteinuria, have a lower chance of live birth and a greater risk for maternal complications, including progression of their renal disease (Box 45-1).

Control of Hypertension

A retrospective analysis of 358 pregnant women with CKD in the United Kingdom found an association between diastolic blood pressure (BP) above 90 mm Hg (treated or untreated) and neonatal death. This relatively mild degree of hypertension also compounded the risk of preterm birth resulting from renal impairment alone.[3]

Progression of Chronic Kidney Disease

The risk of progression of renal disease during the pregnancy likewise depends less on the specific renal disorder and more on baseline serum creatinine, control of hypertension, and increasing proteinuria or onset of superimposed preeclampsia. The natural history of most mild CKD is that accelerated deterioration during a pregnancy is unlikely; the main exception is lupus nephritis, which can flare, leading to worsening renal disease during the pregnancy. However, 50% of women with moderate baseline renal impairment (serum creatinine >1.5 mg/dl; 130 µmol/l) have a significant rise in serum creatinine in the third trimester or early postpartum. If this occurs, almost one in five progress to end-stage renal disease (ESRD) within 6 months after delivery.

Prematurity or Fetal Growth Restriction

Prematurity, fetal growth restriction, and stillbirth are the major concerns for pregnancies of women with renal impairment, particularly if superimposed preeclampsia develops. Uncontrolled hypertension at conception is a poor prognostic feature for fetal outcome (Box 45-2). A new reason to avoid prematurity, besides the immediate effects on the baby, is the association with higher mortality in young adulthood.[4]

Fertility

Fertility rate is reduced in women with moderate to severe CKD, but the only estimates are imprecise. Even women receiving dialysis may become pregnant, so all women should be advised to use contraception unless planning a pregnancy.

MANAGEMENT COMMON TO ALL PREGNANCY WITH PREEXISTING KIDNEY DISEASE

Box 45-3 summarizes the general principles of management of pregnancy in women with CKD.

Pre-pregnancy Counseling

It has long been known that any woman with CKD stage 3 to 5 should receive pre-pregnancy counseling. We now know that this should also apply to women with CKD stage 1 or 2, particularly if they have hypertension, significant proteinuria, a poor obstetric history, recurrent urinary tract infection (UTI), inheritable renal

Maternal Renal Outcomes According to Pre-pregnancy Serum Creatinine

Creatinine <1.5 mg/dl (130 μmol/l)
- Permanent loss of GFR in <10% of women
- Greatest risk if GFR <40 ml/min and proteinuria >1 g/day
- Major determinant of ESRD progression is hypertension
- 40% risk of preeclampsia if baseline proteinuria >500 mg/day

Creatinine 1.5-2.5 mg/dl (130-220 μmol/l)
- Decline or permanent loss of GFR in 30% of women
- Increased to 50% if uncontrolled hypertension
- 10% ESRD soon after pregnancy

Creatinine >2.5 mg/dl (220 μmol/l)
- Progression to ESRD highly likely during or soon after pregnancy

Box 45-1 Maternal renal outcomes according to pre-pregnancy serum creatinine. Note that MDRD or CKD-EPI formulas for estimation of glomerular filtration rate *(GFR)* are *not* valid for pregnancy; *ESRD,* end-stage renal disease.

Fetal Outcomes According to Maternal Pre-pregnancy Serum Creatinine

Outcomes after accounting for first-trimester miscarriage:

Creatinine <1.5 mg/dl (130 μmol/l)
- Live births in >90% of women
- Up to 50% preterm delivery, 60% small for gestational age if baseline proteinuria >500 mg/day

Creatinine 1.5-2.5 mg/dl (130-220 μmol/l)
- Live births in about 85% of women unless uncontrolled hypertension (MAP >105) at conception
- 60% prematurity, mainly iatrogenic (preeclampsia/fetal growth restriction)

Creatinine >2.5 mg/dl (220 μmol/l)
- Fetal loss high; estimates uncertain

Box 45-2 Fetal outcomes according to maternal serum creatinine before pregnancy. Note that MDRD and CKD-EPI formulas for estimating glomerular filtration rate are *not* valid for pregnancy; *MAP,* mean arterial pressure.

disease, or other disease (e.g., SLE) likely to worsen during pregnancy. Studies from Italy have found that preterm delivery, cesarean rates, and need for neonatal intensive care were higher than in the general population, even in women with stage 1 CKD; this was particularly true if baseline proteinuria was more than 1 g/day.[5,6] Another meta-analysis included older studies but also a large number of women in stage 1 CKD; both maternal and fetal outcomes were worse in women with any form of CKD.[7] A study from Arabian Gulf countries examined outcomes of women with stage 1 and 2 CKD and also showed unexpectedly high rates of preterm delivery, fetal growth restriction, and fetal death in women with eGFR as high as 60 to 89 ml/min.[8] Although this may not be a worldwide experience, it now seems prudent to follow all women with any CKD more closely during pregnancy, not just those with impaired GFR or proteinuria above 1 g/day. This is more relevant because CKD stage 1 or 2 affects 3% of women of childbearing age, whereas CKD stage 3 to 5 affects about 1 in 150 of these women.[9] Box 45-4 summarizes issues that should be covered in counseling.

Principles of Antenatal Care with Preexisting Chronic Kidney Disease

- Management of hypertension aiming for BP 110-140/80-90 mm Hg
- Aspirin (75-150 mg daily) if serum creatinine ≥1.5 mg/dl (130 μmol/l) *or* 0.9-1.5 mg/dl (100-130 μmol/l) and proteinuria >1 g/day
- Regular medications review: discontinue statins, ACE inhibitors, ARBs
- Correct interpretation of changes in serum creatinine
- Clinical assessment and maintenance of volume homeostasis
- Interpretation and management of proteinuria including nephrotic syndrome
- Identification of superimposed preeclampsia
- Identification and management of urinary tract infection
- Consideration of the primary renal disease
- Assessment for fetal well-being and consider if delivery is indicated (see Box 45-5)

Box 45-3 Principles of antenatal care in women with preexisting chronic kidney disease. See text for further discussion. *BP,* Blood pressure; *ACE*, angiotensin-converting enzyme; *ARBs*, angiotensin receptor blockers.

Pre-pregnancy Counseling for Women with Chronic Kidney Disease

Maternal Risks
- Accelerated decline in glomerular filtration rate, sometimes precipitating dialysis during pregnancy or soon after
- Severe maternal hypertension with risk of stroke
- Superimposed preeclampsia with renal, hepatic, thrombotic, or bleeding and neurologic risks
- Nephrotic syndrome with risks of thrombosis or sepsis and iron or vitamin D deficiency

Fetal Risks
- Fetal growth restriction or intrauterine fetal death from placental insufficiency
- Prematurity, with both short-term and long-term consequences
- Complications of drug therapy for renal disease during pregnancy
- Inheritance of a renal disorder

Box 45-4 Pre-pregnancy counseling for women with chronic kidney disease.

Excretory Renal Function

During normal pregnancy, GFR rises by about 50%, typically apparent by the end of the first trimester (see Chapter 43). Serum creatinine greater than 1 mg/dL (88 μmol/l) in a pregnant woman generally indicates reduced GFR. The Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations or other formulas that estimate GFR are not valid for pregnancy; whereas it is reasonable to assess pregnancy risks based on pre-pregnancy eGFR, these formulas should not be applied in pregnancy. Measurement of creatinine clearance is the only clinical way of truly assessing GFR in pregnancy but requires 24-hour urine collection, which is cumbersome, and even when conducted diligently, may be inaccurate because of

ureteral dilation, which results in pooling of urine and an incomplete collection. Serum cystatin C is being evaluated but also appears inaccurate. Serum creatinine remains the clinical standard for assessing GFR during pregnancy.

Blood Urea Nitrogen

Increments in blood urea nitrogen (BUN) and creatinine may indicate deteriorating GFR and the need for initiation of dialysis if the pregnancy is to succeed (see Dialysis in Pregnancy). However, a rising BUN, particularly when accompanied by rising hemoglobin or hematocrit, may represent intravascular contraction, typically seen in preeclampsia. The main role for BUN in pregnancy is for monitoring the effectiveness of dialysis.

Serum Electrolytes, Albumin, and Volume Homeostasis

Serum sodium and bicarbonate are slightly reduced, potassium is at the lower end of the normal range, and albumin and uric acid are lower than in the nonpregnant state. Increases in serum sodium to those of nonpregnant women should suggest (reversible) pregnancy-specific diabetes insipidus (from excess placental vasopressinase). In general, this is a mild disorder, but DDAVP should be given if serum sodium rises above 150 mmol/l with low urine osmolality.

Adequate intravascular volume is essential to preservation of GFR and good pregnancy outcome for mother and baby. Clinically, it is difficult to assess maternal volume homeostasis. Edema is an unhelpful sign in pregnancy, so hematocrit should be measured in women with underlying CKD at the initial first trimester visit, along with serum albumin. Both measures should fall slightly as pregnancy progresses. A rise in either value strongly suggests intravascular volume contraction, although there is no absolute discriminant value. Conversely, a significant fall in either value does not by itself diagnose excessive volume expansion, because the hematocrit depends on other factors, and serum albumin may fall in patients with nephrotic syndrome, who in turn may have reduced intravascular volume.

In practice, provided there is no respiratory compromise and BP can be controlled, volume excess is more favorable for maternal renal function and fetal growth than volume depletion. When there is concern about fetal growth or deteriorating GFR in women with CKD, and reduced intravascular volume is suggested by the change in hematocrit and albumin from baseline, a trial of intravenous normal saline (no more than 1 liter) under observation in hospital is a reasonable clinical approach.

Urinalysis

A dipstick test showing negative or trace protein in most (but not all) cases excludes true proteinuria. Any woman with 1+ (0.3 g/L) proteinuria or above should have formal quantification of protein excretion either with a spot urine protein-creatinine (PC) ratio or 24-hour urine collection. Glycosuria may be normal and is not itself diagnostic of diabetes mellitus, but when glycosuria is detected in early pregnancy in a woman with CKD, a 75-g oral glucose tolerance test should be performed. Dipstick hematuria during pregnancy is common and often resolves after delivery. Provided there is no UTI, urine sediment is inactive, and serum creatinine normal, this is not associated with adverse maternal or fetal outcomes during pregnancy and can be investigated if persistent postpartum.[10] Pregnancy may be the woman's first urinalysis, so previously undetected renal disorders are diagnosed at this point.

Proteinuria and Nephrotic Syndrome

The upper limit of normal protein excretion during pregnancy is defined as 300 mg/day. In a midstream specimen of urine, a PC ratio greater than 30 mg/mmol (0.27 mg/mg) correlates with more than 300 mg/day proteinuria.[11]

New-Onset Proteinuria

Isolated non-nephrotic proteinuria may develop *de novo* during pregnancy.[12] In these women, with normal GFR, one of the following three scenarios usually unfolds:

1. Preeclampsia is subsequently evident.
2. No pregnancy complications occur, and the proteinuria disappears postpartum.
3. Intrinsic glomerular disease has developed and remains postpartum.

In my experience, the third scenario is an uncommon event.

Preexisting Proteinuria

Although the spot urine PC ratio in pregnancy is a reasonably reliable method of determining whether protein excretion is abnormal, serial measurements of urine PC ratio are not recommended for reliably predicting *changes* in proteinuria. When a true increase in protein excretion occurs during pregnancy in women with underlying renal disease, few therapeutic options exist besides ensuring BP control (see later discussion).

Nephrotic Syndrome

The one situation in which 24-hour urinary protein excretion should be measured in these women is to diagnose nephrotic syndrome. Serum albumin falls in most pregnancies as a result of volume expansion and is often below 30 g/l, so this is not a reliable indicator of nephrotic syndrome. A spot urine PC ratio greater than 230 mg/mmol indicates protein excretion above 3 g/day,[13] which should be confirmed by 24-hour urinary protein measurement. These women will generally have edema, but this is unhelpful because it occurs in two thirds of normal pregnancies. Although increased serum cholesterol is typical of nephrotic syndrome, this frequently occurs during normal pregnancy.

Confirmation of true nephrotic syndrome has important implications in pregnancy. There will be urinary loss of vitamin D–binding protein, transferrin, immunoglobulins, and antithrombin III (accompanied by increased hepatic synthesis of clotting factors) and a propensity for intravascular volume contraction. These changes can result in calcium deficiency, iron deficiency, increased likelihood of infection, thrombosis, and reduced uteroplacental blood flow with fetal growth restriction or death; some patients have reduced renal blood flow with worsening renal function. Adequate fetal growth and amniotic fluid should be evaluated by serial ultrasound. Treatment requires oral calcium, vitamin D and iron supplementation and subcutaneous heparin for thrombosis prophylaxis, and reassessment of maternal serum creatinine on a regular basis. If nephrotic syndrome occurs early in pregnancy, I add vitamin D for prophylaxis against osteoporosis, although there are no controlled trials to test this practice.

Hypertension

Hypertension in pregnancy is defined as blood pressure above 140/90 mm Hg, and this is generally the threshold for treatment, with an acceptable range on treatment of 110 to 140 systolic and 80 to 90 mm Hg diastolic. This range is not based on solid pregnancy outcome data but is thought to be the range that reduces maternal risk from severe hypertension while providing sufficient systemic BP

to maintain placental perfusion. Although the target BP for nonpregnant women with CKD is also less than140/90 mm Hg, it is probably lower (≤125/75 mm Hg) if proteinuria is more than 1 g/day; therefore a pregnant woman with proteinuric CKD may have about 40 weeks when BP is above usual target, which may contribute to progressive renal impairment postpartum. Nevertheless, if a pregnant woman develops BP below 110/80 mm Hg, my practice is to reduce antihypertensive drugs and avoid the risk of fetal hypoperfusion.

Most pregnant women with CKD will not exhibit the usual first-trimester fall in BP, and in many, BP increases as the pregnancy progresses. The reason is not clear. Normal pregnancy is accompanied by significant volume expansion, which does not usually induce hypertension. In CKD, however, there is often inability to excrete a sodium load with accompanying hypertension, and this mechanism likely contributes in pregnancy. Other factors almost certainly playing a role in this hypertension include stimulation of the renin-angiotensin and sympathetic nervous systems, alterations in endothelial factors such as prostacyclin, nitric oxide, and endothelin, and particularly in transplant patients, the drugs used, such as calcineurin inhibitors and corticosteroids. Regardless of its cause, persistence of hypertension is an adverse factor in pregnancy outcome.[14] Concern about using antihypertensives in pregnancy has been associated with poorer pregnancy outcomes, at least in women with renal transplant.[15]

Blood pressure will often rise significantly soon after delivery. Therefore, BP measurement and treatment should be undertaken diligently in the early postpartum period.

Control of BP is imperative to successful pregnancy outcome in women with underlying renal disease. Diuretics are not recommended during pregnancy because any reduction in maternal plasma volume may have adverse effects on uteroplacental or renal perfusion. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) must be discontinued, preferably before pregnancy but certainly as soon as pregnancy is diagnosed, because of increased risks of fetal growth restriction, oligohydramnios, neonatal renal failure, and probably cardiac and neurologic developmental abnormalities. Aldosterone antagonists should also be avoided, and atenolol has been associated with fetal growth restriction. Suitable antihypertensives include methyldopa, labetalol, oxprenolol, hydralazine, prazosin, and nifedipine, and all may be used in conventional doses. Diltiazem may also have a small benefit on reducing proteinuria, but this has not been addressed specifically for pregnancy.

Superimposed Preeclampsia

Preeclampsia is a placental disorder of unknown etiology that has several predisposing risk factors, one of which is CKD (see Chapter 44). The maternal renal effects of preeclampsia include a reduction in renal blood flow, increased sodium and uric acid reabsorption, reduced circulating renin and aldosterone concentrations, proteinuria, and impaired GFR. Superimposed preeclampsia in a woman with underlying renal impairment will lead to worsening renal function, exaggerated hypertension and proteinuria with risks of nephrotic syndrome, short-term and long-term risks to maternal renal function, as well as increased risks for fetal growth restriction, prematurity, and perinatal mortality.

However, it is difficult to diagnose superimposed preeclampsia in a woman who begins her pregnancy with renal impairment or proteinuria. An increase in BP, decline in GFR, increased plasma uric acid, or increasing protein excretion can all be caused by progression of the underlying renal disorder rather than superimposed preeclampsia, and no definitive diagnostic test yet exists. However, when these features are accompanied by neurologic symptoms, such as hyperreflexia with clonus, or by abnormal liver transaminases or new-onset thrombocytopenia (except in SLE), it is highly likely that superimposed preeclampsia has developed. Typically, these changes occur after 20 weeks' gestation. It has been proposed that an increased ratio of soluble fms-like tyrosine kinase 1 (sFlt-1) to placental growth factor (PlGF) is diagnostic of preeclampsia and distinguishes this condition from pregnant women with CKD.[16] Although promising, incorporated this into routine clinical practice is not yet recommended.

Indications for Delivery in Women with Preeclampsia or CKD

- Inability to control blood pressure
- Deteriorating glomerular filtration rate
- Neurologic abnormalities, such as eclampsia, headaches with accompanying clonus and hyperreflexia, or repeated visual scotomata
- Worsening thrombocytopenia
- Increasing liver transaminase levels
- Failure of fetal growth
- Reversed or absent end-diastolic flow on cardiotocography

Box 45-5 Indications for delivery in women with preeclampsia or chronic kidney disease (CKD). The decision to deliver is based on a global clinical assessment rather than on specific thresholds for each parameter.

Diagnosing superimposed preeclampsia in women with CKD is somewhat unnecessary. Clinicians managing the woman with underlying renal disease should be vigilant for changes in maternal and fetal condition in all cases, and the indications for delivery in women with preeclampsia are broadly the same as those in women with progressive underlying renal disease (Box 45-5). On the other hand, it is now well recognized that preeclampsia is associated with long-term cardiovascular, metabolic, and renal risks for the mother so it is practical to error on the side of caution and "overdiagnose" this disorder because this may prompt better long-term follow-up.[17]

Limited studies suggest that aspirin is of benefit in reducing superimposed preeclampsia and perinatal death in women with underlying renal disease. A review found that the number needed to treat was 9 to 57 women for prevention of preeclampsia and 42 to 357 to prevent perinatal death.[18] The PARIS study also found that aspirin reduced superimposed preeclampsia in women with underlying renal disease, but only 450 women were included in this analysis.[19] My practice is to use low-dose aspirin (100 to 150 mg/day) for all women with CKD and creatinine greater than 1.5 mg/dl (130 µmol/l) or for those with lower creatinine who have had early-onset or severe preeclampsia or fetal loss in a previous pregnancy. The effects of this dose of aspirin on renal function are minimal, and generally this is a safe approach. I also use calcium (1200 mg/day) as prophylaxis against preeclampsia when there is no concern about hypercalcemia. Data for calcium as prophylaxis are less convincing than for aspirin, but when used carefully, calcium has minimal effects and may have benefit.

RENAL BIOPSY IN PREGNANCY

It is rare to require renal biopsy in pregnancy. After 32 weeks' gestation, if the renal state has changed so much that biopsy is considered necessary to guide treatment, it is better to deliver and manage the renal disease outside of pregnancy. Biopsy may provide information that could significantly impact on the pregnancy outcome for mother and infant in the following settings:

1. *De novo* onset of nephrotic-range proteinuria or unexplained impaired GFR with abnormal urine sediment before fetal viability (i.e., <24 weeks' gestation). Nephrotic syndrome after this stage can generally be managed conservatively until delivery, usually at about 32 weeks. Most such cases are caused by preeclampsia.
2. Situations prior to 32 weeks' gestation in which clinician and patient have agreed that immunosuppression and/or plasma exchange will be used, if necessary, while prolonging the pregnancy to about 32 weeks:
   - Rapidly declining GFR without any apparent reversible cause in women with underlying primary glomerulonephritis
   - Acute kidney injury with active urine sediment
   - Declining GFR or increasing proteinuria in a woman with lupus nephritis or lupus without previously known nephritis
3. Deteriorating GFR before 32 weeks' gestation without obvious cause in a woman with a kidney transplant, to exclude acute rejection

Complication rates of renal biopsy in pregnancy are similar to those in general nephrology practice.[20]

ASSESSMENT OF FETAL WELL-BEING

An early pregnancy ultrasound is invaluable in accurately dating the expected birth. The next usual assessment is a fetal morphology scan at 18 to 20 weeks' gestation to confirm gestational age, screen for fetal anomaly, assess fetal well-being, and check placental position. In women with CKD stage 3 to 5, this is followed by regular ultrasounds every 2 to 4 weeks to assess fetal growth and the volume of amniotic fluid, as well as Doppler studies of umbilical artery blood flow. More recently, the combination of tests at 12 weeks' gestation for pregnancy-associated plasma protein A (PAPP-A), inhibin, human chorionic gonadotropin (hCG), and α-fetoprotein, with measurement of uterine artery pulsatility index at 20 weeks' gestation has provided a good negative predictive test for fetal outcome in women with high-risk pregnancies, although these studies are not specific for women with underlying renal disease. An important caveat is that hCG levels are often elevated in women with ESRD and may overestimate the risk of a fetal abnormality when used as part of the 12-week testing.[21] It is important that women are counseled about this in advance of the testing.

Asymmetric intrauterine growth restriction (IUGR), in which abdominal measurements are more decreased than the fetal head and femur measurements, is characteristic of IUGR related to maternal CKD. Amniotic fluid volume correlates well with perinatal outcome, and a low amniotic fluid index helps distinguish babies who are small because of IUGR from those constitutionally small. Second-trimester severe oligohydramnios is associated with very poor outcome, indicating nonfunctioning fetal kidneys, and usually also leads to pulmonary hypoplasia and limb contractures. Absent end-diastolic flow on umbilical artery velocimetry is usually an indication for delivery, depending on gestational age. The development of reversed end-diastolic flow indicates a high risk of fetal hypoxia, acidosis, and death. Fetoplacental assessment by ultrasound for growth and Doppler blood flow should be carried out regularly throughout pregnancy, particularly in the third trimester.

TIMING DELIVERY

In women with stable CKD and no evidence of fetal compromise, pregnancies should be continued to term and spontaneous labor awaited. The method of delivery (vaginal or cesarean) is normally determined by other issues (e.g., previous cesarean section, poor obstetric history) rather than the presence of CKD. Box 45-5 lists the usual indications for delivery.

The goal is to time delivery such that the risks of delivery (to both mother and fetus) are less than the risks of the pregnancy continuing. This is often a difficult and individual decision requiring consultation among nephrologist or obstetric medicine physician, obstetrician, midwife, and neonatologist. The following issues need to be considered:

1. Gestational age is the most important determinant of pregnancy outcome. Decisions are difficult to make at the borderlines of viability (23 to 25 weeks' gestation). Although outcome data vary among countries, approximate survival rates increase from 30% at 23 weeks to 65% at 25 weeks to 95% at 30 weeks of gestation. Babies born at less than 30 weeks' gestation have significant risks of long-term morbidity, including chronic lung disease and cerebral palsy.
2. The most common problem faced by preterm infants is respiratory distress syndrome. Maternally administered antenatal corticosteroids, generally intramuscular betamethasone (11.4 mg, two doses 12 hours apart), have been shown to reduce respiratory distress syndrome by 50%. For best effect, the corticosteroids need to be administered at least 24 hours before delivery.
3. There is less neonatal morbidity and mortality if babies are born in hospitals where there is appropriate neonatal care rather than being transferred after delivery. Thus, if preterm delivery is likely, transfer of the mother to an appropriate unit before delivery should be considered.

Although these pregnancies are certainly high risk compared with normal pregnancy, clinicians and midwives need to remember that the final pregnancy outcome in most cases is successful for both mother and baby, but with long-term implications for both. Clinicians can take a positive approach, at all times emphasizing the need for diligence and assessment for potential complications, while highlighting that the end result in most cases will be good, in turn helping to relieve some of the stress that accompanies pregnancy for these women.

MANAGEMENT OF SPECIFIC RENAL DISORDERS DURING PREGNANCY

The most common chronic kidney diseases predating pregnancy are primary glomerulonephritis (usually IgA nephropathy or focal segmental glomerulosclerosis), diabetic nephropathy, lupus nephritis, and reflux nephropathy.

IgA Nephropathy

Long-term follow-up of childhood IgA nephropathy showed that later pregnancy was complicated by hypertension in half the cases and prematurity in one third,[22] but these outcomes are not peculiar to this renal disease. It seems unlikely that pregnancy in IgA nephropathy of itself causes accelerated renal dysfunction, at least in those with early-stage CKD (1 or 2), but proteinuria may increase in the third trimester.[23] Rare cases are familial, and the pregnant woman should be advised to have her child screened by urinalysis in the first few years of life. Macrohematuria is not more likely during pregnancy unless there is concurrent upper respiratory or gastrointestinal tract infection. IgA nephropathy should be managed as for other CKD during pregnancy.

Diabetic Nephropathy

Studies in the United Kingdom found that 8% of pregnant women with type 1 diabetes and 5% of those with type 2 diabetes had nephropathy. Diabetes increases risks for preterm birth, cesarean section, and perinatal mortality. The presence of overt nephropathy more than doubles the risk of fetal death after 20 weeks. There is an added risk for congenital abnormalities if blood sugar was not adequately controlled at conception.

The Diabetes Control and Complications Trial and EURODIAB trial both concluded that pregnancy does not increase the progression of diabetes to early diabetic nephropathy (microalbuminuria).[24,25] Microalbuminuria alone did not correlate with increased perinatal risk, but both prematurity and superimposed preeclampsia rates were higher than in type 1 diabetic patients without microalbuminuria.

The outcome of established diabetic nephropathy during pregnancy depends on the usual factors of preexisting renal impairment and control of hypertension. Meticulous control is required of blood glucose and BP during pregnancy in women with early or overt diabetic nephropathy. One study showed that failure to achieve mean arterial pressure below 100 mm Hg was associated with increased risk of early delivery, even after adjusting for glucose control.[26] Ideally, ACE inhibitors should be introduced soon after delivery for prevention of progression of diabetic nephropathy, with at least captopril being safe during breastfeeding.

Recent data suggest that having gestational diabetes mellitus (GDM) without developing overt diabetes after the pregnancy, is still associated with about a 10% risk for microalbuminuria by age 50, an intermediate risk between that of nondiabetic and diabetic women.[27] This means that women with a history of GDM, not just those with type 1 or 2 diabetes, should be followed up after pregnancy, assessing renal function and urine albumin excretion, because of their risk of developing later diabetes (see also Chapters 30 to 32).

Lupus Nephritis

Women with lupus nephritis should have quiescent disease at conception to offer the best chance of a successful pregnancy outcome. Those with active disease at conception have a higher likelihood of developing acute lupus nephritis during pregnancy, which is then associated with high fetal risk; about 20% have miscarriage, stillbirth, or neonatal death.[28] Ideally, women with lupus should be in remission for at least 6 months[29,30] before conception and receiving maintenance corticosteroids in doses less than prednisolone 20 mg/day, with or without azathioprine; all should receive aspirin and hydroxychloroquine.[29] In these women, the prior histologic class of lupus nephritis has no influence on pregnancy outcome. Predictors of poor pregnancy outcome are baseline creatinine greater than 100 µmol/l, proteinuria more than 0.5 g/24 h, antiphospholipid syndrome, and hypertension.[31]

New onset or a flare of lupus nephritis, evidenced by increasing proteinuria, active urine sediment, and rising serum creatinine, are a major concern, and some cases have been associated with maternal death. Treatment includes increasing doses of prednisolone with the early introduction of azathioprine. Some prefer to undertake renal biopsy at this point to confirm the histologic changes before introducing immunosuppression. Either approach is reasonable, but my approach is to introduce steroids and azathioprine and reserve biopsy for after delivery.

Other women with known lupus nephritis in remission before conception should continue receiving low-dose prednisolone and azathioprine throughout pregnancy and should also take low-dose aspirin.[32] Cyclophosphamide and mycophenolate mofetil are contraindicated in pregnancy because of teratogenicity, including for mycophenolate microtia, auditory canal atresia, cleft lip and palate, and micrognathia.[33] Although cyclophosphamide has been used successfully in a few patients with lupus nephritis, its use is not recommended.

Lupus nephritis may flare during pregnancy in about 30% or in about 15% postpartum,[31] but prophylactic steroid therapy is not indicated for those not experiencing a flare during pregnancy. The major cause of maternal death in lupus nephritis is sepsis, and immunosuppression should be used with care in pregnant women.[34]

When counseling about future pregnancies, women should be advised that even if their lupus nephritis has been well treated, they appear to have a greater risk of maternal complications and lupus flare in their next pregnancy than do women with SLE who have never had nephritis; this appears only partly explained by increased activity of the SLE at conception. Fortunately, fetal outcomes are not affected adversely in this group,[35] and postpartum renal function appeared unaffected.[36] This means that such women need more surveillance during pregnancy than usual, to detect a renal flare or preeclampsia, their two greatest maternal risks.

Reflux Nephropathy

The outcome of pregnancies in women with reflux nephropathy depends on the preexisting renal function and BP control rather than the disorder itself, as for other renal disorders. Approximately one in four women with reflux nephropathy develop preeclampsia, and about 40% of offspring have vesicoureteral reflux. These women are more predisposed to UTI throughout pregnancy, as are women who have had surgically corrected reflux in childhood.[37] About 20% of women with reflux nephropathy will develop UTI in pregnancy, with about 6% caused by acute pyelonephritis. UTI can be associated with premature labor or spontaneous rupture of membranes. Regular urine culture should be obtained throughout pregnancy in women with underlying reflux nephropathy.

Inherited Renal Disorders

Inherited renal disorders are likely to have been diagnosed before the pregnancy and the specific implications for the offspring discussed. The most common inherited disorder is autosomal dominant polycystic kidney disease. Others include Alport syndrome and familial hyperuricemic nephropathy, the latter having been described in one pregnancy with good renal adaptation but inheritance of the *UMOD* mutation.[38]

The pregnant woman needs to be aware that reflux nephropathy is not inherited by specific mendelian traits but tends to cosegregate within families.

Fetal renal anomalies are usually identified at routine ultrasound screening or during evaluation of a fetus from a family with a known hereditary renal disorder. Invasive procedures such as chorionic villus sampling for DNA analysis is rarely informative and should be undertaken only after advice from a clinical geneticist.

ACUTE AND RECURRENT URINARY TRACT INFECTION

The diagnosis and general management of asymptomatic bacteruria and UTI during pregnancy, including choice of antibiotic regimens, are discussed in Chapter 44.

Standard antenatal care should include culture of a midstream specimen of urine early in the pregnancy. In women with abnormal

urinary tract structure, a history of recurrent UTI, CKD, or diabetes, further regular cultures are required. Women with a history of recurrent UTI should have monthly urine cultures. For those with a predictable history of postcoital cystitis, postcoital single-dose cephalexin (250 mg) or nitrofurantoin (50 mg) can significantly reduce the likelihood of infection. For others with recurrent UTI pre-pregnancy, low-dose cephalexin (or another first-generation cephalosporin) at night may help suppress further infections. Any woman who has recurrent UTI before pregnancy should undergo ultrasound of the urinary tract before conception or in early pregnancy to exclude structural pathology.

RENAL CALCULI IN PREGNANCY

Women with a history of metabolic abnormalities causing stone formation prior to pregnancy need their treatment modified during pregnancy. I advocate adherence to a fluid intake of 2.5 to 3 liters per day and recommend that thiazides (for hypercalciuria), allopurinol (for hyperuricosuria), or captopril or penicillamine (for cystinuria) be discontinued. Fortunately, normal pregnancy is accompanied by increased urine pH, which may help reduce uric acid or cystine stone formation.

Despite relative hypercalciuria and urinary stasis in pregnancy, pregnant women may be protected against renal calculi by the simultaneous increase in endogenous inhibitors of stone formation, such as urinary thiosulfate, which parallels hypercalciuria during gestation and returns to normal postpartum.

Because of concerns about radiation from computed tomography (CT) scanning (~8 mSv) and the uncertain utility of magnetic resonance imaging (MRI) in this setting, ultrasound is the preferred investigation for renal colic in pregnancy, despite its poor sensitivity and specificity for stone diagnosis (30% to 60%). Abdominal radiography provides radiation of about 1.5 mSv.

Definitive management of a calculus is usually best left until after delivery. Because ultrasound will almost always show pelviureteral dilation, which is a feature of normal pregnancy, systemic infection or acute kidney injury are the only indications for urgent decompression of an obstructed system by percutaneous nephrostomy. Conservative therapy with analgesia and hydration will result in spontaneous passage of a stone in the majority of cases. Extracorporeal shock wave lithotripsy is contraindicated because it can be deleterious to fetal hearing. If a surgical procedure is necessary, ureteroscopy with yttrium-aluminum-garnet (YAG) laser lithotripsy has been used and is considered relatively safe in pregnancy.

Perhaps the most important recent finding is that women with renal calculi in pregnancy are more likely to be obese and have higher rates of preeclampsia (also related to obesity), GDM, and recurrent miscarriage. Overall, however, fetal outcomes remain good, with no increase in prematurity or perinatal mortality.[39] Thus, the treatment of women with renal calculi in pregnancy should be expanded to include not only the specific treatment of the calculus disorder, but also increased surveillance for preeclampsia and GDM.

DIALYSIS IN PREGNANCY

There has been significant improvement in the outcome of pregnant women with renal disease requiring dialysis during pregnancy over the past two decades, as well as a reduction in therapeutic terminations, as clinicians and pregnant women come to understand that these pregnancies can have a successful outcome.[21] An analysis of 52 pregnant women, about half starting dialysis after conception and most receiving aspirin and calcium as preeclampsia prophylaxis, demonstrated extremely good outcomes with 85% fetal survival; the development of preeclampsia was the major issue that affected the outcome of these pregnancies. Dialysis included short, daily dialysis, although the dialysis prescription was increased from baseline in all women, accounting for residual function in dialysis of those starting after conception. Not all reports have such good outcomes, but such pregnancies (mostly in women already receiving dialysis) now have one-half to two-thirds chance of fetal survival,[40] although with about 80% chance of prematurity.[41] These improved outcomes have been associated with more intensive dialysis regimens, and advances in neonatal care also allow survival for more premature and growth-restricted infants. Table 45-1 provides recommendations for managing hemodialysis during pregnancy.

Managing Hemodialysis During Pregnancy

Pre-pregnancy	
Discuss risks of pregnancy (miscarriage, fetal death, fetal growth restriction, prematurity, preeclampsia). Ensure all medications safe in pregnancy. Aspirin: 75-150 mg daily Folic acid: 5 mg daily	
During Pregnancy:	
Dialysis	20 h/wk in four or more sessions Aim for predialysis BUN >40 mg/dl (serum urea 15 mmol/l). Heparin requirement may increase because of hypercoagulability of pregnancy.
Anemia	Intravenous iron to maintain iron stores Dose ESA to achieve hemoglobin of 10-11 g/dl.
Bicarbonate	Adjust oral and dialysate bicarbonate to achieve normal serum bicarbonate for pregnancy (18-22 mmol/l).
Nutrition	Dietician advice to ensure adequate protein and nutrient intake Supplement oral or dialysate phosphate to maintain post-dialysis serum phosphate in normal range.
Calcium	Maintain normal serum calcium with additional oral calcium and vitamin D, as well as increased dialysate calcium. Hypercalcemia occasionally provoked by placental PTHrP and vitamin D–like substances.
Phosphate	Supplement oral or dialysate phosphate to maintain postdialysis serum phosphate in normal range.
After Pregnancy	
Return to usual dialysis schedule immediately. Readjust dry weight and antihypertensives weekly for 6 weeks.	

Table 45-1 Managing hemodialysis during pregnancy. *ACE,* Angiotensin-converting enzyme; *ARBs,* angiotensin receptor blockers; *BUN,* blood urea nitrogen; *ESA,* erythropoiesis-stimulating agent; *PTHrP,* parathyroid hormone–related peptide.

Initiating Dialysis for Progressive Chronic Kidney Disease

A key question is when to initiate dialysis in women who have advanced CKD but are not yet receiving dialysis at the time of conception. It is generally recommended to commence dialysis at eGFR below 20 ml/min or BUN 50 mg/dl (serum urea >17 mmol/l) and aim for predialysis blood urea below 15 mmol/l (BUN 45 mg/dl).[42,43] The available data suggest that dialysis initiated during pregnancy is

associated with greater likelihood of successful pregnancy than with continuation of maintenance dialysis, probably because of the benefits of residual renal function.

Women Already Needing Regular Dialysis

Women of childbearing age undergoing dialysis have about a 1 in 20 chance of conceiving throughout their dialysis therapy.[44] Women of childbearing age receiving maintenance dialysis therefore need to be counseled about adequate contraception, particularly in view of the fairly poor outcomes of these pregnancies.

Dialysis Regimens in Pregnancy

Reports of successful pregnancy outcomes, although with high rates of preterm delivery and polyhydramnios, generally include intensified hemodialysis or peritoneal dialysis schedules. Daily hemodialysis may be necessary to achieve the biochemical goal of predialysis BUN of 15 mmol/l or less. Nocturnal hemodialysis may allow improved dialysis clearances with greater hemodynamic stability, improved fertility rates,[21] and good pregnancy outcomes in early reports.[45]

More intensive dialysis improves phosphate control. Phosphate binders become unnecessary, and additional oral phosphate or increased dialysate phosphate may be needed because of the intensified dialysis and the fetal requirements for phosphate.

Minimal data exist on specific requirements of women receiving peritoneal dialysis (PD) during pregnancy. There is no need to switch from PD to hemodialysis, even as the uterus enlarges. Dialysis adequacy can be maintained throughout pregnancy, although a major risk is that PD peritonitis may provoke premature labor or premature rupture of membranes. Other management necessary for a successful pregnancy outcome includes the following:

- Control of maternal BP, generally to 110 to 140/80 to 90 mm Hg. This is difficult to achieve in many women. First, despite little or no endogenous renal function, there still appears to be volume expansion in women on maintenance hemodialysis who become pregnant, as evidenced by anemia and fall in serum albumin. To date, no data recommend assessing volume status in dialysis patients during pregnancy by measurements such as ultrasound of inferior vena cava diameter or bioimpedance.
- Active management of anemia with iron and erythropoiesis-stimulating agents. Target hemoglobin value should be 10 to 11 g/dl.
- Detection and early treatment of sepsis, which may precipitate premature labor or premature rupture of membranes. For those with residual renal function, repeated urine cultures are required to detect and treat asymptomatic bacteriuria.

At least weekly surveillance of pregnant women receiving dialysis is required to optimize outcome. Dialysis intensity should be increased as much as practically possible, ensuring the biochemical goals are achieved. Fetal monitoring should include at least ultrasound scans every 2 to 4 weeks from the time of fetal viability, about 24 weeks' gestation.

RENAL TRANSPLANTATION AND PREGNANCY

Successful renal transplantation is an excellent way of restoring fertility in women with ESRD. It is therefore surprising that the pregnancy rate among female transplant recipients decreased by more than 50% between 1990 and 2003, unexplained by a change in age of women receiving transplant.[46] Women with transplants appear more likely to conceive if they are not diabetic or they have been receiving dialysis 3 or more years before transplant.

The key questions in relation to managing women with a renal transplant in pregnancy are whether the pregnancy will affect graft survival and whether fetal side effects will result from the transplant or the immunosuppressive drugs. Women should be advised to wait 12 months after a successful renal transplant before planning pregnancy, to ensure stable transplant function and maintenance immunosuppression. This interval is not based on solid data; indeed, one small study suggested that pregnancies even within 12 months of transplantation are as successful as those performed later.[47] One year seems a practical time for ensuring clinical stability, with optimal BP control and stable immunosuppression.

Immunosuppressive drugs considered safe in the transplant patient include prednisolone, azathioprine, and cyclosporine. Tacrolimus has been associated with neonatal hyperkalemia, but recent data support its safety. Mycophenolate is associated with embryotoxic effects and should be avoided in pregnancy, as should sirolimus.

A favorable view of pregnancy in women who have undergone successful renal transplantation was supported early on by observations in more than 3000 pregnancies from 2000 women mostly receiving azathioprine and prednisone.[48] About 15% of these pregnancies miscarried spontaneously, and of those continuing past the first trimester, pregnancy was successful in more than 90% of women, provided that hypertension or a decline in renal function had not occurred before 28 weeks' gestation, in which case successful pregnancy outcome was reduced to about 70%. Women with preconception serum creatinine less than 125 µmol/l had 96% pregnancy success, whereas those with higher serum creatinine had a 75% success rate. In keeping with the data for all women with CKD, long-term decline in renal function occurred significantly more often (27%) in those with preconception serum creatinine more than 125 µmol/l.

Hypertension, either accelerated from preexisting hypertension or *de novo* during pregnancy, is present in 58% to 72% of pregnant women. Even with these relatively good outcomes, 30% to 70% of women will have hypertension requiring treatment as the pregnancy progresses, sometimes with superimposed preeclampsia. Fetal growth restriction occurs in 40% to 50% and preterm delivery in as many as two thirds, with attendant long-term risks of prematurity.[49] Cesarean birth is necessary in approximately half of these women.

The United States National Transplantation Pregnancy Registry (NTPR) reported in 2008 on the outcomes of 1208 pregnancies from 781 women who had received kidney alone transplants.[50] This is a voluntary registry, so there is potential for reporting bias. The majority of women were taking cyclosporine or tacrolimus. The mean preconception serum creatinine level was 125 µmol/l. Overall live birth rates were about 75%, 30% had preeclampsia, and babies of these women were smaller, although mean birth weight was about 2500 g. Acute rejection occurred in 2% to 4% of pregnancies, and 5% of infants had a birth defect, comparable to that of the general population. Graft loss within 2 years ranged from 4% to 13%, and 20% to 30% of women had one or more of the following complications: death within 5 years of pregnancy, acute rejection during pregnancy or within 3 months postpartum, loss of graft function within 2 years postpartum, infant with a birth defect, or delivery very preterm (<33 weeks) or of very low birth weight (<1500 g). Box 45-6 summarizes maternal and fetal risks for pregnancy in women with a renal transplant.

There were higher risks in a study of 530 pregnancies in 483 women using U.S. Renal Data System (USRDS) Medicare data.[46]

Maternal and Fetal Outcomes in Renal Transplant Pregnancies

Maternal

- Long-term decline in glomerular filtration rate if preconception serum creatinine <1.4 mg/dl (125 μmol/l); rate of decline is not usually different from transplant women without pregnancy
- Graft loss in 5%-10% at 2 years postpartum
- Hypertension in about two thirds
- Rejection risk in 2%-4%
- Infection in 20%-35%
- Gestational diabetes mellitus in 10%

Fetal

- Overall live birth rate: 75%-80%
- Spontaneous miscarriage: 15%
- Prematurity: 50%
- Fetal growth restriction: 50%
- Birth defects in about 5%, probably no more than in the general population
- Long-term consequences of prematurity, although most infants have normal postnatal growth and development

Box 45-6 Maternal and fetal outcomes in renal transplant pregnancies.

Fetal loss was 45%, with spontaneous abortion rates between 20% and 35% and a stillbirth rate of 1.5%, higher rates than observed in UK or Australian analyses.[51,52] Overall, it seems that there is a high risk of miscarriage, but once past the first trimester, the pregnancy outcomes are quite good. Graft and patient survival are similar in those with and without any pregnancy over follow-up as long as 15 to 20 years, as observed with 577 pregnant women in the Australian and New Zealand data registry, most of whom had glomerulonephritis or reflux nephropathy as their primary diagnosis.[52]

An increase in serum creatinine after pregnancy has been associated with cyclosporine use, possibly because cyclosporine doses were increased during pregnancy as blood levels fell, presumably from the plasma volume expansion of pregnancy. However, it remains controversial whether cyclosporine or tacrolimus doses should be increased during pregnancy. It is not my practice to make dose adjustments unless there are marked deviations from the baseline blood level during pregnancy.

Acute transplant rejection is uncommon, reported in less than 1 in 20 cases. Presentation as acute graft dysfunction is no different in pregnancy; renal biopsy is required to confirm the diagnosis. There is an increased risk of infection (20% to 35%), particularly UTI but also cytomegalovirus infection, with attendant maternal and fetal risks. The consequences of any infection can include premature labor and preterm rupture of membranes. GDM occurs in 3% to 12% of these pregnancies, no more common in tacrolimus-treated women than in those receiving cyclosporine.

Recommendations remain uncertain regarding breastfeeding for women taking immunosuppressive agents. The decision to breastfeed must be an individual one, informing the woman that effects on the baby remain largely unknown but that breastfeeding may have considerable advantages, particularly in premature and growth-restricted babies. Box 45-7 summarizes recommendations for management of pregnancy in women with a renal transplant.

Outcomes of pregnancies fathered by male transplant recipients showed mean gestational age and mean birth weight similar to those of the general population.

General Management of Renal Transplant Patients During Pregnancy

Pre-pregnancy

- Stable graft function at least 1 year after transplantation.
- Discuss risks with transplant recipient and her partner.
- Best pregnancy outcome will occur if:
  - Pre-pregnancy serum creatinine <1 mg/dl (125 μmol/l)
  - Proteinuria <500 mg/day
  - Blood pressure <140/90 mm Hg
- Aspirin (75-150 mg/day) if creatinine ≥1.5 mg/dl (130 μmol/l) *or* 0.9-1.5 mg/dl (100-130 μmol/l) and proteinuria >1 g/day.
- Replace all medications that are not safe in pregnancy.
- Eradicate UTI before pregnancy; prophylactic antibiotics indicated if there has been recurrent UTI since transplant.
- Stable cyclosporine or tacrolimus blood levels.
- Test for and control diabetes.

During Pregnancy

- Visits every 2 weeks until 24 weeks' gestation (alternating between obstetrician and nephrologist), then weekly.
- Assess fetal growth by ultrasound at least every 4 weeks from 24 weeks' gestation.
- Do not adjust CNI dose during pregnancy unless there are extreme variations from stable pre-pregnancy levels.
- Screen for gestational diabetes at 28 weeks' gestation with 1-hour 50-g glucose challenge test.
- At each visit, assess BP (goal 110-140/80-90 mm Hg), proteinuria (dipstick, then PC ratio if dipstick result is positive), urine culture (if history of recurrent UTI, otherwise at 24, 28, and 32 weeks of gestation), electrolytes, creatinine, full blood count, CNI level, and fetal growth.
- Reassess at each visit whether there is an impending indication for delivery (see Box 45-5).

During Delivery

- Vaginal delivery is usually possible despite pelvic kidney.
- Prophylactic antibiotics are not required routinely.

Postpartum

- Monitor CNI and serum creatinine levels daily in hospital.
- Breastfeeding appears safe with CNI drugs, azathioprine, and corticosteroids, but discuss individual case with neonatologist.
- Review weekly or every other week for the first 3 months.

Box 45-7 General management of renal transplant recipients during pregnancy. *ACE,* Angiotensin-converting enzyme; *BP,* blood pressure; *CNI,* calcineurin inhibitor; *PC ratio,* protein-creatinine ratio; *UTI,* urinary tract infection.

PREGNANCY IN THE KIDNEY DONOR

It is usually stated that being a kidney donor does not adversely affect future pregnancy outcomes in terms of fetal birth weight, stillbirth, or prematurity. However, recent studies suggest there may be an increased risk of preeclampsia in pregnancy after organ donation,[53] and that fetal outcomes may also be slightly worse.[54,55] These studies have some limitations, and pregnancy should not be discouraged in women who have been kidney donors. Rather, the key message is that all such women should be treated as "at-risk" pregnancies and should have a higher number of clinical reviews, focusing on maternal BP and urinalysis and fetal growth, than in normal, low-risk pregnancies.

COURSE OF CHRONIC KIDNEY DISEASE AFTER PREGNANCY

In a review of 49 women with stage 3 to 5 CKD before conception and whose pregnancy proceeded beyond 20 weeks, GFR was lower after pregnancy than before conception. This decrease was predicted by the combination of preconception GFR less than 40 ml/min and proteinuria more than 1 g/day, but not by GFR alone.[1]

The course of renal disease postpartum is unpredictable. Even some women with stable renal function throughout their pregnancy develop an acute deterioration postpartum. About 50% of women with moderate renal impairment (serum creatinine >1.5 mg/dl; 130 µmol/l) have a significant rise in serum creatinine in the third trimester or early postpartum, and if this occurs, almost one in five progress to ESRD within 6 months after delivery. Surveillance by the nephrologist therefore needs be just as diligent in the first 3 to 6 months postpartum as during pregnancy. ACE inhibitors or ARBs should be commenced soon after delivery for their antiproteinuric effect if GFR is stable.

Women with biopsy-proven kidney disease in Norway had slightly faster progression to ESRD if they were delivered preterm, but not if they had preeclampsia.[56] A neglected issue is the association between preterm birth/low birth weight and cardiovascular/renal disease later in life.[57] Many women with CKD are delivered prematurely, which in turn passes on risks of later renal disease to their offspring even if the renal disease is not hereditary. On balance, it is prudent to consider both preeclampsia and preterm delivery as risk factors for later kidney disease.

SUMMARY

Box 45-8 summarizes factors to consider in managing a pregnant woman with renal disease. Attention to these issues, from preconception through postpartum, can result in good pregnancy outcomes with preservation of maternal health. These women and often their offspring require lifelong assessment for progressive renal and cardiovascular disease.

Managing Women with Preexisting Renal Disease During Pregnancy

1. Women with chronic kidney disease should be managed by a team comprising obstetrician, nephrologist, and experienced midwife, preferable in a high-risk pregnancy clinic
2. Main determinants of pregnancy outcome are pre-pregnancy GFR, proteinuria, and blood pressure. These should be the focus in counseling
3. GFR should be estimated using serum creatinine and proteinuria using changes in spot urine PC ratio after calculation of initial ratio on 24-hour urine collection
4. Low-dose aspirin should be given to reduce risk of preeclampsia or perinatal death. Subcutaneous heparin if nephrotic syndrome develops
5. Primary issues during pregnancy are control of blood pressure, watching for emerging preeclampsia, and regular assessment of fetal well-being
6. An appropriate schedule of visits is every 2 weeks until 24 weeks' gestation (alternating between obstetrician and nephrologist) then weekly until delivery
7. Appropriate laboratory evaluations are:
   - Initial visit at 12 weeks' gestation: full blood count, serum creatinine and electrolytes, liver function, 24-hour urine PC ratio if proteinuria on dipstick testing
   - If baseline GFR normal, repeat at 24 weeks' gestation
   - If baseline GFR abnormal, repeat every 4 weeks
   - Midstream urine culture at 24, 28, and 32-34 weeks' gestation (monthly throughout pregnancy if woman has history of UTI)
8. Fetal assessment by ultrasound, in those with impaired GFR, or with heavy proteinuria
   - At 20 weeks: uterine artery pulsatility index b
   - Monthly from 24 weeks: fetal growth, blood flow, amniotic fluid index
9. Obstetric review at 6 weeks' postpartum, nephrology review within the first 4 weeks because impairment of renal function can occur after delivery. Transplant patients should be seen more often

Box 45-8 Managing Women with preexisting renal disease during pregnancy. *GFR*, Glomerular filtration rate; *PC ratio*, protein-creatinine ratio.

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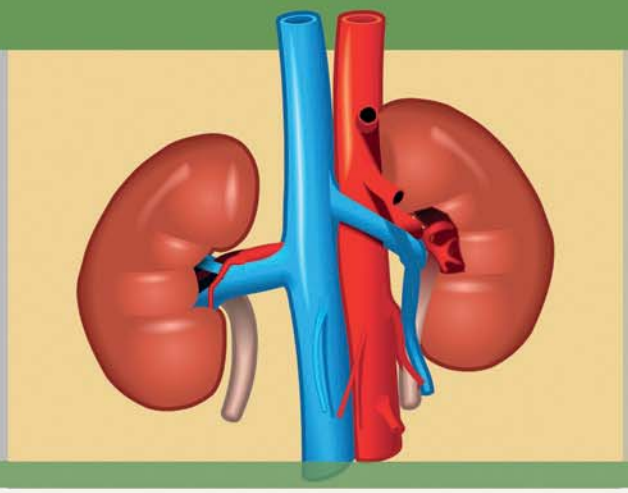

SECTION VIII

Hereditary and Congenital Diseases of the Kidney

CHAPTER 46

Autosomal Dominant Polycystic Kidney Disease

Vicente E. Torres and Peter C. Harris

DEFINITION

Autosomal dominant polycystic kidney disease is a multisystem disorder characterized by multiple, bilateral renal cysts associated with cysts in other organs, such as liver, pancreas, and arachnoid membranes.[1] It is a genetic disorder caused by mutations in one of two different genes and is expressed in an autosomal dominant pattern, with variable expression. Although benign renal cysts are common, multiple bilateral cysts are not. Therefore, an underlying inherited disease should be considered in patients with normal renal function and multiple bilateral renal cysts.

ETIOLOGY AND PATHOGENESIS

The autosomal dominant polycystic kidney disease (ADPKD) proteins now known as polycystin-1 and polycystin-2 play a critical role in the normal function of the primary cilium that is essential to maintaining the differentiated phenotype of tubular epithelium.[2,3]

Genetic Mechanisms

Autosomal dominant polycystic kidney disease (ADPKD) is genetically heterogeneous with two genes identified (Fig. 46-1), *PKD1* (chromosome 16p13.3) and *PKD2* (4q21). Autosomal dominant polycystic liver disease (ADPLD) also exists as an independent entity and is genetically heterogeneous; the first two genes identified (*PRKCSH* in chromosome 19 and *SEC63* in chromosome 6) account for about one third of isolated ADPLD cases.

Evidence from animal models of ADPKD and analysis of cystic epithelia have shown that renal cysts may develop from loss of functional polycystin with somatic inactivation of the normal allele. However, cysts can develop even if the protein is not completely lost, as demonstrated by animal models expressing incompletely penetrant alleles.[4] Furthermore, transgenic rodents overexpressing *Pkd1* or *Pkd2* develop renal cystic disease, which suggests that multiple genetic mechanisms causing an imbalance in expression of polycystins can lead to the development of cysts.[2,3]

Polycystic Kidney Disease Proteins

Polycystin-1 (PC1) and polycystin-2 (PC2) belong to a subfamily of transient receptor potential (TRP) channels. PC1 (TRPP1; ~460 kd) has the structure of a receptor or adhesion molecule and contains a large extracellular N region, 11 transmembrane regions, and a short intracellular C region (Fig. 46-1). PC1 interacts with PC2 through a coiled-coil domain in the C-terminal portion and with multiple other proteins at different extracellular and intracellular sites. PC1 is found in the primary cilia, cytoplasmic vesicles, plasma membrane at focal adhesions, desmosomes, adherens junctions, and possibly endoplasmic reticulum and nuclei. PC1 may regulate the mechanical strength of adhesion between cells by controlling the formation of stabilized, actin-associated adherens junctions. PC2 (TRPP2; ~110 kd) contains a short N-terminal cytoplasmic region, six transmembrane domains, and a short C-terminal portion. PC2 is localized predominantly to the endoplasmic reticulum but also to the plasma membrane, primary cilium, centrosome, and mitotic spindles in dividing cells.[2,3] PC1 and PC2 are also found at high concentrations in exosomes, which are shed into the urine and physically interact with primary cilia, possibly exerting a urocrine function of cell-cell communication.[5]

Mechanisms of Cyst Formation

Experimental data indicate that the timing of ciliary loss or *Pkd1* inactivation determines the rate of development of cystic disease. Inactivation in the developing kidney results in rapid progression.[6] Cysts also develop rapidly in the corticomedullary region (pars recta and thick ascending limbs of Henle loop) of adult mouse kidneys subjected to ischemic injury to stimulate cell proliferation.[7]

The polycystins are involved in the detection of extracellular cues at primary cilia, cell-cell contacts, and cell-matrix contacts and are essential to maintain the differentiated phenotype of the tubular epithelium. Reduction in one of the polycystins below a critical threshold results in inability to maintain planar polarity, increased rates of proliferation and apoptosis, expression of a secretory phenotype, and remodeling of the extracellular matrix.[2,3] PC1 and PC2 in the primary cilium are required for a calcium transient in response to ciliary bending.[8] PC2 is a TRP channel (TRPP2), and functions as a calcium release channel in the endoplasmic reticulum.[9] PC1 interacts with and modulates the function of PC2. PC1 and PC2 also interact with additional calcium channel proteins. Precisely how intracellular calcium homeostasis is altered in ADPKD remains uncertain, but many studies show reduced resting intracellular calcium, endoplasmic reticulum calcium stores, and store-operated calcium entry in primary cell cultures or microdissected samples from human and rodent polycystic tissues[2-3] (Fig. 46-2).

A common finding in animal models of PKD is increased levels of cyclic adenosine monophosphate (cAMP), not only in the kidney but also in the liver and vascular smooth muscle.[10] Tissue levels of cAMP are determined by the activities of membrane-bound and soluble adenylyl cyclases (ACs) and cAMP phosphodiesterases (PDEs), themselves subject to complex regulatory mechanisms. Reduced intracellular calcium in PKD may activate calcium inhibitable AC6, directly inhibit calcium/calmodulin-dependent PDE1, and indirectly inhibit cGMP inhibitable PDE3, therefore accounting for the accumulation of cAMP and activation of protein kinase A (PKA),

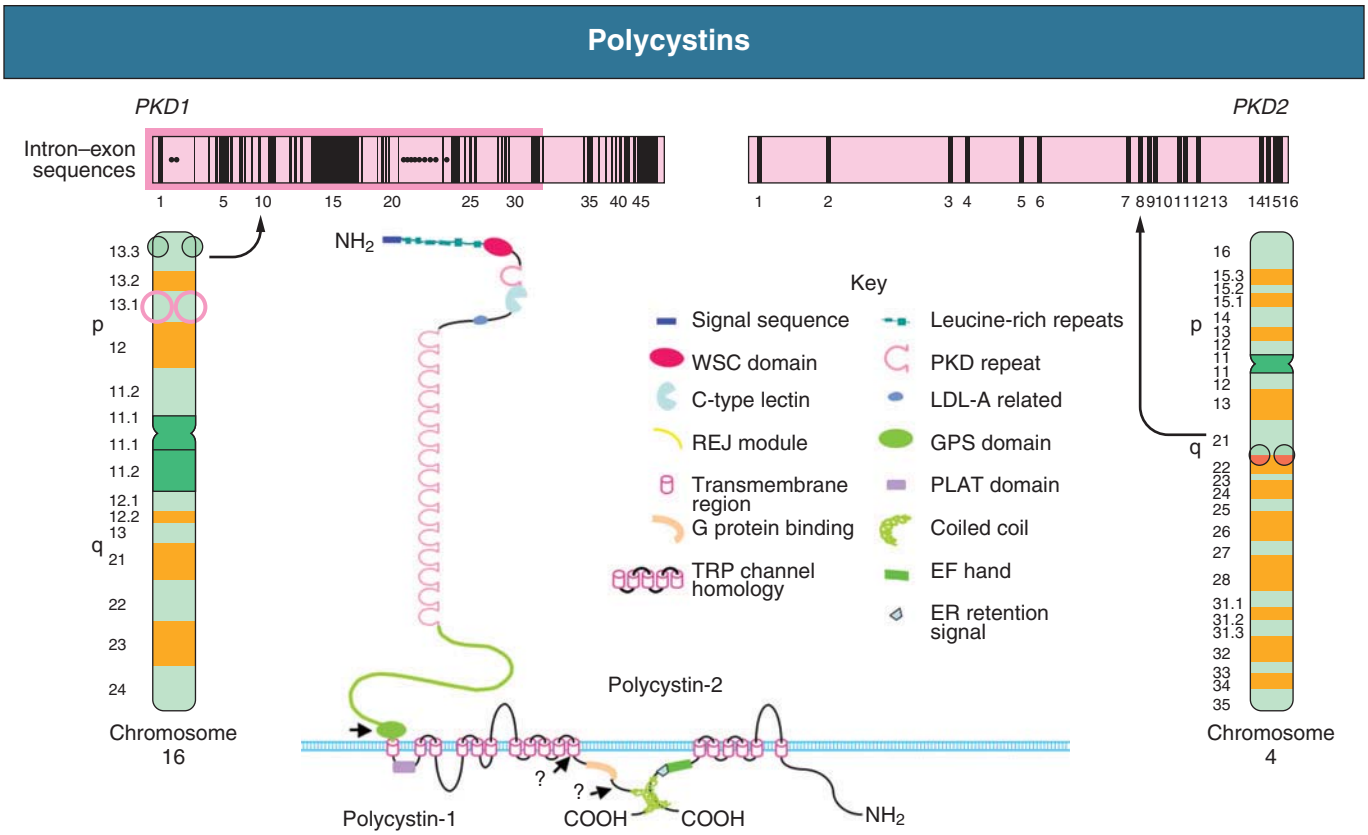

Figure 46-1 Polycystins: genes, messenger RNAs, and proteins. Diagrammatic representation of chromosome 16 *(left)* and chromosome 4 *(right)*. Intron-exon sequences of *PKD1 (upper left)* and *PKD2 (upper right)*. Diagram of proposed structural features of the polycystin-1 and polycystin-2 proteins *(center)*.

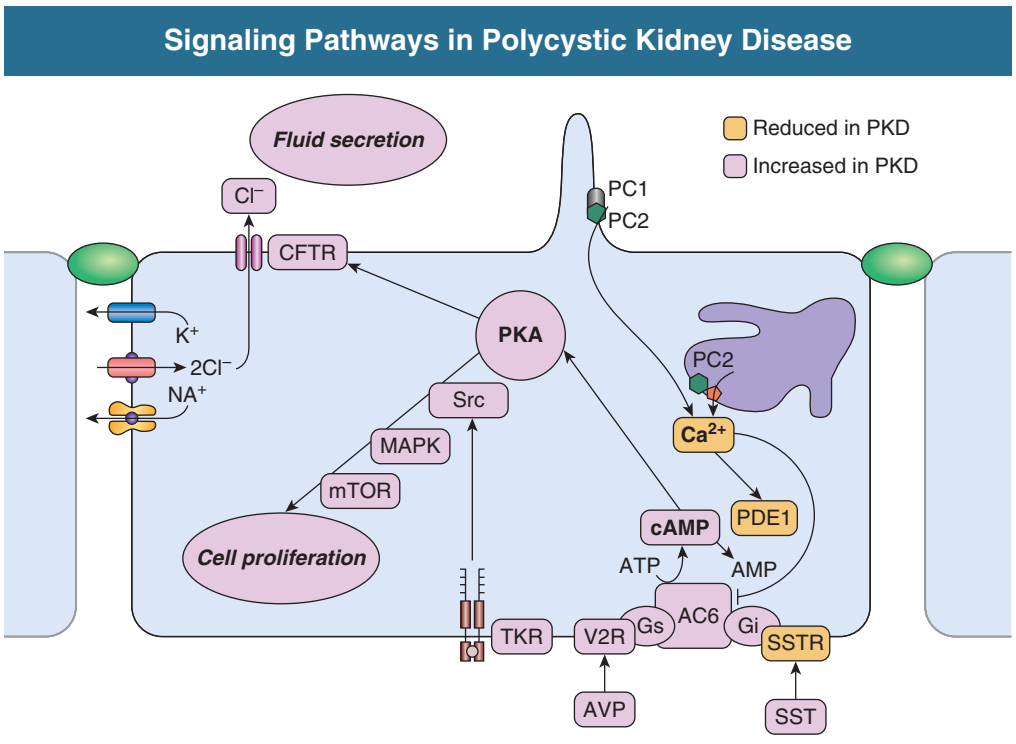

Figure 46-2 Signaling pathways in polycystic kidney disease (PKD). Pathways that are upregulated or downregulated in polycystic kidney disease and rationale for potential therapies. Dysregulation of intracellular calcium homeostasis leads to intracellular accumulation of cyclic adenosine monophosphate *(cAMP)*, activation of protein kinase A *(PKA)*, cystic fibrosis transmembrane conductance regulator *(CFTR)* phosphorylation, and stimulation of chloride-driven fluid secretion. In the setting of reduced intracellular calcium, PKA activates Src, mitogen-activated protein kinase *(MAPK)*/extracellular signal–regulated kinase (ERK), and mammalian target of rapamycin *(mTOR)* signaling. Activation of tyrosine kinase receptors *(TKR)* for several growth factors contributes to the activation of Src and downstream pro-proliferative pathways. Therapies currently under clinical investigation target G protein–coupled receptors (modulating activity of adenylyl cyclase 6 *[AC6]* and generation of cAMP), Src, mTOR, and TKRs. *AVP,* Arginine vasopressin; *PDE1*, phosphodiesterase-1; *SST,* somatostatin; *SSTR,* somatostatin receptor.

which in turn contributes to the development and progression of PKD by stimulating CFTR-driven chloride and fluid secretion and cell proliferation (Fig. 46-2).

Chloride enters across basolateral Na-K-2Cl cotransporters, driven by the sodium gradient generated by basolateral Na^+,K^+-ATPase, and exits across apical PKA–stimulated cystic fibrosis transmembrane conductance regulator (CFTR). Basolateral recycling of potassium occurs through the KCa3.1 channel.

Cyclic AMP exerts opposite effects on cell proliferation in different cell types. Cyclic AMP and PKA signaling enhance several pro-proliferative pathways (extracellular signal–regulated kinase, ERK) in cells derived from polycystic kidneys, while inhibiting proliferation in cells derived from normal human kidney cortex.[11,12] Treatment of normal human kidney or murine collecting duct cells with calcium channel blockers replicates the proliferative response of the ADPKD cells to cAMP, thus linking this response to the reduction in intracellular calcium that results from disrupting the polycystin pathway.[13] Conversely, treatment of ADPKD cyst derived cells with calcium channel activators or calcium ionophores restores the normal antimitogenic response to cAMP (Fig. 46-2). Activation of mTOR signaling downstream from PKA through ERK-mediated phosphorylation of tuberin has been linked to transcriptional activation of aerobic glycolysis, increased levels of adenosine triphosphate (ATP), and, together with ERK-dependent inhibition of liver kinase B1 (LKB1) and inhibition of AMP kinase (AMPK).[14-16]

Liver Cyst Development

Liver cysts arise by excessive proliferation and dilation of biliary ductules and peribiliary glands. Estrogen receptors, insulin-like growth factor 1 (IGF-1), IGF-1 receptors, and growth hormone receptor are expressed in the epithelium lining the hepatic cysts, and estrogens and IGF-1 stimulate hepatic cyst–derived cell proliferation.[17] Cyst growth is also promoted by growth factors and cytokines secreted into the cyst fluid.

Hypertension

Hypertension is a major clinical manifestation and predictor of outcome in ADPKD (see Clinical Manifestations). Several factors contribute to the development of hypertension in ADPKD. Activation of the intrarenal renin-angiotensin system (RAS) likely plays an important role, but controversy surrounds whether the circulating RAS is inappropriately activated.[18] The expression of PC1 and PC2 in vascular smooth muscle and endothelium, along with enhanced vascular smooth muscle contractility and impaired endothelium-dependent vasorelaxation in ADPKD, suggest that disruption of polycystin function directly contributes to hypertension. Other factors include increased sympathetic nerve activity and plasma endothelin-1 levels and insulin resistance.[19]

Endothelial vasodilation and constitutive nitric oxide synthase (NOS) activity are reduced in subcutaneous resistance vessels from patients with ADPKD and normal glomerular filtration rate (GFR). Flow-induced vasodilation of the brachial artery is inconsistently impaired, whereas pulse wave reflection is amplified, suggesting a predominant involvement of small resistance vessels. Reduced coronary flow velocity reserve and increased carotid intima-media thickness in normotensive patients with normal GFR suggest that atherosclerosis starts early in the course of ADPKD.[20]

Reduced nitric oxide (NO) endothelium-dependent vasorelaxation in ADPKD may be caused by increased plasma levels of asymmetric dimethylarginine, a mechanism common to all hypertension associated with kidney disease (see Chapter 82).

EPIDEMIOLOGY

Autosomal dominant PKD occurs worldwide and in all races, with a prevalence of genetically affected individuals at birth estimated at 1:400 to 1:1000.[1] In most patients, however, the diagnosis is made decades later, and some patients are never diagnosed. Therefore, at any point in time, only a fraction of genetically affected individuals are aware of having the disease. The percentage of end-stage renal disease (ESRD) caused by ADPKD is less among African Americans than among Caucasians because of a higher incidence of other causes of ESRD. Yearly incidence rates for ESRD caused by ADPKD in men and women, respectively, are 8.7 and 6.9 per 1 million (1998 to 2001, United States), 7.8 and 6.0 per million (1998 and 1999, Europe), and 5.6 and 4.0 per million (1999 and 2000, Japan). Age-adjusted gender ratios greater than unity (1.2 to 1.3) suggest more progressive disease in men than in women. In recent studies, the age of patients with ESRD has increased in both genders; the age-adjusted male-female ratio for onset of ESRD has trended toward unity; and all-cause mortality has decreased, possibly because of improved detection and control of hypertension.[21,22]

PHENOTYPIC VARIABILITY

Genic, allelic, and gene-modifier effects contribute to the high phenotypic variability of ADPKD. *PKD1*-associated disease is more severe than *PKD2*-associated disease (age at ESRD, 54 years vs. 74 years for *PKD1* and *PKD2,* respectively). The greater severity of *PKD1* is caused by development of more cysts at an early age, not faster cyst growth.[23] Both *PKD1* and *PKD2* can be associated with severe polycystic liver disease and vascular abnormalities. Because of the lesser severity of the renal involvement, the prevalence of *PKD2*-associated disease has likely been underestimated in clinical studies.

Mutations in *PKD1* and *PKD2* are highly variable and usually "private" (unique to a kindred). The ADPKD Mutation Database (http://pkdb.mayo.edu) lists 868 truncating *PKD1* mutations identified in 1243 families with a total of 2322 variants, including missense mutations and silent polymorphisms. Also, 162 *PKD2* truncating mutations are listed in 278 families, with a total of 374 different variants.

Allelic factors (mutation type or location) have an effect on the severity of ADPKD. Patients with mutations in the 5′ region of *PKD1* were found to have more severe disease than patients with 3′ mutations. More recent studies in larger cohorts have shown that the type of *PKD1* mutation, but not its position, correlates strongly with renal survival. The median age at onset of ESRD was 55 years for carriers of a truncating mutation and 67 years for carriers of a nontruncating mutation.[24] Hypomorphic or incompletely penetrant *PKD1* or *PKD2* alleles have been described.[25] These alleles alone may result in mild cystic disease; two such alleles cause typical to severe disease and in combination with an inactivating allele, may be associated with early-onset disease that mimics ARPKD.[26]

The large intrafamilial variability of ADPKD highlights a role for genetic background in disease presentation. Age at clinical manifestations in ADPKD is less variable within than between families, which suggests a common familial modifying background for early and severe disease expression (e.g., mutations or variants in genes encoding other cystoproteins). The contiguous deletion of the adjacent *PKD1* and *TSC2* is characterized by childhood PKD with additional clinical signs of tuberous sclerosis complex. Other modifying loci are likely to account for more common and subtle intrafamilial variability.

DIAGNOSIS

Only individuals who have been properly informed about the advantages and disadvantages of screening should be offered presymptomatic screening. If ADPKD is diagnosed, the patient should receive appropriate genetic counseling, and risk factors such as hypertension can be identified and treated early. If ADPKD is absent, the patient can be reassured. Disadvantages of presymptomatic screening relate to insurability and employability. Presymptomatic screening of children is not recommended, but this advice will likely change when more effective therapy for the disease becomes available.

Renal Ultrasound

Renal ultrasound is used for presymptomatic testing because of cost and safety. Revised criteria have been proposed to improve the diagnostic performance of ultrasound in ADPKD (Table 46-1). At least three (unilateral or bilateral) renal cysts and two cysts in each kidney are sufficient for diagnosis of at-risk individuals age 15 to 39 and 40 to 59 years, respectively.[27] For at-risk individuals age 60 and older, four or more cysts in each kidney are required.

Whereas the overall specificity and positive predictive value (PPV) of ultrasound are high by use of these criteria, their sensitivity and negative predictive value (NPV) when applied to *PKD2* patients age 15 to 59 are low. This is a problem in the evaluation of potential kidney donors, in which exclusion of the diagnosis is important.[17] Different criteria have therefore been proposed to exclude a diagnosis of ADPKD in an individual at risk from a family with an unknown genotype. An ultrasound finding of normal kidneys or one renal cyst in an individual age 40 or older has an NPV of 100%. The absence of any renal cyst provides near certainty that ADPKD is absent in at-risk individuals age 30 to 39, with a false-negative rate of 0.7% and NPV of 98.7%. A normal or indeterminate ultrasound scan does not exclude ADPKD with certainty in an at-risk individual younger than 30; normal magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CT) provides further assurance, but data are insufficient to quantify its predictive accuracy.

Ultrasound Criteria for the Diagnosis of ADPKD

Age (years)	Criteria	PPV	NPV
Original Ravine's PKD1 Diagnostic Criteria			
15-29	≥2 cysts, unilateral or bilateral	99	88
30-39	≥2 cysts in each kidney	100	88
40-59	≥2 cysts in each kidney	100	95
≥60	≥4 cysts in each kidney	100	100
Revised Unified Diagnostic Criteria			
15-29	≥3 cysts, unilateral or bilateral	100	86
30-39	≥3 cysts, unilateral or bilateral	100	86
40-59	≥2 cysts in each kidney	100	95
≥60	≥4 cysts in each kidney	100	100
Revised Criteria for Exclusion of Diagnosis			
15-29	≥1 cyst	97	91
30-39	≥1 cyst	94	98
40-59	≥2 cysts	97	100
≥60	≥3 cysts in each kidney	100	100

Table 46-1 Ultrasound criteria for diagnosis of autosomal dominant polycystic kidney disease (ADPKD). *NPV,* Negative predictive value; *PPV,* positive predictive value. *(From reference 61.)*

Genetic Testing

Genetic testing can be performed when a precise diagnosis is needed and the results of imaging are indeterminate. However, there are limitations to genetic testing, by either linkage or mutation analysis. Linkage analysis requires accurate diagnosis and the availability and willingness of sufficient affected family members to be tested; it is feasible in less than 50% of families. *De novo* mutations can also complicate interpretation of results. Molecular testing by direct DNA sequencing is now informative in about 90% of patients.[28] However, because most mutations are unique and up to one third of *PKD1* changes are missense, the pathogenicity of some changes is difficult to prove.

In preimplantation genetic diagnosis, genetic analysis is performed on single blastomeres from preimplantation embryo biopsy specimens obtained after *in vitro* fertilization (IVF), and only embryos unaffected by the disease are selected for transfer. Preimplantation genetic diagnosis for ADPKD is complicated by the genetic heterogeneity of the disease and by the large size and complex structure of the *PKD1* gene. Demand is limited in this late-onset disorder, and it has been performed in very few cases.

DIFFERENTIAL DIAGNOSIS

Renal cystic disease can be a manifestation of many other systemic diseases. Conditions to consider when renal cystic disease is detected but presentation is not typical of ADPKD include autosomal recessive PKD, tuberous sclerosis complex, von Hippel–Lindau disease, renal cysts and diabetes (RCAD) from *HNF1β* mutations, and oro-faciodigital syndrome type I, as well as medullary sponge kidney and simple renal cysts. These are discussed further, including differential diagnosis, in Chapter 47. If the patient has ESRD, acquired cystic disease should also be considered (see Chapter 89).

CLINICAL MANIFESTATIONS

Autosomal dominant PKD is a multisystem disorder. Multiple renal and extrarenal manifestations of ADPKD have been described that cause significant complications.

Renal Manifestations

A number of clinical features that result from renal damage can be identified (Box 46-1). Reduction in urinary concentrating capacity and glomerular hyperfiltration are early functional abnormalities that can be observed in some children and adolescents with ADPKD.

Renal Size

Renal size increases with age, and renal enlargement eventually occurs in 100% of patients with ADPKD. The severity of the structural abnormality correlates with the manifestations of ADPKD, such as pain, hematuria, hypertension, and renal impairment.[29] Massive renal enlargement can lead to compression of local structures, resulting in such complications as inferior vena cava (IVC) compression and digestive symptoms. Most manifestations are directly related to the development and enlargement of renal cysts. The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP), a prospective study of 241 patients by annual MRI,

Renal Manifestations of Autosomal Dominant Polycystic Kidney Disease

Functional Manifestations
Concentrating defect
Reduced renal blood flow

Hypertension → Target Organ Damage
Cardiac
Cerebrovascular
Arteriolosclerosis and glomerulosclerosis
Peripheral vascular disease

Pain, Caused by
Cyst hemorrhage
Gross hematuria
Nephrolithiasis
Infection
Renal enlargement

Renal Failure, Possibly Caused by
Interstitial inflammation
Apoptosis of tubular epithelial cells
Hypertensive glomerulosclerosis
Compression atrophy

Box 46-1 Renal manifestations of autosomal dominant polycystic kidney disease (ADPKD).

has shown that total kidney volume and cyst volumes increased exponentially.[30] Rates of growth were relatively constant, averaging 5.3% per year, but highly variable from patient to patient. Baseline total kidney volume predicted the subsequent rate of increase in renal volume and decline in GFR.[31]

Pain

Episodes of acute renal pain are seen frequently; causes include cyst hemorrhage, infection, stone, and rarely tumor, and these must be investigated thoroughly. A few ADPKD patients with renal enlargement and structural distortion develop chronic flank pain without specifically identifiable etiology.

Hematuria and Cyst Hemorrhage

Visible hematuria may be the initial presenting symptom and occurs in up to 40% of ADPKD patients over the course of the disease. Many have recurrent episodes. Differential diagnosis includes cyst hemorrhage, stone, infection, and tumor. Cyst hemorrhage is a frequent complication and produces gross hematuria when the cyst communicates with the collecting system. Frequently, the cyst does not communicate with the collecting system, and flank pain without hematuria occurs. It can present with fever, raising the possibility of cyst infection. On occasion, a hemorrhagic cyst will rupture, resulting in a retroperitoneal bleed that can be significant, potentially requiring transfusion. In most patients, cyst hemorrhage is self-limited, resolving within 2 to 7 days. If symptoms of hematuria or flank pain last longer than 1 week or if the initial episode of hematuria occurs after age 50 years, investigation to exclude neoplasm should be undertaken.

Urinary Tract Infection and Cyst Infection

Urinary tract infection (UTI) is common in ADPKD, but its incidence may have been overestimated because sterile pyuria is common in these patients. UTI presents as cystitis, acute pyelonephritis, cyst infection, and perinephric abscesses. As in the general population, women are affected more frequently than men. Most infections are caused by *Escherichia coli, Klebsiella* and *Proteus* species, and other Enterobacteriaceae. The route of infection in acute pyelonephritis and cyst infection is usually retrograde from the bladder; therefore, cystitis should be promptly treated to prevent complicated infections.

Both CT and MRI are sensitive to detect complicated cysts and to provide anatomic definition, but the findings are not specific for infection. Nuclear imaging, especially indium-labeled white blood cell scanning, is useful, but false-negative and false-positive results are possible. ^{18}F-labeled fluorodeoxyglucose (FDG) positron emission tomography (PET) has recently been used for detection of infected cysts.[32] FDG is taken up by inflammatory cells because of their high metabolic rate but is filtered by the kidneys, is not reabsorbed, and appears in the collecting system, which may limit its use in diagnosis of renal cyst infections; its present role is for diagnosis of infected liver cysts. FDG PET is expensive and not yet widely available, but it provides rapid imaging with high spatial resolution, high target-background ratio, low radiation burden, and high interobserver agreement.

When there is fever and flank pain with suggestive diagnostic imaging but blood and urine cultures are negative, cyst aspiration under ultrasound or CT guidance should be undertaken to culture the organism and to assist in selection of antimicrobial therapy.

Nephrolithiasis

Renal stone disease occurs in about 20% of patients with ADPKD. Most stones are composed of uric acid, calcium oxalate, or both. Uric acid stones are more common in ADPKD than in stone formers without ADPKD. Urinary stasis secondary to distorted renal anatomy may play a role in the pathogenesis of nephrolithiasis. Predisposing metabolic factors include decreased ammonia excretion, low urinary pH, and low urinary citrate concentration.[1]

Stones can be difficult to diagnose on imaging in ADPKD because of cyst wall and parenchymal calcification. The distorted anatomy can cause difficulty in localizing stones to the collecting system on plain films. Intravenous (IV) urography has the advantage of specifically localizing stone material to the collecting system and may provide clues to stone composition. IV urography can also detect pericalyceal tubular ectasia, found in 15% of ADPKD patients. CT scanning is more sensitive in detecting small or radiolucent stones and for differentiating stones from tumor, clot, and cyst wall or parenchymal calcification. Dual-energy CT is increasingly used to distinguish between calcium and uric acid stones.

Hypertension

Hypertension is the most common manifestation of ADPKD and a major contributor to renal disease progression and cardiovascular morbidity and mortality (Fig. 46-3). Microalbuminuria, proteinuria, and hematuria, which are independent risk factors for renal functional decline, are more common in hypertensive patients with ADPKD. Hypertension may also increase morbidity from valvular heart disease and intracranial aneurysms, which are common in ADPKD.

Ambulatory blood pressure (BP) monitoring of children or young adults without diagnosed hypertension often reveals elevated BP, attenuated nocturnal BP dipping, and exaggerated BP response during exercise. A study stratified 65 children by BP into three cohorts: hypertensive (≥95th percentile), borderline hypertensive (75th to 95th percentile), and normotensive (≤75th percentile).[33] Both the hypertensive and the borderline hypertensive children had

significantly higher left ventricular mass indices than the normotensive children. Among normotensive children, indices were significantly higher in those within the upper quartile of normal BP. These observations suggest that target organ damage develops early in ADPKD and that antihypertensive treatment may be indicated in children with ADPKD and borderline hypertension.

End-Stage Renal Disease

In most patients, renal function is maintained within the normal range, despite relentless growth of cysts, until the fourth to sixth decade of life. By the time renal function starts declining, the kidneys usually are greatly enlarged and distorted with little recognizable parenchyma on imaging studies. At this stage, the average rate of GFR decline is 4.4 to 5.9 ml/min per year. Nevertheless, ESRD is not inevitable in ADPKD. Up to 77% of patients are alive with preserved renal function at age 50 years, and 52% at age 73. Men tend to progress to renal failure more rapidly and require renal replacement therapy at a younger age than women. Other risk factors for renal failure include black race, diagnosis of ADPKD before age 30, first episode of hematuria before age 30, onset of hypertension before age 35, hyperlipidemia, low level of high-density lipoprotein cholesterol, and sickle cell trait.

Several mechanisms account for renal function decline. The CRISP study has confirmed that kidney and cyst volumes are the strongest predictors of renal functional decline.[31] CRISP also found that renal blood flow (or vascular resistance) is an independent predictor.[34] This points to the importance of vascular remodeling in the progression of the disease and may account for cases in which the decline of renal function seems disproportionate to the severity of the cystic disease. Other factors, such as heavy use of analgesics, may contribute to chronic kidney disease progression in some patients.

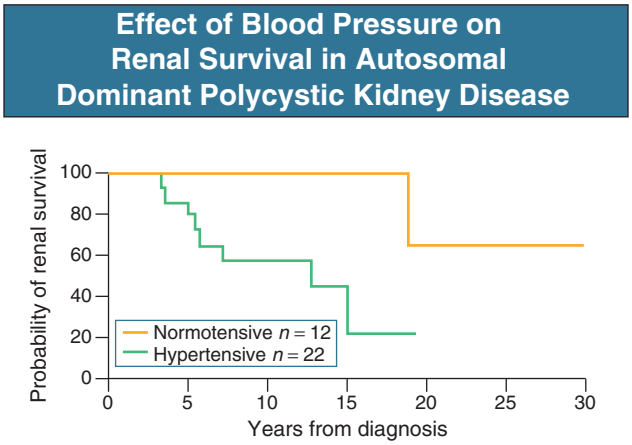

Figure 46-3 Patients with polycystic kidney disease and hypertension at diagnosis have less probability of renal survival than those with normal blood pressure. *(From reference 62.)*

Extrarenal Manifestations

Polycystic Liver Disease

Polycystic liver disease (PLD) is the most common extrarenal manifestation of ADPKD. PLD is associated with both *PKD1* and *PKD2* genotypes. In addition, PLD also occurs as a genetically distinct disease in the absence of renal cysts. Most simple hepatic cysts are solitary, and PLD should be suspected when four or more cysts are present in the hepatic parenchyma. The liver in PLD contains multiple microscopic or macroscopic cysts that result in hepatomegaly (Fig. 46-4), but typically there is preservation of normal hepatic parenchyma and liver function.

Hepatic cysts are exceedingly rare in children with ADPKD. Their frequency increases with age and may have been underestimated by ultrasound and CT studies. Their prevalence by MRI in the CRISP study was 58%, 85%, and 94%, respectively, in participants age 15 to 24, 25 to 34, and 35 to 46 years.[35] Women develop more cysts at an earlier age than men. Women who have multiple pregnancies or who have used oral contraceptives (OCs) or estrogen replacement therapy (ERT) in the postmenopausal period have worse disease.

Typically, PLD is asymptomatic, but reported symptoms have become more frequent as the life span of ADPKD patients is prolonged with dialysis and transplantation. Symptoms result from mass effect or from complications related to the cysts themselves.[36] Symptoms typically caused by massive enlargement of the liver or by mass effect from a single or a limited number of dominant cysts include dyspnea, orthopnea, early satiety, gastroesophageal reflux, mechanical low back pain, uterine prolapse, and even rib fracture. Other complications caused directly by mass effect include hepatic venous outflow obstruction, IVC compression, portal vein compression, and bile duct compression presenting as obstructive jaundice. Hepatic venous outflow obstruction is an uncommon condition caused by severe extrinsic compression of the intrahepatic IVC and hepatic veins by cysts, rarely with superimposed thrombosis. Symptomatic cyst complications include cyst hemorrhage, which occurs less frequently than renal cyst hemorrhage; cyst infection; and the rare occurrence of torsion or rupture of cysts. Hepatic cyst infection can be a serious complication and typically presents with localized pain, fever, leukocytosis, elevated sedimentation rate, and often elevated

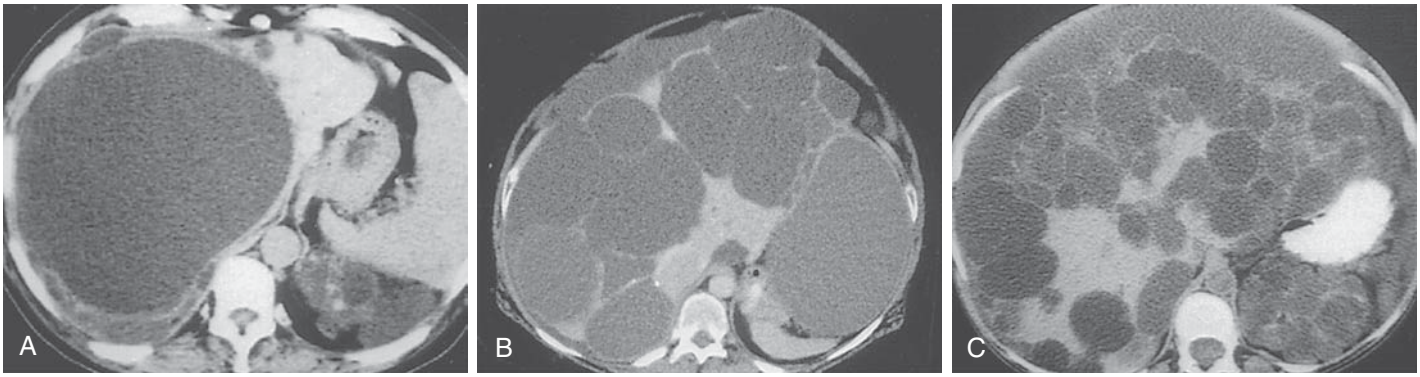

Figure 46-4 Variable presentation of symptomatic polycystic liver disease. A, Hepatomegaly caused by a very large, isolated, dominant cyst. **B,** Hepatomegaly caused by several large cysts. **C,** Hepatomegaly caused by multiple smaller cysts throughout the hepatic parenchyma.

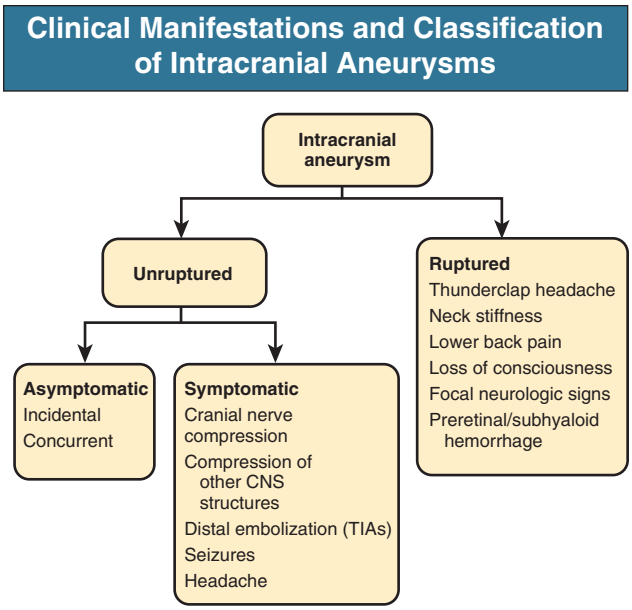

Figure 46-5 Intracranial aneurysms. Clinical manifestations and classification. *CNS,* Central nervous system; *TIAs,* transient ischemic attacks.

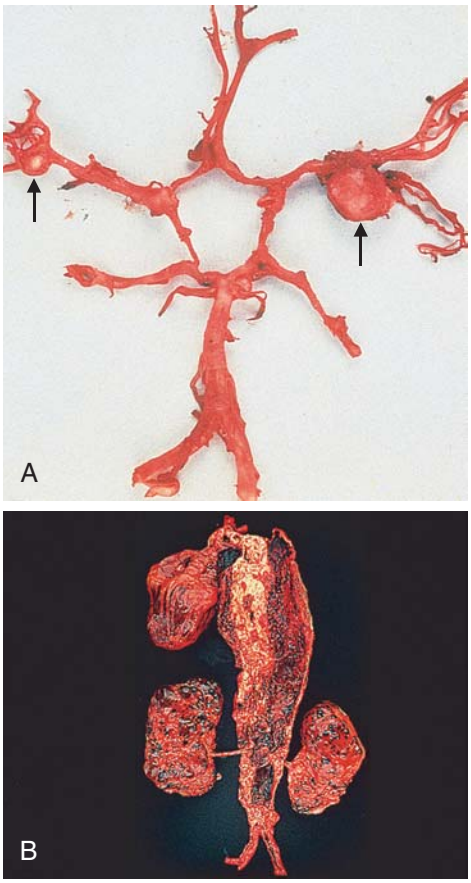

Figure 46-6 Vascular manifestations of autosomal dominant polycystic kidney disease. A, Gross specimen demonstrating bilateral aneurysms of the middle cerebral arteries *(arrows)*. **B,** Gross specimen demonstrating a thoracic aortic dissection extending into the abdominal aorta in a patient with ADPKD.

alkaline phosphatase. Enterobacteriaceae are the most common microorganisms causing cyst infection. The same imaging techniques discussed for the investigation of renal cyst infections may be useful for the localization of infected cysts in the liver.

Congenital hepatic fibrosis (CHF), always found in association with autosomal recessive PKD, can rarely coexist with autosomal dominant PKD.[37] Contrary to PKD, which affects members of several generations in these families, CHF is seen in only one generation and is not transmitted vertically, suggesting the importance of modifier genes. These patients present with manifestations of portal hypertension, but hepatocellular function is normal.

Intracranial Aneurysms

Intracranial aneurysms occur in about 8% of patients with ADPKD. There is some familial clustering; intracranial aneurysms occur in 6% of patients with a negative family history and 16% of those with a positive family history.[38] Most are asymptomatic. Focal findings, such as cranial nerve palsy and seizure, may result from compression of local structures by an enlarging aneurysm (Fig. 46-5). Yearly rupture rates increase with size, ranging from less than 0.5% for aneurysms smaller than 5 mm in diameter to 4% for aneurysms larger than 10 mm. Rupture carries a 35% to 55% risk for combined severe morbidity and mortality. The mean age at rupture in ADPKD is 39 years (vs. 51 years in general population), with a range of 15 to 69 years. Most patients have normal renal function, and up to 29% have normal BP at rupture.

Screening is not indicated for all patients with ADPKD because most intracranial aneurysms found by presymptomatic screening are small, have a low risk for rupture, and require no treatment because the risks of intervention exceed any risk of rupture.[39] Indications for screening in patients with a good life expectancy include family history of intracranial aneurysm or subarachnoid hemorrhage, previous aneurysmal rupture, preparation for elective surgery with potential hemodynamic instability, high-risk occupations (e.g., airline pilots), and significant patient anxiety despite adequate information about the risks. MR angiography is the diagnostic imaging modality of choice for presymptomatic screening because it is noninvasive and does not require IV contrast administration. CT angiography is a satisfactory alternative if there is no contraindication to IV contrast.

Other Vascular Abnormalities

In addition to intracranial aneurysms, ADPKD has been associated with other vascular abnormalities, such as thoracic aortic and cervicocephalic arterial dissections, coronary artery aneurysms, and retinal artery and vein occlusions (Fig. 46-6). Thoracic aortic dissection is seven times more common in ADPKD than in the general population in autopsy series, but reported cases are rare. Rare patients with coronary aneurysms can present with cardiac ischemia and thrombus in the aneurysm in the absence of atherosclerotic disease. Several case reports describe abdominal aortic aneurysms in ADPKD. However, a prospective ultrasound study showed neither a wider aortic diameter nor a higher prevalence of abdominal aortic aneurysms in ADPKD patients compared with unaffected kindred in any age group.

Valvular Heart Disease and Other Cardiac Manifestations

Mitral valve prolapse is the most common valvular abnormality and has been demonstrated in up to 25% of ADPKD patients by echocardiography. Mitral regurgitation, tricuspid regurgitation, and tricuspid prolapse also occur more frequently in ADPKD than in unaffected kindred. Aortic regurgitation may be associated with

dilation of the aortic root. On histologic examination, valvular tissue shows myxoid degeneration with disruption of collagen, as seen in Marfan and Ehlers-Danlos syndromes. Although the lesions may progress with time, they rarely require valve replacement. Screening echocardiography is not indicated unless a murmur is detected on physical examination. Small, hemodynamically insignificant pericardial effusion can be detected by CT scanning in up to 35% of ADPKD patients.[1]

Other Associated Conditions

Cyst formation has been described in such diverse organs as the pancreas, seminal vesicles, and arachnoid membrane (Fig. 46-7). Seminal vesicle cysts, usually multiple and bilateral, are found in 40% of ADPKD compared with 2% of nonaffected males. Ovarian cysts are not associated with ADPKD. Pancreas and arachnoid membrane cysts are present in 5% and 8% of patients, respectively. Pancreatic cysts are almost always asymptomatic, with rare occurrences of recurrent pancreatitis and possibly chance associations of intraductal papillary mucinous tumor or carcinoma. Epididymal and prostate cysts may also occur with increased frequency. Sperm abnormalities with defective motility are common in ADPKD and rarely may be a cause of male infertility. Spinal meningeal diverticula may occur with increased frequency and rarely present with intracranial hypotension (orthostatic headache, diplopia, hearing loss, ataxia) caused by cerebrospinal fluid (CSF) leak. The prevalence of colonic and duodenal diverticula may also be increased.[1]

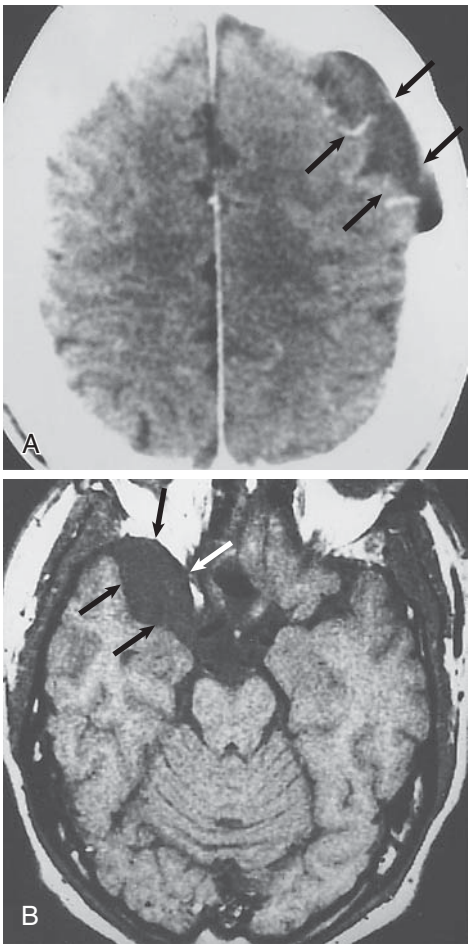

Figure 46-7 Extrarenal manifestations of autosomal dominant polycystic kidney disease. Computed tomography (**A**) and magnetic resonance imaging (**B**) scans demonstrate cysts in the arachnoid membrane *(arrows)* in ADPKD.

PATHOLOGY

Polycystic kidneys are diffusely cystic and enlarged (Fig. 46-8). Size varies from normal to weighing more than 4 kg. The outer and cut surfaces show numerous spherical cysts of varying size, which are distributed evenly between cortex and medulla. The collecting system typically is distorted. The epithelium lining the cysts is characterized by hyperplastic changes, including flat nonpolypoid hyperplasia, polypoid hyperplasia, and microscopic adenomas (Fig. 46-9),

Figure 46-8 Polycystic kidneys. Greatly enlarged polycystic kidneys from a patient with ADPKD compared with a normal kidney *(middle)*.

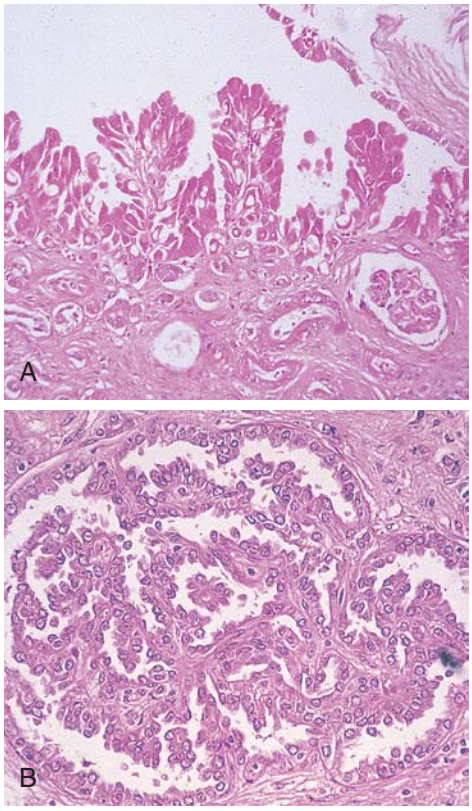

Figure 46-9 Renal cyst histology in autosomal dominant polycystic kidney disease. A, Papillary hyperplasia of cyst epithelium. **B,** Papillary microscopic adenoma in kidney of ADPKD patient. (Magnification ×200.)

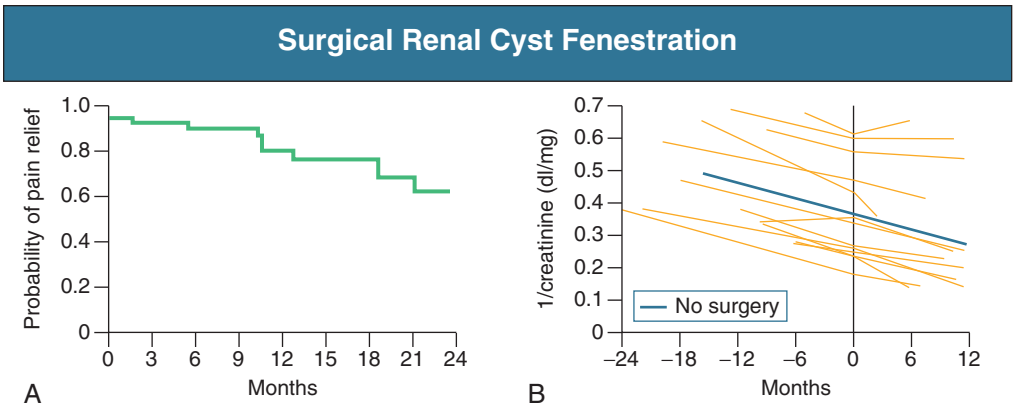

Figure 46-10 Surgical cyst fenestration for symptomatic autosomal dominant polycystic kidney disease. A, Effects on relief of pain. **B,** Rate of decline of renal function. *Orange lines* indicate the course of renal function in individual patients who underwent cyst fenestration at month 0. *(From reference 63.)*

as well as increased rates of cell proliferation and apoptosis. Despite the frequency of hyperplastic lesions and microscopic adenomas, the incidence of renal cell carcinoma is not increased.

Cysts arise from all segments of the nephron and collecting ducts. As they grow, cysts dissociate from the parent tubule and eventually become isolated, fluid-filled sacs. There is no agreement on whether the cysts originate preferentially from particular tubular segments. Most studies indicate that cysts are predominantly of distal nephron and collecting duct origin. Studies in advanced renal disease showing proximal tubular cysts may be confounded by the effects of obstruction and acquired renal cystic disease.

Polycystic kidneys demonstrate advanced sclerosis of preglomerular vessels, interstitial fibrosis, and tubular epithelial hyperplasia, even in patients with normal renal function or early renal failure. Sclerosis involves both afferent arterioles and interlobular arteries. Interstitial fibrosis is also prominent, even in early disease. It is associated with an interstitial infiltrate of macrophages and lymphocytes.

TREATMENT

Current therapy is directed toward the renal and extrarenal complications of ADPKD in an effort to limit morbidity and mortality. Advances in the understanding of the genetics of ADPKD and mechanisms of cyst development and growth have raised hopes for treatments specifically directed toward limiting the development and progression of the disease, and some of these treatments are now being evaluated in clinical trials (see Novel Therapies).

Flank Pain

Causes of flank pain that may require intervention, such as infection, stone, and tumor, should be excluded. Care should be taken to avoid long-term administration of nephrotoxic agents, such as combination analgesics and nonsteroidal anti-inflammatory drugs. Narcotic analgesics should be reserved for the management of acute pain. Patients with chronic kidney pain are at risk for narcotic and analgesic dependence, and a psychological evaluation and a supportive attitude by the physician are essential. Reassurance, lifestyle modification, and avoidance of aggravating activities may be helpful. Tricyclic antidepressants are helpful as in other chronic pain syndromes, with a generally well-tolerated side effect profile. Splanchnic nerve blockade with local anesthesia or corticosteroids results in pain relief prolonged beyond the duration of the local anesthetic.

When distortion of the kidneys by large cysts is deemed responsible for the pain and conservative measures fail, cyst decompression should be considered. Cyst aspiration, under ultrasound or CT guidance, is a relatively simple procedure. To prevent the reaccumulation of cyst fluid, sclerosing agents such as 95% ethanol or acidic solutions of minocycline may be used. Minor complications include microhematuria, localized pain, transient fever, and systemic absorption of the alcohol. More serious complications, such as pneumothorax, perirenal hematoma, arteriovenous fistula, urinoma, and infection, are rare. Complications from aspiration of centrally located cysts are more common, and the morbidity of the procedure is proportional to the number of cysts treated.

If multiple cysts are contributing to pain, laparoscopic or surgical cyst fenestration may be of benefit. Surgical decompression is effective in 80% to 90% of patients at 1 year, and 62% to 77% have sustained pain relief for more than 2 years (Fig. 46-10, *A*). Surgical intervention does not accelerate the decline in renal function, as once thought, but does not appear to preserve declining renal function either (Fig. 46-10, *B*). Laparoscopic fenestration is as effective as open surgical fenestration in short-term follow-up in patients with limited disease, and there is a shorter, less complicated recovery period compared with open surgery. Previous abdominal surgery with possible adhesion formation is a relative contraindication to the procedure.

There are a number of other interventions for the management of pain in ADPKD whose roles have not been fully defined. Laparoscopic renal denervation has been used in combination with cyst fenestration and may be considered, particularly in polycystic kidneys without large cysts. A nonrandomized, open-label, uncontrolled trial of video thoracoscopic sympatho-splanchnicectomy is under way (www.clinicaltrials.gov, NCT00571909). Laparoscopic and retroperitoneoscopic nephrectomy and arterial embolization have been used to treat symptomatic polycystic kidneys in ADPKD patients with ESRD.

Cyst Hemorrhage

Episodes of cyst hemorrhage are self-limited, and patients respond well to conservative management with bed rest, analgesics, and adequate fluid intake to prevent obstructing clots. Rarely, bleeding is more severe, with extensive subcapsular or retroperitoneal hematoma causing significant decrease in hematocrit and hemodynamic instability. This requires hospitalization and transfusion. The antifibrinolytic agent tranexamic acid has been successfully used in some patients, but no controlled studies have been performed.[40] The dose needs to be reduced in the presence of renal impairment. Potential adverse effects of tranexamic acid therapy include glomerular thrombosis and ureteral obstruction from clots. In patients with unusually severe or persistent hemorrhage, segmental arterial

embolization can be successful. If not, surgery may be required to control bleeding.

Urinary Tract and Cyst Infection

Because most renal cyst infections begin as cystitis, prompt treatment of symptomatic cystitis and asymptomatic bacteriuria is indicated to prevent retrograde seeding of the renal parenchyma. Antibiotics that require glomerular filtration, such as highly polar aminoglycosides, are not effective for upper UTI in severe renal impairment. Cyst infection is often difficult to treat despite prolonged therapy with an antibiotic to which the organism is susceptible. Treatment failure occurs if antibiotics do not penetrate the cyst epithelium and achieve therapeutic concentrations within the cysts. Lipophilic agents have been shown to penetrate cysts reliably and have a pK_a that allows favorable electrochemical gradients into acidic cyst fluid. Therapeutic agents of choice include trimethoprim-sulfamethoxazole and fluoroquinolones, both of which have favorable intracystic therapeutic concentration gradients at physiologic pH in gradient and nongradient cysts.

If fever persists after 1 to 2 weeks of appropriate antimicrobial therapy, percutaneous or surgical drainage of infected cysts should be undertaken. In the case of end-stage polycystic kidneys, nephrectomy should be considered. If fever recurs after stopping antibiotics, complicating features such as obstruction, perinephric abscess, and stone should be excluded. If no such complicating features are identified, the antibiotic course should be extended and may require several months to fully eradicate infection.

Nephrolithiasis

Treatment of nephrolithiasis in patients with ADPKD is the same as that in patients without ADPKD. Potassium citrate is the treatment of choice in the three stone-forming conditions associated with ADPKD: uric acid lithiasis, hypocitraturic calcium oxalate nephrolithiasis, and distal acidification defects. Extracorporeal shock wave lithotripsy and percutaneous nephrostolithotomy are reported to be 82% and 80% successful, respectively, without increased complications compared to patients without ADPKD.[41] Flexible ureterorenoscopy with laser fragmentation has also been used safely and effectively and cannot cause traumatic nephron loss.[42,43]

Hypertension

Control of hypertension is essential because uncontrolled hypertension accelerates the decline in renal function and aggravates extrarenal complications. Antihypertensive agents of choice and optimal blood pressure targets in ADPKD have not been established. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) increase renal blood flow in ADPKD, have a low side effect profile, and may have renoprotective properties that go beyond BP control. Although studies have failed to demonstrate a beneficial effect of ACE inhibitors on the progression of ADPKD, these studies have been limited by the use of low drug dosages, small numbers of patients, short duration of follow-up, and inclusion of patients with widely different renal function. An ongoing study (HALT PKD) is designed to determine whether combined therapy with an ACE inhibitor and an ARB is superior to an ACE inhibitor alone in delaying the progression of the cystic disease in patients with preserved renal function or in slowing the decline of renal function in patients with chronic kidney disease (CKD) stage 3. HALT PKD will also determine whether a low BP target is superior to a standard BP target in patients with preserved renal function.[44] Although these definitive studies are needed, on available evidence, we recommend tight BP control to 125/75 mm Hg with a regimen that includes ACE inhibitors or ARBs.

Progressive Renal Failure

General strategies to delay progression of CKD are discussed in Chapter 80. A subgroup analysis of the Modification of Diet in Renal Disease (MDRD) study showed no beneficial effect on renal function in ADPKD of strict versus standard BP control and marginal benefit of a very-low-protein diet. A long-term follow-up of participants in this study, however, showed that individuals with ADPKD randomized to a low BP target (mean arterial pressure [MAP] <92 mm Hg) experienced significantly less ESRD and combined ESRD/death than those randomized to the usual BP target (MAP <107 mm Hg).[45]

Based on evidence suggesting that increased vasopressin effect on the kidney and cAMP levels are involved in cyst progression and on preclinical studies, the ingestion of supplemental water sufficient to achieve a low urinary osmolality below 250 mOsm/kg H_2O has been recommended for ADPKD patients with an estimated GFR greater than 30 ml/min, although there are no randomized controlled trials (RCTs) to support the value of this approach.[46,47] Exclusions would include severe protein or sodium restriction, volume contraction, or reduced effective intravascular volume, taking diuretics or drugs enhancing the release of arginine vasopressin (AVP), or presenting abnormal voiding or urologic problems. Serum sodium concentration should be monitored.

Patients with ADPKD have reduced morbidity and mortality on dialysis compared to patients with ESRD from other causes. Women appear to do better than men. The good outcome in ADPKD may result from higher endogenous erythropoietin production and better maintenance of hemoglobin, or lower comorbidity. Rarely, hemodialysis can be complicated by intradialytic hypotension if there is IVC compression by a medially located renal cyst. Despite renal size, peritoneal dialysis can usually be performed in ADPKD, although there is increased risk for inguinal and umbilical hernias, which require surgical repair.

Polycystic Liver Disease

Usually asymptomatic, PLD requires no treatment. When symptomatic, therapy is directed toward reducing cyst volume and hepatic size. Noninvasive measures include avoiding ethanol, other hepatotoxins, and possibly cAMP agonists (e.g., caffeine), which have been shown to stimulate cyst fluid secretion *in vitro*. Histamine H_2 blockers and somatostatin have been suggested to reduce secretion of secretin and secretory activity of cyst walls. Estrogens are likely to contribute to cyst growth, but the use of OCs and postmenopausal ERT are contraindicated only if the liver is significantly enlarged and the risk for further hepatic cyst growth outweighs the benefits of estrogen therapy. Rarely, symptomatic PLD may require invasive measures to reduce cyst volume and hepatic size. Options include percutaneous cyst aspiration and sclerosis, laparoscopic fenestration, and open surgical fenestration.[48] Cyst aspiration is the procedure of choice if symptoms are caused by one or a few dominant cysts or by cysts that are easily accessible to percutaneous intervention. To prevent the reaccumulation of cyst fluid, sclerosis with minocycline or 95% ethanol is often successful. Laparoscopic fenestration can be considered for large cysts that are more likely to recur after ethanol sclerosis, or if several cysts are present that would require multiple percutaneous passes to be treated adequately. Partial hepatectomy with cyst fenestration is an option because PLD often spares a part of the liver with adequate preservation of hepatic parenchyma and

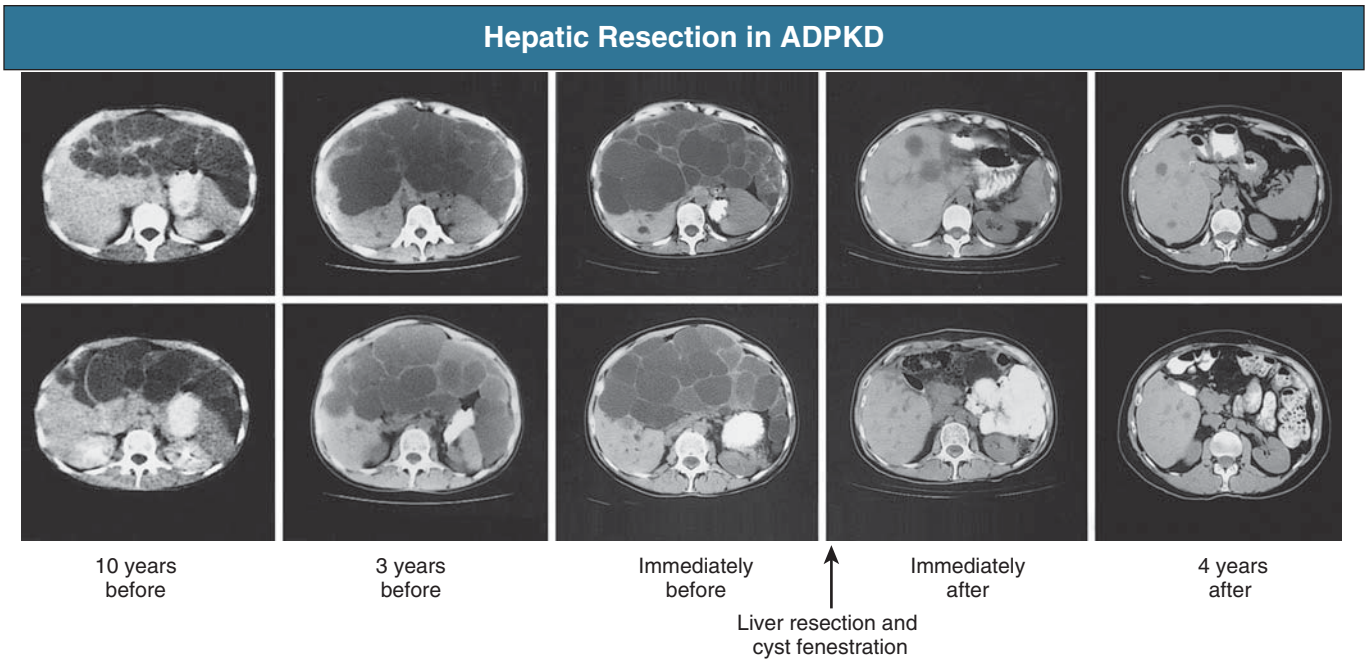

Figure 46-11 Hepatic resection in autosomal dominant polycystic kidney disease. CT scans of the abdomen 10 years before (column 1), 3 years before (column 2), immediately before (column 3), immediately after (column 4), and 4 years after (column 5) liver resection and cyst fenestration, demonstrating long-term, sustained reduction in liver size after the procedure. *(From reference 64.)*

liver function (Fig. 46-11). In the rare case in which no segments are spared, liver transplantation may be necessary.

When a hepatic cyst infection is suspected, any cyst with unusual appearance on an imaging study should be aspirated for diagnostic purposes. The best management is percutaneous cyst drainage in combination with antibiotic therapy. Long-term oral antibiotic suppression or prophylaxis should be reserved for relapsing or recurrent cases. Antibiotics of choice are trimethoprim-sulfamethoxazole and the fluoroquinolones, which are effective against the typical infecting organisms and concentrate in the biliary tree and cysts.

Intracranial Aneurysm

Ruptured or symptomatic intracranial aneurysm requires surgical clipping of the neck of the aneurysm. Asymptomatic aneurysms measuring less than 5 mm, diagnosed by presymptomatic screening, can be observed with repeated MR angiography at 6 months, then annually and less frequently after stability of the aneurysm has been established. If the size increases, surgery is indicated. Definitive management of aneurysms between 6 and 9 mm remains controversial. Surgical intervention is usually indicated for all unruptured aneurysms 10 mm in diameter or larger. For patients with high surgical risk or with technically difficult lesions, endovascular treatment with detachable platinum coils may be indicated.[39]

NOVEL THERAPIES

A better understanding of the pathophysiology and the availability of animal models have facilitated the development of promising candidate drugs for clinical trials (see Fig. 46-2).

Vasopressin Antagonists

The effect of vasopressin, through V_2 receptors, on cAMP levels in the collecting duct, the major site of cyst development in ADPKD, and the role of cAMP in cystogenesis provided the rationale for successful preclinical trials of vasopressin V_2 receptor antagonists.[2,3] High water intake by itself also exerted a protective effect on the development of PKD in PCK rats, probably because of suppression of vasopressin. Genetic elimination of AVP in these rats yielded animals born with normal kidneys that remained relatively free of cysts unless an exogenous V_2 receptor agonist was administered.[49]

In a large, Phase III parallel-arm RCT in ADPKD patients with estimated creatinine clearance above 60 ml/min, a split daily dose of *tolvaptan* administered over 3 years slowed the increase in kidney volume and decline in kidney function and lowered the frequency of ADPKD-related adverse events (kidney pain, hematuria, UTI).[50] However, tolvaptan was associated with a higher frequency of aquaresis-related adverse events (polyuria, thirst, urinary frequency) that led to drug discontinuation in 8.3% of tolvaptan-treated patients. More important, clinically significant increases in liver enzymes (>2.5 times the upper limit of normal) were seen in 4.9% of tolvaptan-treated versus 1.2% of placebo-treated patients and led to discontinuation of the drug in 1.8% of patients taking tolvaptan and 0.2% of the placebo group. Moderate increases in serum sodium and uric acid levels were also seen more frequently in the patients taking tolvaptan. At present, tolvaptan is not approved for ADPKD therapy and should not be used outside of an approved research study. The value of tolvaptan as a long-term treatment in ADPKD patients will depend on the balance between benefits and risks. Patients taking tolvaptan should have easy access to and be able to tolerate water. Liver function should be monitored closely during therapy. Serum sodium and uric acid require monitoring. Efficacy in more advanced stages of disease has not yet been thoroughly ascertained.

Somatostatin Analogues

Somatostatin acting on somatostatin receptors inhibits cAMP accumulation not only in the kidney but also in the liver. Somatostatin has a half-life of approximately 3 minutes, so more stable synthetic

peptides (octreotide, lanreotide, pasireotide) have been developed for clinical use, which vary in stability and receptor affinity. In preclinical studies, these drugs reduced cAMP levels and proliferation of cholangiocytes *in vitro,* expansion of liver cysts in three-dimensional collagen culture, and development of kidney and liver cysts and fibrosis in animal models orthologous to ARPKD and ADPKD. Three small RCTs of octreotide or lanreotide have been completed.[51-54] Two have been extended as open-label, uncontrolled studies.[55-57] The published studies have shown similar results. Kidney growth is halted during the first year of treatment and then resumes, possibly at a lower rate than without treatment. Liver volume decreases by 4% to 6% during the first year of treatment, and this reduction is sustained during the second year. Observation periods have been too short to assess an effect on renal function. Another study has shown that the addition of everolimus to treatment with octreotide does not provide added benefit.[57] Additional clinical trials of somatostatin analogues for ADPKD and for PLD are currently active. Octreotide and lanreotide are generally well tolerated. Self-resolving abdominal cramps and loose stools are common in the first few days following the injections. Other adverse effects include injection site granuloma and pain, cholelithiasis, steatorrhea, weight loss, and rarely hair loss.

mTOR Inhibitors

The mammalian target of rapamycin (mTOR) is activated in animal models of PKD. Patients with the contiguous *PKD1/TSC2* gene syndrome exhibit a more severe form of PKD than those with ADPKD alone. This observation suggests a convergence of signaling pathways downstream from PC1 and the TSC proteins tuberin and hamartin that control the activity of mTOR. Studies in three rodent models of PKD have shown that the mTOR inhibitors sirolimus and everolimus significantly impair cyst expansion and protect renal function. Small retrospective studies of ADPKD patients after transplantation have shown a significant reduction in the volume of the polycystic kidneys or polycystic liver in patients treated with sirolimus compared with patients treated with calcineurin inhibitors. However, two large randomized trials using everolimus and sirolimus for 18 to 24 months have not consistently delayed the increase in kidney size or slowed the decline in progressive renal impairment.[58,59]

Other Investigational Therapies

Other strategies targeting molecular mechanisms that are altered in PKD have shown promising results in animal studies. A Phase II, multicenter, double-blind RCT of the Src inhibitor bosutinib and a Phase I and II clinical trial of the multikinase inhibitor KD019 are ongoing. Other possible therapies not yet assessed in clinical studies include AMP-activated protein kinase (metformin), PPARγ agonists, and inhibitors of channels required for chloride secretion (CFTR inhibitors, KCa3.1 inhibitor), tumor necrosis factor receptor antagonist, and inhibitors of MEK or cyclin-dependent kinases (see Fig. 46-2).

TRANSPLANTATION

Transplantation is the treatment of choice for ESRD in patients with ADPKD. There is no difference in patient or graft survival between ADPKD patients and other ESRD populations. Living donor transplants also have graft survival no different from that of non-ADPKD populations. However, living related transplantation has only recently been widely practiced in the ADPKD population. In 1999, 30% of kidney transplants for ADPKD patients were from living donors in the United States, compared with 12% in 1990.

Complications after transplantation are no greater in the ADPKD population than in the general population, and specific complications directly related to ADPKD are rare. Cyst infection is not increased after transplantation, and there is no significant increase in the incidence of symptomatic mitral valve prolapse or hepatic cyst infection. One study showed an increased rate of diverticulosis and bowel perforation in ADPKD. Whether ADPKD increases the risk for development of new-onset diabetes mellitus after transplantation is controversial.

Although practiced routinely in the past, pretransplantation nephrectomy has fallen out of favor. By 1 and 3 years after renal transplantation, kidney volumes decrease by 37.7% and 40.6%, whereas liver volumes increase by 8.6% and 21.4%, respectively.[60] Indications for nephrectomy include a history of infected cysts, frequent bleeding, severe hypertension, and massive renal enlargement with extension into the pelvis. No evidence shows an increased risk for development of renal cell carcinoma in native ADPKD kidneys after transplantation. When nephrectomy is indicated, hand-assisted laparoscopic nephrectomy is associated with less intraoperative blood loss, less postoperative pain, and faster recovery compared with open nephrectomy and is increasingly being used.

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CHAPTER 47

Other Cystic Kidney Diseases

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In addition to autosomal dominant polycystic kidney disease (ADPKD), numerous other disorders share renal cysts as a common feature[1,2] (Table 47-1). These disorders may be inherited or acquired; their manifestations may be confined to the kidney or expressed systemically. They may present at a wide range of ages, from the perinatal period to old age (Fig. 47-1). The renal cysts may be single or multiple, and the associated renal morbidity may range from clinical insignificance to progressive parenchymal destruction with resultant renal impairment.

The clinical context often helps distinguish these renal cystic disorders from one another. Echogenic, enlarged kidneys in a neonate or infant should suggest autosomal recessive polycystic kidney disease (ARPKD), ADPKD, tuberous sclerosis complex (TSC), or one of the many congenital syndromes associated with renal cystic disease. Renal impairment in an adolescent suggests juvenile nephronophthisis–medullary cystic disease complex or ARPKD as possible etiologies. The finding of a solitary cyst in a 5-year-old child may indicate a calyceal diverticulum, whereas this finding in a 50-year-old patient is most compatible with a simple renal cyst. Renal stones occur in ADPKD and medullary sponge kidneys. For disorders with systemic manifestations, such as ADPKD, TSC, and von Hippel–Lindau disease, the associated extrarenal features may provide other important differential diagnostic clues.

For an increasing number of the single-gene disorders, genetic testing is available in expert laboratories around the world. Genetic testing resources are listed at Gene Tests (http://www.genetests.org) and the U.S. National Institutes of Health (NIH) Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr).

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

Definition

Autosomal recessive polycystic kidney disease (ARPKD) is a severe, typically early-onset form of cystic disease that primarily involves the kidneys and biliary tract. Affected patients have a spectrum of clinical phenotypes that depend in part on the age at presentation.[3]

Etiology and Pathogenesis

Genetic Basis of ARPKD

All typical forms of ARPKD are caused by mutations in a single gene, *PKHD1* (polycystic kidney and hepatic disease), which encodes multiple, alternatively spliced isoforms predicted to form both membrane-bound and secreted proteins.[4] The largest protein product of *PKHD1*, the fibrocystin/polyductin complex (FPC), contains one membrane-spanning domain and an intracellular C-terminal tail. FPC localizes, at least in part, to the primary cilium and the centrosome in renal epithelial cells.[5] The basic defects observed in ARPKD suggest that FPC mediates the terminal differentiation of the collecting duct and biliary tract. However, the exact function of the numerous isoforms has not been defined, and the widely varying clinical spectrum of ARPKD may depend partly on the nature and number of splice variants that are disrupted by specific *PKHD1* mutations.

Pathogenetic Mechanisms

ARPKD typically begins *in utero,* and the renal cystic lesion appears to be superimposed on a normal developmental sequence. The tubular abnormality primarily involves fusiform and/or saccular dilation of the collecting ducts. Microdissection studies have excluded tubular obstruction as a primary pathogenic mechanism. The biliary lesion involves defective remodeling of the ductal plate *in utero*. As a result, primitive bile duct configurations persist, and progressive portal fibrosis evolves.[6] The remainder of the liver parenchyma develops normally. The defect in ductal plate remodeling is accompanied by abnormalities in the branching of the portal vein. The resulting histopathologic pattern is termed *congenital hepatic fibrosis.*

Autosomal recessive PKD is one of a number of renal cystic diseases associated with congenital hepatic fibrosis, prompting these disorders to be described as *hepatorenal fibrocystic diseases.*[7] The primary cilium appears to play a central role in the pathogenesis ARPKD and other hepatorenal fibrocystic diseases,[8] and thus this set of disorders is encompassed under the broader term *ciliopathies,* in which dysfunction of the cilia-centrosome complex appears to underpin the development of a wide array of phenotypes including renal cystic disease.[9]

Epidemiology

The estimated incidence of ARPKD is 1 per 20,000 live births. It occurs more frequently in Caucasians than in other ethnic populations.[3]

Clinical Manifestations

The clinical spectrum of ARPKD is variable. The majority of cases are identified either *in utero* or at birth. The most severely affected fetuses have enlarged echogenic kidneys and oligohydramnios caused by poor fetal urine output. These fetuses develop the "Potter" phenotype, with pulmonary hypoplasia, a characteristic facies, and deformities of the spine and limbs. At birth, these neonates often have a critical degree of pulmonary hypoplasia that is incompatible with survival. The estimated perinatal mortality is about 30%. Although frequently compromised, renal function is rarely a cause of neonatal death.

For those who survive the first month of life, the reported mean 5-year patient survival is 85% to 90%.[3,10] Morbidity and mortality results from severe systemic hypertension, renal impairment, and portal hypertension from portal-tract hyperplasia and fibrosis.[3,10,11]

Hypertension usually develops in the first several months and ultimately affects 70% to 80% of patients. ARPKD patients have defects in both urinary diluting capacity and concentrating capacity. Newborns can have hyponatremia, presumably resulting from defects in free water excretion.[3] Net acid excretion may be reduced, but metabolic acidosis is not a significant clinical feature.[12] Retrospective studies have noted an increased incidence of pyuria on urinalysis, as well as culture-confirmed urinary tract infections (UTIs).[3]

In the first 6 months of life, ARPKD infants may have a transient improvement in glomerular filtration rate (GFR) caused by renal maturation. Subsequently, a progressive but variable decline in renal function occurs, with patients presenting in the first month of life progressing more rapidly to end-stage renal disease (ESRD) than those presenting at more than one month of age.[12] With advances in effective therapy for ESRD, prolonged survival is common, and for many patients the hepatic complications become the predominant clinical issue.

On average, infants with serum creatinine values above 2.2 mg/dl (200 µmol/l) progress to ESRD within 5 years, but this is highly variable. In longitudinal studies, the probability of renal survival without ESRD is about 85% at 1 year, 70% at 10 years, 65% at 15 years, and 40% at 20 years.[10,11]

In children who present later in childhood or in adolescence, portal hypertension is frequently the predominant clinical abnormality, with hepatosplenomegaly and bleeding esophageal or gastric varices, as well as hypersplenism with consequent thrombocytopenia, anemia, and leukopenia. Hepatocellular function is usually preserved. Ascending suppurative cholangitis is a serious complication and can cause fulminant hepatic failure.[13,14]

Other associated features include growth restriction,[3] although the mechanism is not yet defined, and rarely intracranial aneurysms.[15]

Renal Cystic Disorders
Nongenetic
Developmental
Medullary sponge kidney*
Renal cystic dysplasia Multicystic dysplasia Cystic dysplasia associated with lower urinary tract obstruction
Diffuse cystic dysplasia: syndromal and nonsyndromal
Acquired
Simple cysts
Solitary multilocular cysts
Hypokalemic cystic disease
Acquired cystic disease (in advanced renal failure)
Genetic
Autosomal Dominant
Autosomal dominant polycystic kidney disease
Adult-onset medullary cystic disease
Tuberous sclerosis
von Hippel–Lindau disease/syndrome
Autosomal Recessive
Autosomal recessive polycystic kidney disease
Juvenile nephronophthisis
Meckel-Gruber syndrome
X-Linked
Orofaciodigital syndrome type I

Table 47-1 Renal cystic disorders. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM. *MSK is generally considered to be a sporadic disorder, but recent studies provide evidence for familial clustering, involving autosomal dominant inheritance with reduced disease penetrance and variability in disease expression.[44]

Pathology

Kidney

The renal involvement is invariably bilateral and largely symmetric. The histopathology varies depending on the age of presentation and the extent of cystic involvement (Fig. 47-2, *A* and *B*).

In the affected neonate, the kidneys can be 10 times normal size but can retain the typical kidney contour. Dilated, fusiform collecting ducts extend radially through the cortex. In the medulla, the dilated collecting ducts are more often cut tangentially or transversely. Up to 90% of the collecting ducts are involved. Associated interstitial fibrosis is minimal in neonates and infants, but increases with progressive disease.

In patients diagnosed later in childhood, the kidney size and extent of cystic involvement tend to be more limited. Cysts can

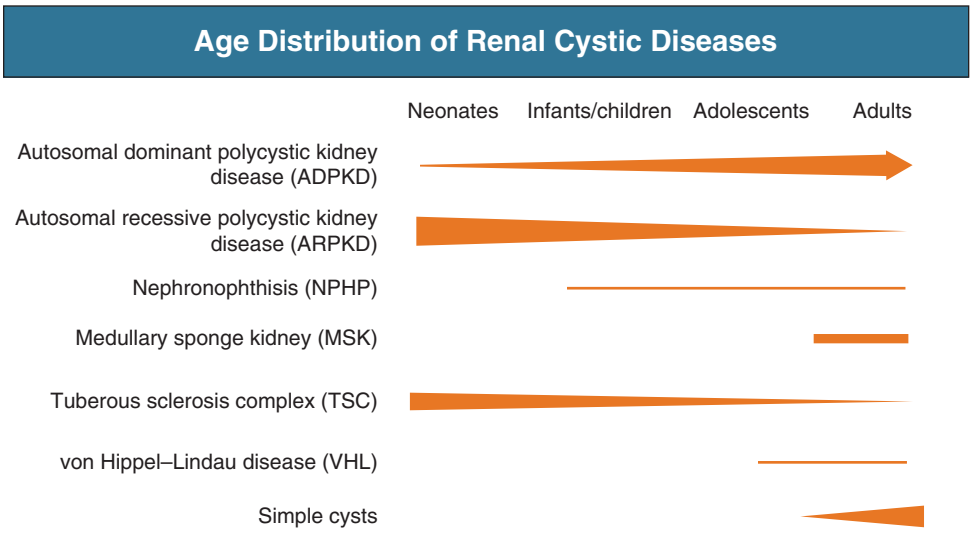


Figure 47-1 Age distribution of patients with renal cystic disorders.

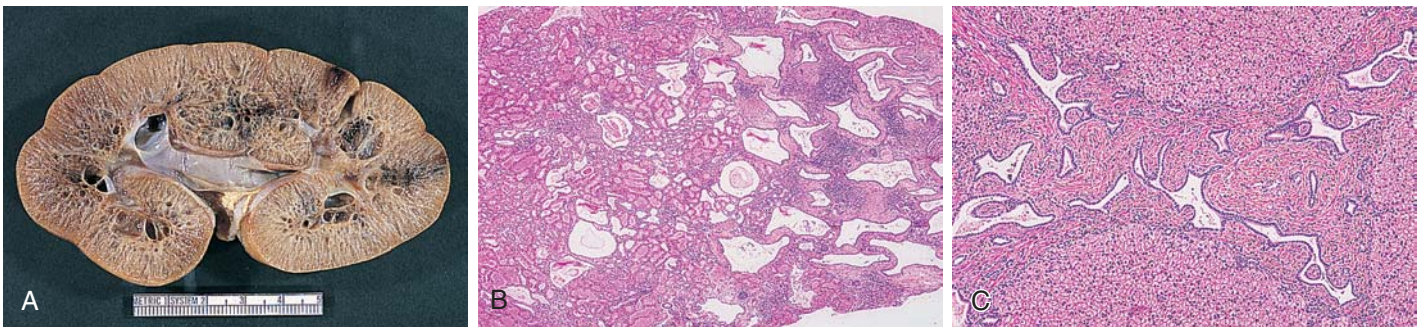


Figure 47-2 Pathologic features of autosomal recessive polycystic kidney disease. A, Cut section of ARPKD kidney from 1-year-old child shows discrete medullary cysts and dilated collecting ducts. **B,** Light microscopy shows later-onset ARPKD kidney with prominent medullary ductal ectasia (hematoxylin-eosin [HE] stain; magnification ×10). **C,** Light microscopy of congenital hepatic fibrosis shows extensive fibrosis of the portal area with ectatic, tortuous bile ducts and hypoplasia of the portal vein (HE stain; ×40).

expand up to 2 cm in diameter and assume a more spherical configuration. Progressive interstitial fibrosis is probably responsible for secondary tubular obstruction. In older children, medullary ductal ectasia is the predominant finding.

Cysts are lined with a single layer of nondescript cuboidal epithelium. The glomeruli and nephron segments proximal to the collecting ducts are initially structurally normal, but are often crowded between ectatic collecting ducts or displaced into subcapsular wedges. The presence of cartilage or other dysplastic elements indicates a diagnosis other than ARPKD, such as cystic dysplasia.

Liver

The liver lesion in ARPKD is characterized by ductal plate malformation.[6] The liver can be either normal in size or somewhat enlarged. Bile ducts are dilated (biliary ectasia) and marked cystic dilation of the entire intrahepatic biliary system (Caroli syndrome) is well described.[16] In neonatal ARPKD, the bile ducts are increased in number, tortuous in configuration, and often located around the periphery of the portal tract. In older children, the biliary ectasia is accompanied by increasing portal tract fibrosis and hypoplasia of the small portal vein branches (Fig. 47-2, *C*). The hepatic parenchyma may be intersected by delicate fibrous septa that link the portal tracts, but the hepatocytes themselves are seldom affected.

Diagnosis

Autosomal recessive PKD must be differentiated from a range of other pediatric renal cystic disorders (Table 47-2).

Imaging

In the past decade, clinical diagnosis has increasingly relied on imaging instead of histopathologic analysis. ARPKD belongs to the hepatorenal fibrocystic diseases,[7] most of which are characterized by large, echogenic kidneys in the fetus and neonate. However, recent studies indicate that to a large extent these disorders can be distinguished by ultrasound.[17] ARPKD kidneys *in utero* are hyperechogenic and display *decreased* corticomedullary differentiation because of the hyperechogenic medulla (Fig. 47-3, *A*). With high-resolution ultrasound, the radial array of dilated collecting ducts may be imaged. In comparison, ADPKD kidneys *in utero* tend to be moderately enlarged with a hyperechogenic cortex and relatively hypoechogenic medulla causing *increased* corticomedullary differentiation.

Kidney size typically peaks at 1 to 2 years of age, then gradually declines relative to the child's body size, and stabilizes by 4 to 5 years.

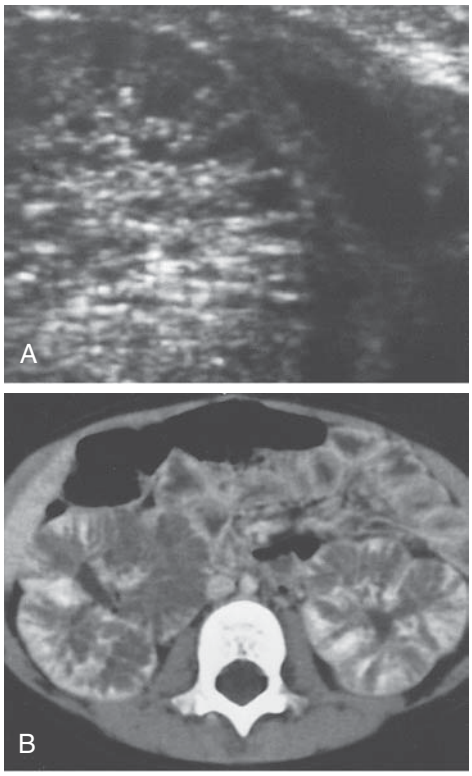


Figure 47-3 Radiologic findings associated with autosomal recessive polycystic kidney disease. A, ARPKD in a neonate. High-resolution ultrasound reveals radially arrayed dilated collecting ducts. **B,** ARPKD in symptomatic 4-year-old girl. Contrast-enhanced CT shows striated nephrogram and prolonged corticomedullary differentiation.

As patients age, there is increased medullary echogenicity, with scattered small cysts measuring less than 2 cm in diameter. These cysts and progressive fibrosis can alter the usual kidney contour, causing ARPKD in some older children to be mistaken for ADPKD. Contrast-enhanced computed tomography (CT) scanning can be useful in delineating the renal architecture in these children (Fig. 47-3, *B*). Bilateral pelvicaliectasis and renal calcifications have been reported in 25% and 50% of ARPKD patients, respectively.[11,18] In adults with medullary ectasia alone, the cystic lesion may be confused with medullary sponge kidney.

The liver may be either normal in size or enlarged. It is usually less echogenic than the kidneys. Prominent intrahepatic bile duct

Features of Pediatric Renal Cystic Disease						
Feature	**ARPKD**	**NPHP**	**Meckel-Gruber**[1]	**GCKD**[2]	**ADPKD**	**TSC**
Clinical Characteristics						
Clinical onset	Perinatal	NPHP2: 0-5 yr NPHP: 10-18 yr	Perinatal, infancy	Infancy, older children	Infancy,[3] older children	Infancy,[3] older children
Enlarged kidneys	Yes	NPHP2: yes NPHP3: some cases NPHP: no	Yes	No	Occurs	Occurs
Renal pathology	Multiple cysts	NPHP2: multiple cysts NPHP: few cysts at CM junction	Multiple cysts	Multiple cortical cysts	Multiple cysts	Few to multiple cysts; angiomyolipoma
Cyst infection	Uncommon	No	Uncommon	No	Occurs	Uncommon
Blood pressure	Normal/ increased	NPHP2: increased NPHP: normal	Normal	Normal/ increased	Normal/ increased	Normal/increased
Renal function	Normal/impaired	Normal/impaired	Normal/impaired	Normal	Normal	Normal
Nephrocalcinosis/ nephrolithiasis	Nephrocalcinosis up to 25%	No	No	No	Nephrolithiases occur	No
CHF[4]	Yes	Rare	Yes	No	10%-15% infantile ADPKD	No
Pancreas lesions	No	No	No	MODY5	No	No
CNS involvement	No	(Joubert)[5]	Encephalocele; mental retardation	No	No	Seizures, mental retardation
Genetics						
Disease gene	*PKHD1*	*NPHP1-NPHP15*	*MSK1-MSK10*	*PKD1* *TCF2*	*PKD1* *PKD2*	*TSC1* *TSC2*
Genetic testing[6]	Yes	Most*	Most*	Yes	Yes	Yes

Table 47-2 Features of pediatric renal cystic disease. *ARPKD,* Autosomal recessive polycystic kidney disease; *CM,* corticomedullary. [1]Meckel-Gruber syndrome (MKS) is a severe, often lethal autosomal recessive disorder characterized by bilateral renal cystic dysplasia, biliary ductal dysgenesis, bilateral postaxial polydactyly, and variable central nervous system (CNS) malformations. The triad of renal cystic disease, occipital encephalocele, and polydactyly is most common. Genes disrupted in MKS have also been identified in nephronophthisis (NPHP) and Joubert patients, suggesting a phenotypic spectrum. [2]Glomerulocystic kidney disease (GCKD) can occur as the infantile manifestation of autosomal dominant polycystic kidney disease (ADPKD). Familial hypoplastic GCKD, caused by mutations in *TCF2*, the gene encoding hepatocyte nuclear factor (HNF-1β), can be associated with maturity-onset diabetes of the young, type 5 (MODY5). [3]A contiguous germ-line deletion of both the *PKD1* and the *TSC2* gene (the PKDTS contiguous gene syndrome; MIM 600273) occurs in a small group of patients with features of tuberous sclerosis complex (TSC), as well as massive renal cystic disease reminiscent of ADPKD, severe hypertension, and a progressive decline in renal function with the onset of end-stage renal disease (ESRD) in the second or third decade of life. [4]Congenital hepatic fibrosis (CHF). [5]Joubert syndrome (JBTS; MIM 213300) is a genetically heterogeneous (JBTS 1-20), autosomal recessive disorder characterized by developmental defects in the cerebellum (cerebellar vermis aplasia) and the eye (coloboma), as well as retinitis pigmentosa, congenital hypotonia, and either ocular motor apraxia or irregularities in breathing patterns during the neonatal period. The disease can be associated with NPHP, and mutations in several *NPHP* genes have been described in JBTS patients. [6]Genetic testing: listed at GeneTests (http://www.genetests.org) and the NIH Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr). *Testing is available for most *NPHP* and *MKS* genes.

dilation suggests associated Caroli syndrome. With age, the portal fibrosis tends to progress, and in older children, ultrasound typically shows hepatosplenomegaly and a patchy increase in hepatic echogenicity.[16,19]

Genetic Testing

With the identification of *PKHD1* as the principal disease gene in ARPKD, genetic testing is available as a clinical diagnostic tool. The mutation detection rate is 80% to 87%. Current diagnostic algorithms include gene-based analysis and haplotype-based genotyping (in informative families).[20,21] Genetic testing is primarily applied in the context of prenatal testing and preimplantation genetic diagnosis.[22] To date, there is limited evidence for genotype-phenotype correlations, except perhaps in affected fetuses.[23] Although patients with two truncating mutations have been reported to have a higher risk of perinatal demise,[21,24] recent studies identified a large, homozygous deletion in an 8-year-old boy.[25] ARPKD is associated with a high frequency of unique, missense changes in *PKHD1*, which can complicate the unequivocal interpretation of gene-based testing. Moreover, about 20% of ARPKD siblings have discordant clinical phenotypes.[10] These data may complicate genetic counseling, and caution must be exercised in predicting the clinical outcome of future affected children.[26]

Treatment

The survival of ARPKD neonates has improved significantly in the last two decades because of advances in mechanical ventilation for neonates and other supportive measures. Aggressive interventions such as unilateral or bilateral nephrectomies and continuous hemofiltration have been advocated in neonatal management, but prospective, controlled studies have yet to be performed.

For those children who survive the perinatal period, blood pressure control is a major clinical issue. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), adrenergic antagonists, and loop diuretics are effective antihypertensive agents.

The management of ARPKD children with declining GFR should follow the standard guidelines established for chronic kidney disease (CKD) in pediatric patients.[27]

Given the relative urinary concentrating defect, ARPKD children should be monitored for dehydration during intercurrent illnesses associated with fever, tachypnea, nausea, vomiting, or diarrhea. For infants with severe polyuria, thiazide diuretics may be used to decrease distal nephron solute and water delivery. Acid-base balance should be closely monitored and supplemental bicarbonate therapy initiated as needed.

Close monitoring for portal hypertension is warranted in all ARPKD patients. There is no correlation between the severity of the kidney and liver disease.[3,19] Recent studies suggest that the platelet count combined with serial abdominal ultrasound (assessing liver and splenic size) and Doppler flow studies provide good surrogate markers for the portal hypertension severity.[19] Medical management may include sclerotherapy or variceal banding.[16] Surgical approaches such as portocaval or splenorenal shunting may be indicated in some patients. Although hypersplenism occurs quite often, splenectomy is seldom warranted. Unexplained fever with or without elevated transaminase levels suggests bacterial cholangitis and requires meticulous evaluation, sometimes including a percutaneous liver biopsy, to make the diagnosis and guide aggressive antibiotic therapy.

Effective management of systemic and portal hypertension, coupled with successful renal replacement therapy, has allowed long-term patient survival. Therefore, the prognosis in ARPKD, particularly for children who survive the first month of life, is much less bleak than generally thought, and aggressive medical therapy is warranted.

Current treatment of patients with ARPKD is entirely supportive, although preclinical studies suggest that new, targeted therapies may have future benefit for this cohort of patients.[28]

Transplantation

A prolonged period of dialysis in childhood has been associated with both cognitive and educational impairment. Therefore, renal transplantation is the treatment of choice for ESRD in ARPKD patients, and at least one report advocates preemptive nephrectomy in neonates with greatly enlarged kidneys.[29] ARPKD is a recessive disorder, and therefore either parent may be a suitable kidney donor. However, the recent identification of subtle renal and liver ultrasound abnormalities in ARPKD parents[30] suggests caution that requires more extensive follow-up analyses. Native nephrectomies may be warranted in patients with massively enlarged kidneys to allow allograft placement.

In some patients, combined kidney-liver transplantation may be appropriate.[31] Indications include the combination of renal failure and either recurrent cholangitis or significant complications of portal hypertension (e.g., recurrent variceal bleeding, refractory ascites, hepatopulmonary syndrome). In addition, liver transplantation may be a consideration for patients with a single episode of cholangitis in the context of marked abnormalities in the biliary system (Caroli syndrome).[16]

JUVENILE NEPHRONOPHTHISIS–MEDULLARY CYSTIC DISEASE COMPLEX

Definitions

Juvenile nephronophthisis (NPHP) and medullary cystic kidney disease (MCKD) share the same triad of histopathologic features: tubular basement membrane irregularities, tubular atrophy with cyst formation, and interstitial cell infiltration with fibrosis. These histopathologically similar disorders differ only in their mode of transmission, age of onset, and genetic defects. NPHP is an autosomal recessive disorder that presents in childhood, whereas MCKD is an autosomal dominant disorder that occurs in adults. The inclusive term *juvenile nephronophthisis–medullary cystic kidney disease complex* has been used to describe these disorders. NPHP is much more common than MCKD, however, and NPHP has been reported both as an isolated renal disease and in association with a wide range of systemic manifestations, including retinitis pigmentosa, congenital hepatic fibrosis, oculomotor apraxia, and skeletal anomalies. Therefore, these entities are considered separately.

Autosomal Recessive Juvenile Nephronophthisis

An autosomal recessive tubulointerstitial nephropathy, NPHP is one of the most frequent inherited causes of ESRD in children and adolescents.[32] The term *nephronophthisis* derives from the Greek, meaning "progressive loss of nephrons."

Genetic Basis of NPHP

Multiple disease-causing genes have been identified in NPHP patients. Defects in *NPHP1* account for 21% of NPHP, with large, homozygous deletions detected in 80% of affected family members and in 65% of sporadic cases. Mutations in each of the remaining *NPHP* genes cause no more than 3% of NPHP-related disease.[32] Clinical disease expression seems to be exacerbated by oligogenic inheritance, that is, patients carrying two mutations in a single *NPHP* gene, as well as a single-copy mutation in an additional *NPHP* gene. In addition, multiple allelism, or distinct mutations in a single gene, appears to explain the continuum of multiorgan phenotypic abnormalities observed in NPHP, Meckel syndrome, and Joubert syndrome.[33,34]

Most of the protein products of the NPHP-associated genes are expressed in the cilia-centrosome complex,[32,34] and NPHP is considered as one of the ciliopathies.

Clinical Manifestations

Renal Disease Three distinct forms of NPHP—infantile, juvenile, and adolescent—were initially described, based on the age of onset of ESRD. In the infantile form, ESRD consistently occurs before 5 years of age, whereas in juvenile NPHP, the most common form, ESRD occurs at a mean age of 13 years. However, no clear genotype-phenotype correlation exists for this spectrum of presentations, and these disorders should be referred to with the single designation, NPHP.[35,36]

Decreased urinary concentrating capacity is invariable in NPHP and usually precedes the decline in renal function, with typical onset between 4 and 6 years of age. Polyuria and polydipsia are common. Salt wasting develops in most patients with renal impairment, and sodium supplementation is often required until the onset of ESRD. One third of patients become anemic before onset of renal impairment, attributed to a defect in the functional regulation of erythropoietin production by peritubular fibroblasts.[37] Growth restriction disproportionate to the degree of renal impairment is a common finding.

Slowly progressive decline in renal function is typical of NPHP. Although symptoms can be detected after age 2 years, they may progress insidiously, such that 15% of affected patients are recognized only after ESRD has developed. There is no specific treatment. The disease is not known to recur in renal allografts.

Children with the infantile variant develop symptoms in the first few months of life and rapidly progress to ESRD, usually before age 2 years but invariably by age 5. Severe hypertension is common in this disorder.

Unlike patients with polycystic kidney disease or medullary sponge kidney, NPHP patients rarely develop flank pain, hematuria, hypertension, UTIs, or renal calculi.

Associated Extrarenal Abnormalities Extrarenal abnormalities have been described in approximately 10% to 15% of NPHP patients.[38] The most frequently associated anomaly is *retinal dystrophy* caused by tapetoretinal degeneration (Senior-Loken syndrome). Severely affected patients present with coarse nystagmus, early blindness, and a flat electroretinogram (Leber congenital amaurosis); whereas those with moderate retinal dystrophy typically have mild visual impairment and retinitis pigmentosa. Other extrarenal anomalies include oculomotor apraxia (Cogan syndrome), cerebellar vermis aplasia (Joubert syndrome), and cone-shaped epiphyses of the bones. Congenital hepatic fibrosis occurs on occasion in NPHP patients, but the associated bile duct proliferation is mild and qualitatively different from that in ARPKD.

Pathology

In classic NPHP, the kidneys are moderately contracted, with parenchymal atrophy causing a loss of corticomedullary demarcation. Histopathological findings include tubular atrophy with thickened tubular basement membrane, diffuse and severe interstitial fibrosis, and cysts of variable size distributed in an irregular pattern at the corticomedullary (CM) junction and in the outer medulla. However, up to 25% of NPHP kidneys have no grossly visible cysts.

In the typical NPHP renal lesion, clusters of atrophic tubules either alternate with groups of viable tubules showing dilation or with marked compensatory hypertrophy or with groups of collapsed tubules. Multilayered thickening of tubular basement membranes is a prominent histopathologic feature (Fig. 47-4). This pattern is not unique, but the abrupt transition from one type of tubular profile to another suggests NPHP. Moderate interstitial fibrosis, usually without a significant inflammatory cell infiltrate, is interspersed among the atrophic tubules. Spherical, thin-walled cysts lined with a simple cuboidal epithelium may be evident at the CM junction, in the medulla, and even in the papillae. Microdissection studies indicate that these cysts arise from the loop of Henle, distal convoluted tubules, and collecting ducts. Glomeruli may be normal, although some may be completely sclerosed. Other glomeruli show periglomerular fibrosis, and still others have dilation of Bowman space, suggestive of glomerulocystic kidney disease.[39]

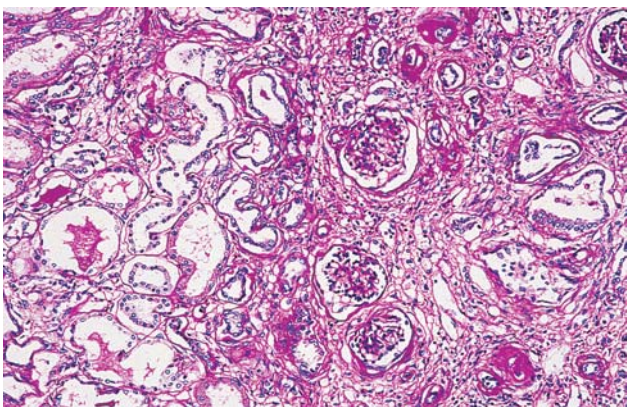


Figure 47-4 Renal pathology in juvenile nephronophthisis. Light microscopy shows tubulointerstitial nephropathy. Atrophic tubules with irregularly thickened basement membranes are surrounded by interstitial fibrosis. Dilated tubules are evident at the corticomedullary junction. (HE stain; ×40.)

In comparison, the infantile form has features of both classic NPHP, such as tubular cell atrophy, interstitial fibrosis, and tubular cysts, and polycystic kidney disease (PKD), including enlarged kidneys and widespread cystic involvement.[36]

Diagnosis

In a child with NPHP and renal impairment, ultrasound typically reveals normal-sized or small kidneys with increased echogenicity and loss of corticomedullary differentiation. On occasion, cysts can be detected at the CM junction or in the medulla. Thin-section CT scanning may be more sensitive than ultrasound in detecting these cysts.

The pathologic findings in NPHP are not unique. Thus, in the early stages of the disease, neither renal imaging nor histopathology can confirm the clinical diagnosis. Molecular testing can be useful in establishing the diagnosis of *NPHP1*-related disease.[40] Newer strategies using next-generation sequencing technologies should allow high-throughput mutation detection for known *NPHP* genes, although defects in these genes account for disease in only 30% to 40% of NPHP patients.[41]

Treatment

Current treatment of NPHP is entirely supportive. However, preclinical studies suggest that new, targeted therapies may have benefit for these patients. Specifically, treatment with OPC31260, a vasopressin receptor 2 antagonist, remarkably attenuated renal cystic disease progression in the *pcy* mouse, a model of *NPHP3*-related disease. Roscovitine, a cyclin-dependent kinase inhibitor, arrested cystic disease progression in the *jck* mouse, a model of *NPHP9*-related disease.[28]

Autosomal Dominant Medullary Cystic Kidney Disease

An autosomal dominant condition, MCKD is much rarer than autosomal recessive NPHP, but histopathologically indistinguishable. Some patients with MCKD have had phenotypically unaffected parents but an affected second- or third-degree relative, suggesting that the disease is poorly recognized in affected family members, or that there is variable penetrance.

Genetic studies indicate that defects in at least two loci (*MCKD1* and *MCKD2*) cause medullary cystic kidney disease. Uremia occurs after age 60 in MCKD1 (Mendelian Inheritance in Man [MIM] 174000), whereas in MCKD2 (MIM 603860), progression to ESRD occurs about age 30. Mutations in the gene *UMOD,* which encodes uromodulin or Tamm-Horsfall protein, have been identified in MCKD2 patients. Subsequently, *UMOD* mutations have also been identified in families with familial juvenile hyperuricemic nephropathy (FJHN; MIM 162000), a dominantly transmitted disorder characterized by MCKD, hyperuricemia, and gout, as well as familial glomerulocystic disease with hyperuricemia (MIM 609886).

Recent studies using new next-generation sequencing technologies in a set of six MCKD1 families have identified an apparently independent mutation that involves the insertion of a single nucleotide into a coding variable-number tandem repeat (VNTR) sequence within the *MUC1* gene that encodes mucin-1.[42]

The diagnosis can usually be made based on the family history, the clinical associations of hyperuricemia and gout, and the ultrasound finding of medullary cysts. Genetic testing is available for *UMOD*-related disease (http://www.genetests.org/).

MEDULLARY SPONGE KIDNEY

Definition

Medullary sponge kidney (MSK) is a relatively common disorder characterized by dilated medullary and papillary collecting ducts that give the renal medulla a spongy appearance. This renal malformation is typically associated with nephrocalcinosis, recurrent calcium nephrolithiasis, bone mineralization defects, and an increased risk of UTI.

Etiology and Pathogenesis

The occasional presence of embryonal tissue in the affected papillae and coexistence of other urinary tract anomalies suggest that MSK results from a developmental defect in the medullary pyramids. In addition, MSK occurs more frequently in individuals with other developmental anomalies or tumors (e.g., congenital hemihypertrophy, Beckwith–Wiedemann syndrome, CAKUT syndrome, Wilms tumor).[43]

In general, MSK is considered to be a sporadic disorder, but recent studies have provided strong evidence for familial clustering of MSK involving autosomal dominant inheritance with reduced disease penetrance and variability in disease expression.[44]

Epidemiology

In the general population, the frequency of MSK may be underestimated because some affected individuals remain entirely asymptomatic. Up to 20% of patients with nephrolithiasis have at least a mild degree of MSK, but excretory urography in *unselected* patients indicates a disease frequency of approximately 1 in 5000 individuals.

Clinical Manifestations

Medullary sponge kidney disease is asymptomatic unless complicated by nephrolithiasis, hematuria, or infection. Symptoms typically begin between the fourth and fifth decade of life, but adolescent presentations have been reported. Stones or granular debris in MSK patients are composed of either pure apatite (calcium phosphate) or a mixture of apatite and calcium oxalate. Several factors appear to contribute to stone formation, including urinary stasis within the ectatic ducts, hypercalciuria, and hypocitraturia. Hyperparathyroidism has also been reported.

Hematuria, unrelated to either coexisting stones or infection, may be recurrent. The bleeding is usually asymptomatic, unless gross hematuria causes clot-related colic. UTI may occur in association with nephrolithiasis or as an independent event. In those with stones, infections are more likely to occur in female than male patients.

Decreased renal concentrating ability and impaired urinary acidification are common clinical features. In most patients, the acidification defect is not associated with overt systemic acidosis, but bone mineralization defects are well described in MSK patients.[43]

Pathology

The pathologic changes are confined to the renal medullary and intrapapillary collecting ducts. Multiple spherical or oval cysts measuring 1 to 8 mm may be detected in one or more papillae. These cysts may be isolated or may communicate with the collecting system. The cysts are frequently bilateral and often contain spherical concretions composed of apatite. The affected pyramids and associated calyces are usually enlarged, and nephromegaly can result when many pyramids are involved. The renal cortex, medullary rays, calyces, and pelvis appear normal, unless complications such as pyelonephritis or urinary tract obstruction become superimposed.

Diagnosis

Abdominal plain radiographs often reveal radiopaque concretions in the medulla (Fig. 47-5, *A*). Historically, the diagnosis has been established by excretory urography (Fig. 47-5, *B*). Retention of contrast media by the ectatic collecting ducts appears either as spherical cysts or more often as diffuse linear striations. The latter imparts a characteristic blush-like pattern to the papillae, the so-called bouquet of flowers or paintbrush appearance. Medullary nephrocalcinosis is a

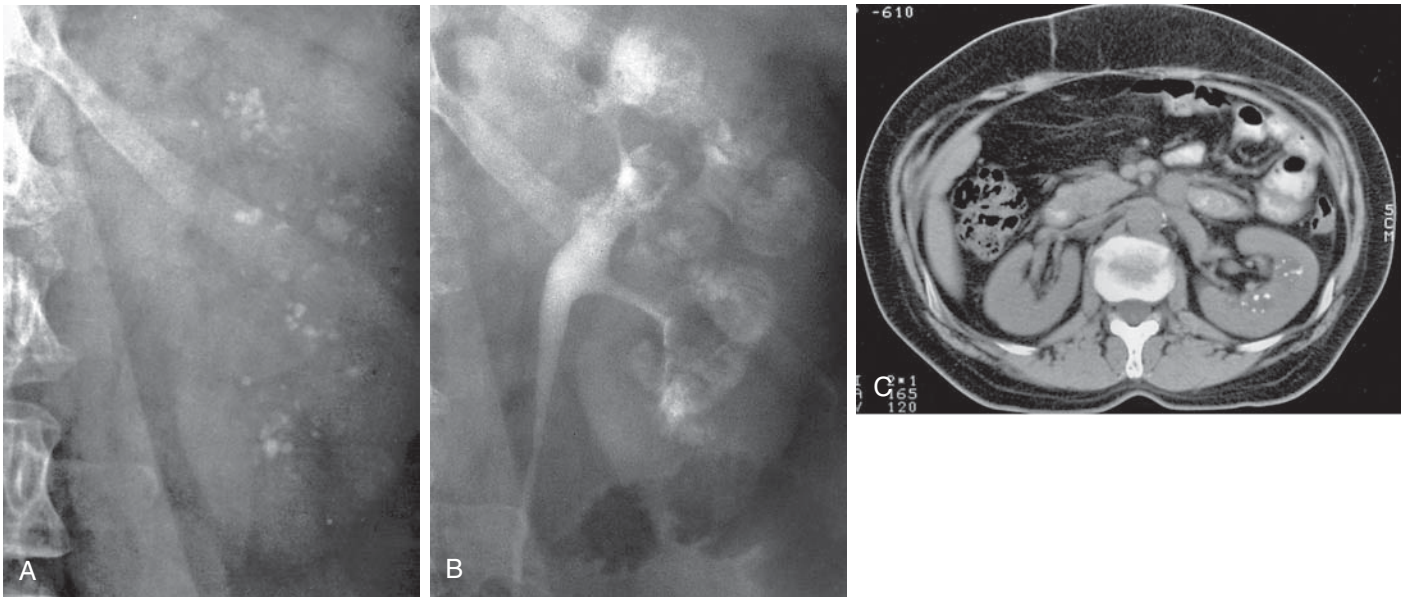


Figure 47-5 Radiologic findings associated with medullary sponge kidney. MSK in symptomatic 52-year-old woman. **A,** Preliminary film shows medullary nephrolithiases. **B,** Ten-minute film from excretory urography shows clusters of rounded densities in the papillae among discrete linear opacities (paintbrush appearance). **C,** Nonenhanced CT reveals densely echogenic foci in the medulla.

common, but not invariable, finding. Urography has been almost completely replaced by CT for routine clinical imaging. Nonenhanced CT may help distinguish MSK from papillary necrosis or even ADPKD (Fig. 47-5, *C*).

Treatment

Asymptomatic patients in whom MSK is detected as an incidental finding require no therapy. Hematuria in the absence of stones or infection requires no intervention. If the tubular ectasia is unilateral and segmental, partial nephrectomy may alleviate recurrent nephrolithiasis and UTI. However, for the majority of patients who have bilateral disease, medical management is sufficient.

Hypercalcuria and hypocitrituria are the predominant factors contributing to nephrolithiasis in MSK. The mainstays of treatment are potassium citrate and high fluid intake. Patients with persistent hypercalcuria and/or recurrent stone formers may benefit from thiazide diuretics. If thiazides are poorly tolerated or contraindicated, inorganic phosphate therapy may be useful. To avoid struvite stone formation, oral phosphates should *not* be used in patients with previous urinary tract infections caused by urease-producing organisms. Patients who form and pass stones recurrently may require lithotripsy or surgical intervention (see Chapter 61).

Urinary tract infection should be treated with standard antibiotic regimens, and for some patients, prolonged therapy may be warranted. Urease-producing organisms, such as coagulase-negative staphylococcus, are particularly problematic as urinary pathogens in MSK. Positive urine cultures, even with relatively insignificant colony counts, must be vigorously pursued.

With proper management of the clinical complications, the long-term prognosis of patients with MSK is excellent. Progression to renal impairment is unusual.

TUBEROUS SCLEROSIS COMPLEX

Definition

Tuberous sclerosis complex (TSC) is an autosomal dominant, tumor-suppressor gene syndrome in which tumor-like malformations, called hamartomas, develop in multiple organ systems, including the kidneys, brain, heart, lungs, and skin.

Etiology and Pathogenesis

Tuberous sclerosis complex results from inactivating mutations in one of two genes, *TSC1* on chromosome 9q32-q34 and *TSC2* on chromosome 16p13, adjacent to the *PKD1* gene.[45] Large deletions involving both *PKD1* and *TSC2* results in the PKD1/TSC2 (PKDTS) contiguous gene deletion syndrome.[46]

The focal nature of TSC-associated disease and the variability of disease expression even within families suggest that *TSC1* and *TSC2* function as tumor suppressor genes.[45] This paradigm hypothesizes that two successive mutations are necessary to inactivate a tumor suppressor gene and cause tumor formation. The first mutation, inherited and therefore present in all cells, is necessary but not sufficient to produce tumors. A second mutation occurs after fertilization and is required to induce tumor transformation. The inactivating germ-line mutations identified in *TSC1* and *TSC2*, as well as the loss of heterozygosity detected in *TSC2*-associated and *TSC1*-associated hamartomas, support the hypothesis that both *TSC1* and *TSC2* function as tumor suppressor genes.[47]

The *TSC2* gene product, tuberin, interacts with hamartin, the product of the *TSC1* gene. The hamartin/tuberin (TSC1/TSC2) complex functions in multiple cellular pathways, primarily by inhibiting the kinase activity of mTOR, the mammalian target of rapamycin, which functions in a protein complex (mTORC1) to regulate nutrient uptake, cell cycle progression, cell growth, and protein translation[45,48] (Fig. 47-6). The *PKD1* gene product, polycystin-1, plays a key role in regulating mTORC1 activity by complexing with tuberin and mTOR, thereby inhibiting the mTOR pathway.[49] In normal, adult kidney, mTOR is inactive. With loss of function of either polycystin-1 or tuberin, mTOR activity is upregulated, contributing to dysregulated cell growth and cystogenesis. In addition, hamartin appears to function via TORC1-independent pathways to regulate the structural integrity of the primary cilium, suggesting that ciliary dysfunction is an additional mechanism in TSC pathogenesis.[50]

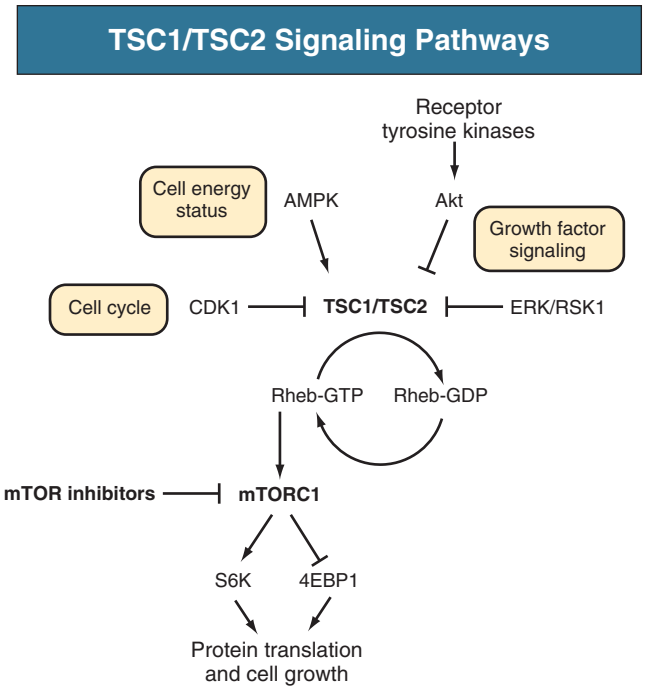


Figure 47-6 The TSC1/TSC2 signaling pathways. Hamartin (TSC1) and tuberin (TSC2) integrate signals from extracellular growth factor binding (via Akt and ERK/RSK1), the intracellular energy status (via AMPK) and the cell cycle (via CDK1) to direct signaling pathways that regulate cellular proliferation, differentiation, and migration. Tuberin contains a guanosine triphosphatase (GTPase)–activating protein (GAP) domain in its carboxy terminus, and when it forms a complex with hamartin (TSC1/TSC2 complex) the small GTPase Rheb is converted from its active GTP-bound state to an inactive GDP-bound state. Rheb is an activator of the mTORC1 kinase, which regulates a number of processes linked to protein synthesis and cell growth (via the ribosomal S6 kinases and the eukaryotic initiation factor 4E–binding protein (4E-BP1). mTORC1 is activated physiologically in response to growth factor signaling, which causes phosphorylation of tuberin, dissociation of the TSC1/TSC2 complex, and increased levels of Rheb-GTP. Inactivation of the TSC1/TSC2 complex through mutations in *TSC1* or *TSC2* leads to inappropriate activation of mTORC1. *(Modified from reference 78.)*

Epidemiology

Tuberous sclerosis complex affects 1 in 6000 to 10,000 individuals.[48] The disease penetrance is quite variable. About 70% of TSC patients are sporadic cases with no family history, and the disease apparently results from new mutational events. Among patients with sporadic disease, mutations in *TSC2* are approximately five times more common than mutations in *TSC1*; whereas the ratio is 1 : 1 in familial

cases.[51] *TSC1*-related disease is milder, apparently because of a reduced rate of "second hits."

Clinicopathologic Manifestations

The clinical features of *TSC1*- and *TSC2*-linked disease are similar, although *TSC2*-linked disease tends to be more severe.[52] The most common clinical manifestations include seizures, mental retardation and/or autism, skin lesions, interstitial lung disease, and tumors in the brain, retina, kidney, and heart. In affected individuals over 5 years of age, the most common skin lesions are facial angiofibromas (Fig. 47-7), hypomelanotic macules, and ungual fibromas.[53]

Kidney involvement occurs frequently in TSC, with up to 60% of patients manifesting renal lesions that include angiomyolipomas (85%), cysts (30% to 47%), and malignancies (2% to 4%).[48,54] Some of the malignant tumors originally thought to be renal cell carcinoma (RCC) have been reclassified as epithelioidangiomyolipomas.[55] Other renal neoplasms, interstitial fibrosis with focal segmental glomerulosclerosis (FSGS), glomerular microhamartomas, and peripelvic and perirenal lymphangiomatous cysts have also been observed in TSC patients. Renal involvement in TSC often progresses insidiously but can result in considerable morbidity, including retroperitoneal hemorrhage, renal impairment (~1%), and death. Renal complications are the most frequent cause of death in TSC patients.[48]

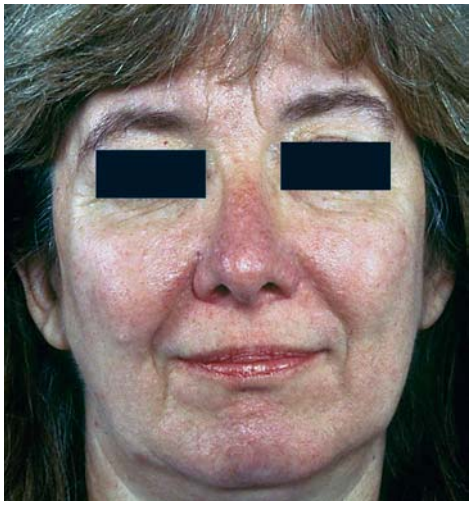


Figure 47-7 Facial angiofibromas in tuberous sclerosis complex. The angiofibromas are small red bumps giving a facial rash in a butterfly distribution and on the chin.

Renal Angiomyolipomas

Angiomyolipomas are hamartomatous structures composed of abnormal, thick-walled vessels, varying amounts of smooth muscle–like cells, and adipose tissue (Fig. 47-8, *A* and *B*). These are the most common renal lesion in TSC patients, evident in about 80% of cases by age 10 years.[48] While solitary angiomyolipomas are found in the general population, particularly among older women, TSC-associated angiomyolipomas are multiple and bilateral, with a young age of onset. Angiomyolipomas rarely occur before 5 years, but increase in frequency and size with age.[48] These angiomyolipomas can be locally invasive, extending into the perirenal fat or more rarely, the collecting system, renal vein, and even the inferior vena cava and right atrium. Lymph node and splenic involvement likely represent multifocal origin rather than metastases.

Clinical manifestations result from hemorrhage (intratumoral or retroperitoneal) or mass effects (abdominal or flank masses and tenderness, hypertension, renal impairment). Women tend to have more numerous and larger angiomyolipomas than men. Pregnancy appears to increase the risk of rupture and hemorrhage.

Renal Cysts

Renal cysts occur less frequently than angiomyolipoma in TSC patients. However, as with angiomyolipoma, renal cysts tend to increase in size and number over time. The concurrence of cysts and angiomyolipomas, easily detected by CT, is strongly suggestive of TSC.

The cysts in TSC can develop in any nephron segment. When limited in number and size, TSC-related cysts are predominantly cortical. In some cases, glomerular cysts predominate.[39] The epithelial lining of the cysts is distinctive and appears to be unique to TSC, with large and acidophilic epithelia containing large, hyperchromatic nuclei with occasional mitotic figures (Fig. 47-8, *C*). Associated papillary hyperplasia and adenomas are common.

A small subset of affected infants can present with massive renal cystic disease, severe hypertension, and a progressive decline in renal function with the onset of ESRD in the second or third decade of life. The majority of these patients have a contiguous germ-line deletion involving both the *TSC2* and the *PKD1* gene, the PKDTS contiguous gene syndrome.[46] Early detection, strict blood pressure control, and prompt therapy for the associated infantile spasms may favorably impact the overall prognosis.

Renal Neoplasms

Many cases of benign epithelial tumors, such as papillary adenomas and oncocytomas, have been reported in TSC patients. However, despite the multiplicity of benign tumors, malignant transformation

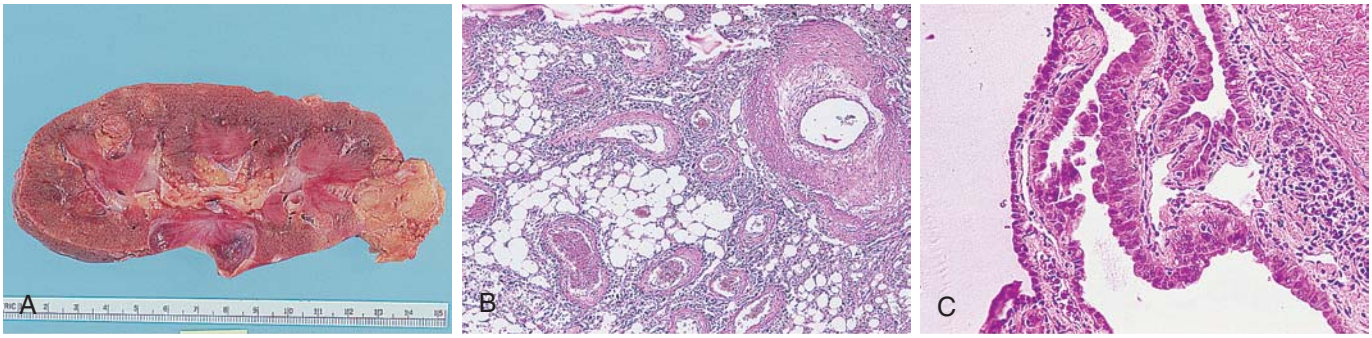


Figure 47-8 Renal pathology in tuberous sclerosis complex (TSC). A, Cut section shows multiple angiomyolipomas in kidney of 60-year-old symptomatic woman. **B,** Light microscopy shows angiomyolipoma containing adipose tissue and spindle smooth muscle–like cells interspersed between abnormal vessels with thickened walls (HE stain; ×16). **C,** Light microscopy shows TSC cysts lined with distinctive epithelia consisting of large, acidophilic cells with hyperchromatic nuclei (HE stain; ×65).

Clinical Diagnostic Criteria for Tuberous Sclerosis Complex*

Major
Facial angiofibromas or forehead plaque
Nontraumatic ungual or periungual fibroma
Hypomelanotic macules (>3)
Shagreen patch (connective tissue nevus)
Multiple retinal nodular hamartomas
Cerebral cortical nodules (tubers)
Subependymal nodule
Subependymal giant cell astrocytoma
Cardiac rhabdomyomas (≥1)
Lymphangioleiomyomatosis
Renal angiomyolipoma

Minor
Multiple, random dental pits
Hamartomatous gastrointestinal or rectal polyps
Bone cysts
White matter radial migration lines
Gingival fibromas
Nonrenal hamartoma
Retinal achromic patch
"Confetti" skin lesions
Multiple renal cysts

Box 47-1 Clinical diagnostic criteria for tuberous sclerosis complex (TSC). *Two major features or one major feature with two minor features indicate definite TSC; one major feature and one minor feature indicate probable TSC; and one major feature or two minor features indicates possible TSC. *(Modified from reference 53.)*

is rare. TSC-associated renal neoplasms are predominantly clear cell renal carcinoma, but there is pathologic heterogeneity, with papillary and chromophobe carcinomas reported.[57] The prognosis of TSC-associated renal carcinomas compared to sporadic renal carcinomas in the general population is unknown. The lifetime risk of developing RCC in the context of TSC is 2% to 3%.[56]

Diagnosis

Tuberous sclerosis complex is a pleiotropic disease in which the size, number, and location of the lesions can be variable, even among affected individuals within the same family. Major and minor criteria have been developed to guide the diagnostic approach (Box 47-1). In this context, the diagnosis of TSC is made when two major features, or one major and two minor ones, can be demonstrated.[53] Imaging is the mainstay for diagnosis of TSC-associated renal lesions. The presence of small cysts and fat-containing angiomyolipomas strongly suggests TSC. The median age at presentation for both renal cysts and angiomyolipoma is 10 years, although these lesions have been detected in infancy.[58]

Annual renal imaging is advised for TSC patients. Historically, ultrasound screening has been the preferred modality because it does not involve radiation, is fast and relatively inexpensive, and has high sensitivity in detecting the fat-rich angiomyolipomas and renal cysts. However, ultrasound is relatively insensitive for detecting fat-poor lesions. CT is superior for detecting fat-poor lesions as well as small angiomyolipomas in diffusely hyperechoic kidneys and in differentiating small angiomyolipomas from perinephric or renal sinus fat (Fig. 47-9). Given that CT carries the risks of contrast nephrotoxicity and radiation exposure, magnetic resonance imaging (MRI) is becoming the preferred renal imaging modality in TSC patients.[48] On occasion, the distinction between an angiomyolipoma and carcinoma cannot be reliably established by imaging, and biopsy is indicated.

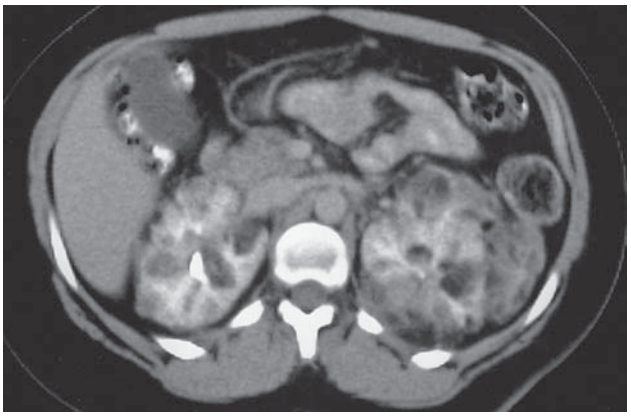


Figure 47-9 Radiologic findings associated with tuberous sclerosis complex. Contrast-enhanced CT showing bilateral angiomyolipomas in a 34-year-old symptomatic woman.

The TSC-associated renal cysts can radiologically mimic simple cysts and, when numerous, ADPKD. In the absence of angiomyolipomas, TSC-related renal cystic disease is suggested by the limited number of cysts compared with ADPKD and the absence of associated hepatic cysts. Although 10% of TSC patients have hepatic angiomyolipomas, hepatic cysts are rare.

Gene-based diagnosis is currently available for *TSC1*- and *TSC2*-related disease, as well as to detect large-scale deletions associated with the PKDTS contiguous gene syndrome (http://www.genetests.org).

Treatment

Renal Angiomyolipomas

Renal angiomyolipomas are benign lesions and often require no treatment. However, given the potential for growth and associated complications, such as pain, bleeding, and hypertension, annual imaging is recommended. Larger angiomyolipomas frequently develop microaneurysms and macroaneurysms, and the risk of serious hemorrhage correlates with aneurysms over 5 mm in diameter.[48] Therefore, these large angiomyolipomas require preemptive treatment with surgical removal in a nephron-sparing procedure or with embolization.[58] In addition to size and complications such as pain or hemorrhage, the inability to exclude an associated renal carcinoma should prompt intervention. When an associated malignancy cannot be excluded, renal-sparing surgery is preferred, such as enucleation or partial nephrectomy.

The increased frequency and size of the angiomyolipomas in women and the reports of hemorrhagic complications during pregnancy suggest that female sex hormones may accelerate the growth of these lesions. Therefore, it is prudent to caution patients with multiple angiomyolipomas about the potential risks of pregnancy and estrogen administration.

As noted, defective mTORC1 signaling is a central feature of TSC. A recent report of the first randomized, double-blind, placebo-controlled Phase III trial of the mTOR inhibitor everolimus, demonstrated a clear advantage for mTOR inhibition over placebo in reducing angiomyolipoma volume, with an acceptable safety profile in patients with TSC.[59]

Renal Cysts

The mainstay of treatment of the TSC-associated renal cystic disease is strict blood pressure control. Surgical decompression of cystic kidneys has been suggested, but no significant beneficial effect has been established.

Renal Carcinoma

Renal carcinoma should be suspected in enlarging, fat-poor lesions or when intratumoral calcifications are present. In these cases, biopsy is indicated. Because renal carcinoma is frequently bilateral in TSC, renal-sparing surgery should be performed whenever possible.

Transplantation

Chronic kidney disease, while rare in tuberous sclerosis, can occur by several different mechanisms, including angiomyolipoma-related parenchymal destruction, progressive renal cystic disease, interstitial fibrosis and FSGS. A large survey study of French dialysis centers indicated that the approximate prevalence of TSC-associated ESRD was 0.7 cases per 1 million. ESRD occurred in 1 per 100 TSC patients and was more frequent in females (63%), with a mean age diagnosis of 29 years.[60] Of note, both dialysis and renal transplantation provide appropriate modes of renal replacement therapy, but the risk of renal hemorrhage related to angiomyolipomas and malignant degeneration in TSC poses special risks. Therefore, it may be advisable that patients with TSC and ESRD undergo bilateral nephrectomy before initiation of renal replacement therapy.

VON HIPPEL–LINDAU DISEASE

Definition

Von Hippel–Lindau disease (VHL) is a dominantly transmitted, multisystem cancer predisposition syndrome associated with tumors of the eyes, cerebellum, spinal cord, adrenal glands, pancreas, and epididymis, as well as renal and pancreatic cysts.[61]

Etiology and Pathogenesis

Von Hippel–Lindau disease is a tumor suppressor disorder, with disease resulting from a germ-line mutation in the *VHL* gene and the subsequent development of a somatic mutation in this gene. In about 80% of patients, VHL is familial, and disease in 20% of cases results from *de novo* mutations. Moreover, *VHL* mutations have been identified in both the germ-line of VHL patients and the sporadic clear cell renal carcinomas, implying that *VHL* plays an important role in the pathogenesis of clear cell renal carcinoma.[62]

The VHL protein (pVHL) plays a critical role as a negative regulator of hypoxia-inducible gene. In the normal physiologic state, pVHL functions in a multiprotein complex that directs a number of proteins, most notably the alpha subunits of the transcription factor, hypoxia-inducible factor (HIF-α), for destruction via the ubiquitination pathway. In cells that lack pVHL, HIF-α subunits are stabilized and bind to HIF-β family members proteins. The heterodimer then translocates to the nucleus, leading to overexpression of HIF-target genes, which encode proteins that regulate glucose uptake, metabolism, extracellular pH, erythropoiesis, angiogenesis (vascular endothelial growth factor [VEGF] and platelet-derived growth factor B), and mitogenesis (transforming growth factor β). This transcriptional dysregulation promotes the pathologic growth and survival of endothelial cells, pericytes, and stromal cells and ultimately their malignant transformation.[48,62,63]

Classification of von Hippel–Lindau Disease Based on Tumor Spectrum

VHL Subtype	Tumor Manifestations
Type 1	Hemangioblastoma (CNS, retina), renal cell carcinoma Low risk for pheochromocytoma and pancreatic endocrine tumors
Type 2A	Hemangioblastoma (CNS, retina), pheochromocytoma, pancreatic endocrine tumors Low risk for renal cell carcinoma
Type 2B	Hemangioblastoma (CNS, retina), renal cell carcinoma, pheochromocytoma, pancreatic endocrine tumors
Type 2C	Predominantly pheochromocytoma Very limited risks for hemangioblastoma and renal cell carcinoma

Table 47-3 Classification of von Hippel–Lindau disease (VHL) based on tumor spectrum. *(Modified from reference 63.)*

Clinical Manifestations

Von Hippel–Lindau disease has an incidence of 1 in 36,000 newborns and has been observed in all ethnic groups.[48,61] Biallelic *VHL* inactivation leads to increased risk of central nervous system (CNS) and retinal hemangioblastomas, clear cell renal carcinomas, pheochromocytomas, pancreatic islet cell tumors, endolymphatic sac tumors, and papillary cystadenomas of the broad ligament (females) and epididymis (males). In addition, cystic changes can occur in the kidney and pancreas.

The VHL-associated diseases appear to cluster into two disease complexes (Table 47-3). In the initial stratification, VHL patients can be subclassified based on a low risk (type 1) or high risk (type 2) of developing pheochromocytoma. Type 1 disease is characterized by large deletions or truncations of the *VHL* gene, which cause complete inactivation of the gene and result in high levels of HIF activity. Type 2 disease primarily involves missense mutations and is associated with partial activity of pVHL. Type 2 patients can be further divided into three subtypes: type 2A, which has a low incidence of renal lesions; type 2B, associated with a high risk of RCC; and type 2C, associated only with pheochromocytoma and no other malignancies.[48,62,63]

Renal cell carcinomas are typically multiple and bilateral. Although RCC may present with hematuria or back pain, detection occurs more often as an incidental finding on unrelated imaging studies or during a screening protocol. The mean age of symptomatic presentation is 35 to 40 years, although patients have been diagnosed in adolescence. In VHL, men and women are equally affected with RCC, in contrast to the male predominance in sporadic RCC. VHL-associated RCC metastasizes to the lymph nodes, liver, lungs, and bones and accounts for about 50% of VHL-related deaths.

In VHL, renal cysts arise from tubular cells that have undergone somatic loss of the wild-type allele. Renal cysts occur in about 60% of patients and are usually bilateral. Deterioration of renal function caused by cystic kidney disease has been reported but is unusual.

Pathology

Renal cell carcinoma is one of the most common tumors in VHL, with a lifetime risk of about 70% for patients with VHL disease.[61] VHL-associated RCCs are mostly of the clear cell type and usually bilateral and multifocal in distribution. Detailed microscopic examination of VHL-associated renal cystic lesions often reveals small foci

Features of Adult Renal Cystic Disease						
Feature	**Simple Cysts**	**ADPKD**	**MSK**	**VHL**	**TSC**	**Acquired Cystic Disease**
Clinical Characteristics						
Clinical onset	>40 yr	30-40 yr	20-40 yr	30-40 yr	10-30 yr	With ESRD
Cysts	Single/multiple	Multiple	Multiple	Few, bilateral	Multiple	Multiple
Cyst infection	Uncommon	Common	Common	Uncommon	Uncommon	Uncommon
Tumors	No	Rare	No	RCC, often bilateral	AML/RCC	Common
Blood pressure	Normal/increased	Increased	Normal	Normal/increased	Normal/increased	Normal/increased
Renal function	Normal	Normal/impaired	Normal	Normal	Normal/impaired	Impaired/ESRD
Nephrolithiasis	No	Common	Common	No	No	No
Liver cysts	No	Common	No	Rare	No	No
Pancreas cysts	No	Few	No	Multiple	No	No
CNS involvement	No	Aneurysms	No	Hemangioblastomas	Seizures, mental retardation	No
Skin lesions	No	No	No	No	See Fig. 47-7	No
Genetics						
Disease gene	No	*PKD1* *PKD2*	No	*VHL*	*TSC1* *TSC2*	No
Genetic testing*	No	Yes	No	Yes	Yes	No

Table 47-4 Features of adult renal cystic disease. *ADPKD,* Autosomal dominant polycystic kidney disease; *AML,* angiomyolipoma; *CNS,* central nervous system; *ESRD,* end-stage renal disease; *MSK,* medullary sponge kidney; *RCC,* renal cell carcinoma; *TSC,* tuberous sclerosis complex; *VHL,* von Hippel–Lindau disease. *Genetic testing: listed at GeneTests (http://www.genetests.org) and the NIH Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr).

of carcinoma. VHL-associated RCCs tend to have low-grade histology and a better 10-year survival than sporadic RCCs. More advanced RCCs do metastasize and metastatic disease is a major cause of death in VHL patients.

Renal cysts may express carcinoma *in situ* with subsequent progression over time to RCC, presumably from mutations affecting other genetic loci.[48,61]

Diagnosis

The minimum clinical criteria for the diagnosis of VHL in an "at-risk" individual include the presence of a single retinal or cerebellar hemangioblastoma, or RCC, or pheochromocytoma.[61] Up to 50% of affected individuals with familial VHL may manifest only one feature of the syndrome. In presumed sporadic cases (20% of patients), the clinical diagnosis requires two or more retinal or CNS hemangioblastomas, or a single hemangioblastoma and a characteristic visceral tumor.

Molecular analysis of the *VHL* gene is indicated in patients with known or suspected VHL, or in at-risk children from VHL families, given that unsuspected, untreated tumors can cause significant morbidity.[62] Presymptomatic genotyping can be useful in determining the phenotypic classification of VHL and can be used to direct monitoring for a specific subset of tumors. In addition, genotyping can be useful in distinguishing whether a pheochromocytoma has occurred in the context of a *VHL* type 2 mutation, multiple endocrine neoplasia (MEN) type 2, or is nonsyndromic.[63] Genetic testing information is available (http://www.genetests.org/).

In patients with type 2 VHL disease, annual assessment of blood pressure, measurement of urinary catecholamine metabolites, as well as abdominal ultrasound imaging should be initiated at age 2 years. Abdominal MRI and iodine 131–metaiodobenzyl-guanidine (MIBG) scans are indicated if abnormalities are detected. By age 16 years, all patients with VHL should have annual MR scans of the abdomen. Ultrasound is a useful alternative imaging modality in pregnant women. Early detection of renal disease and a multidisciplinary approach to follow-up can substantially improve the longevity of VHL patients.[48,61]

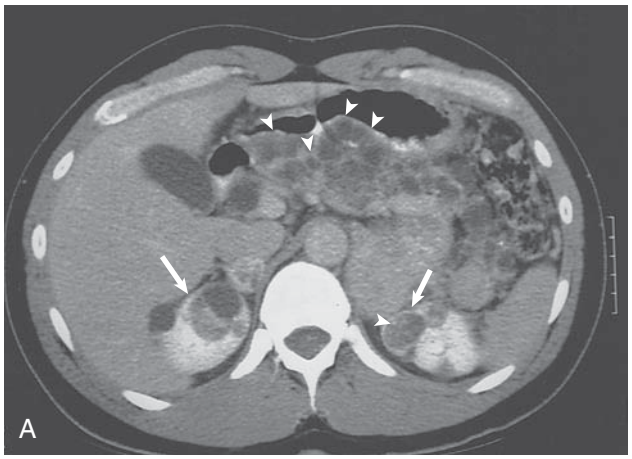
Differential Diagnosis

The differential diagnosis of VHL-associated renal lesions includes several conditions, most notably ADPKD and TSC (Table 47-4). As with VHL, ADPKD affects both genders with a similar mean age at presentation. However, kidney involvement in VHL is characterized by a few bilateral cysts, RCC, normal kidney size, normal blood pressure, and usually normal renal function. Cyst infection, a frequent finding in ADPKD, is uncommon in VHL. RCC is an infrequent complication of ADPKD. Cysts in the liver are frequent in ADPKD and rare in VHL. Pancreatic cysts are rare in ADPKD but can be numerous and scattered through the pancreas in VHL (Fig. 47-10, *A*). The CNS in ADPKD is affected by arterial aneurysms, whereas hemangioblastomas are the CNS manifestation of VHL (Fig. 47-10, *B*).

Tuberous sclerosis complex should be considered in the differential diagnosis of multiple renal tumors. In both TSC and VHL, multiple renal cysts occur. However, the TSC-associated renal tumor is usually an angiomyolipoma and extrarenal lesions readily distinguish VHL and TSC.

Treatment

Surgery continues to be the mainstay for RCC therapy in VHL patients. Optimal management requires surgical intervention before



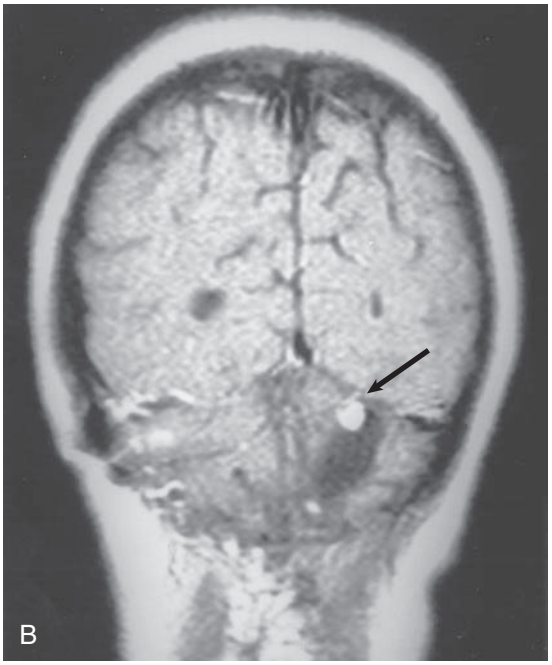


Figure 47-10 Radiologic findings associated with von Hippel–Lindau syndrome. A, Noncontrast CT shows massive cystic involvement of the pancreas *(arrowheads)* and bilateral renal cysts *(arrows)*. **B,** Contrast-enhanced MR image shows a right cerebellar hemangioblastoma with a small enhancing mass *(arrow)*.

renal vein invasion and distant metastases occur, because metastatic lesions respond poorly to chemotherapy and radiation. Nephron-sparing surgery is the procedure of choice when possible (see Chapter 61). Repeated surgical intervention may be required as tumors continue to develop. Laparoscopic surgery may have a role in the future management of these patients.

Bilateral nephrectomy and renal transplantation may be an acceptable alternative to repeated nephron-sparing surgery in patients with VHL-associated RCC. It remains to be determined whether post-transplant immunosuppression enhances the growth of the retinal and CNS hemangioblastomas and other lesions found in patients with VHL.

In terms of medical management, drugs that inhibit HIF-α, or its downstream targets (e.g., VEGF receptor kinase inhibitors), may be therapeutically useful in VHL-related hemangioblastomas and clear cell renal carcinomas.[62,64] A number of clinical trials are currently in progress (http://clinical trials.gov).

SIMPLE CYSTS

Definition

Simple renal cysts are the most commonly acquired renal cystic lesion and occur twice as frequently in men as in women. Simple cysts are usually unilateral and may be solitary or multiple. They rarely occur in children, but become increasingly common with age.[65] In a seminal ultrasound study, unilateral cysts were detected in 1.7% of patients age 30 to 49 years, 11% of patients age 50 to 70, and 22% to 30% of patients over age 70.[66] This age-related increase in cyst incidence has been corroborated by MR studies.[67]

Etiology and Pathogenesis

Simple renal cysts likely originate from the distal convoluted tubule or collecting ducts and may arise from renal tubular diverticula, but the pathogenic mechanisms are unknown. Focal tubular obstruction and renal parenchymal ischemia have both been suggested as etiologic processes. Less likely is the possibility that simple cysts arise from calyceal diverticuli, because simple cysts are often found in the renal cortex, and their frequency increases with age.

Age, smoking, renal dysfunction, and hypertension[68] have been implicated as risk factors for simple cysts. However, these associations may be coincidental, given that the studies were largely retrospective, the cohorts had variable reasons for diagnostic referral, and the observations were not optimally controlled for patient age.[65]

Clinical Manifestations

Simple cysts are typically asymptomatic. However, increasing evidence supports a relationship between simple renal cysts and hypertension.[68] In addition, red blood cell (RBC) abnormalities (increased RBC mass, hematocrit, and hemoglobin) are well described in patients with simple renal cysts.[69] Patients can also present with hematuria, flank pain, evidence of infection or gout, or obstruction of the collecting system. Clinical symptoms are more common with neoplasms than simple cysts. Therefore, the onset of symptoms should suggest an associated malignancy and prompt additional diagnostic studies.[65]

Pathology

Whether unilateral or bilateral, simple cysts are usually spherical in shape and unilocular. They may be solitary or multiple. On average, simple cysts measure 0.5 to 1.0 cm diameter, but 3-cm to 4-cm cysts are not uncommon. Simple cysts can occur in the cortex, where they can protrude from the cortical surface (exophytic cysts), the CM junction or in the medulla. By definition, simple cysts do not communicate with the renal pelvis. The cyst walls are typically thin and transparent, lined with a single layer of flattened epithelium. Cyst fluid is essentially an ultrafiltrate of plasma. After infection, cyst walls can become thickened, fibrotic, and even calcified.

Diagnosis

Simple cysts are most often detected as incidental findings during abdominal imaging studies. Occasionally, they are discovered during radiologic evaluation of palpable abdominal masses, pyelonephritis, or hematuria after abdominal trauma. The critical clinical issue is to distinguish single or multiple simple cysts from cysts associated with ADPKD, other cystic diseases, or RCC. This distinction can usually be made on the basis of patient age, family history, and renal imaging patterns.[65,70]

The ultrasound features of simple cysts include smooth walls, no septae, and no intracystic debris. If the ultrasound pattern is indeterminate, CT should be performed. A classification system for renal cysts based on their appearance and enhancement on CT, described by Bosniak (see Table 61-5), is widely used.[70] Benign cysts (Bosniak Class I) have homogeneous attenuation, no contrast enhancement, thin smooth cyst walls, and no associated calcifications, unless prior infection has occurred.

Treatment

Simple cysts associated with pain or renin-dependent hypertension can be punctured with ultrasound guidance and drained, with a sclerosing agent instilled into the cyst cavity.[71] Laparoscopic or retroperitoneoscopic cyst unroofing may be more appropriate for large cysts containing volumes in excess of 100 ml. Infection with Enterobacteriaceae, staphylococci, and *Proteus* has been reported in simple cysts, and operative or percutaneous drainage is often required in addition to antibiotic treatment.

SOLITARY MULTILOCULAR CYSTS

Solitary multilocular cysts are generally benign neoplasms that arise from the metanephric blastema. These solitary cysts have also been designated multilocular cystic nephroma, benign cystic nephroma, and papillary cystadenoma. By definition, the cystic structures are unilateral, solitary, and multilocular. The cystic locules do not communicate with each other or with the renal pelvis. These locules are lined with a simple epithelium, and the interlocular septa do not contain differentiated renal epithelia structures.

Multilocular cysts represent a spectrum.[72] At one end is cystic nephroma (CN) and at the other end, cystic partially differentiated nephroblastoma (CPDN), in which the septa contain foci of blastemal cells. It is uncertain whether a multilocular cyst represents a congenital abnormality in nephrogenesis, a hamartoma, a partially or completely differentiated Wilms tumor, or a benign variant of Wilms tumor.

A bimodal age distribution has been described,[73] with approximately half the cases occurring in children less than 4 years of age and half the cases detected in adults. The childhood cases (mostly CPDN) are usually found in boys; whereas, multilocular cysts presenting in adulthood (mostly CN) occur more commonly in women. An abdominal or flank mass is the most common clinical feature, as these cysts are typically quite large and often replace an entire pole. Associated hematuria, calculi, urinary tract obstruction, and infection occur in rare cases. Diagnosis can be made by ultrasound or CT (Fig. 47-11).

Almost all multilocular cysts are Bosniak Class III (see Table 61-5), complex renal cysts suspicious for malignancy.[70] CPDN in children may contain blastema and incompletely differentiated metanephric tissue, but usually has a benign course. In adults, associated foci of RCC or sarcoma must be excluded. For both diagnostic accuracy and treatment, partial nephron-sparing surgery is usually required. However, the typical prognosis of solitary multilocular cysts is excellent.

RENAL LYMPHANGIOMATOSIS

Renal lymphangiomatosis is a rare, generally benign disorder characterized by developmental malformation of renal lymphatic channels.[74] It has also been referred to as hilar, pericalyceal, paracalyceal, peripelvic, or parapelvic lymphangiectasis.

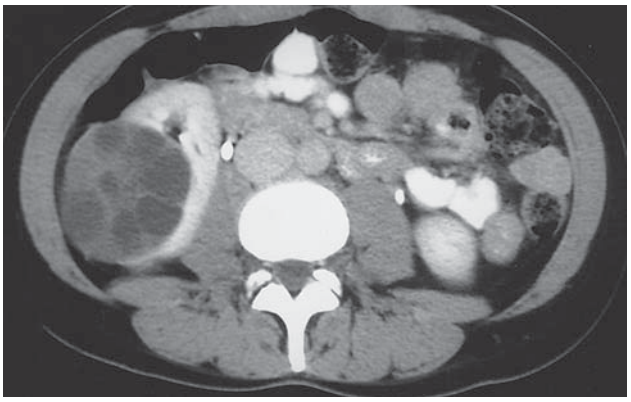


Figure 47-11 Solitary multilocular cyst. Contrast-enhanced CT shows a solitary, septated, and well-circumscribed renal cystic lesion in the right kidney.

The cystic phenotype is widely variable, and the underlying pathogenesis is unclear. The dilation may involve a single lymphatic channel or multiple channels. The lymphangiectasis may be unilateral or bilateral, may be limited to the hilar region, or may extend into the renal parenchyma to the corticomedullary junction. On occasion, renal lymphangiomatosis may be extensive and simulate ADPKD. The thin-walled cysts are lined by lymphatic endothelium, and the cyst fluid is quite distinct from that in ADPKD cysts, because it contains lymphatic constituents such as albumin and lipid.

The characteristic ultrasound or CT findings include multiple, bilateral, small peripelvic cysts that splay the renal hilum, as well as capsular cysts in the perirenal space, both separated by thin septations. Renal lymphangiomas are most often asymptomatic and require no treatment. However, the condition may be exacerbated by pregnancy, resulting in large, perinephric lymph collections and ascites that may require percutaneous drainage.[75]

GLOMERULOCYSTIC KIDNEY DISEASE

Cystic glomeruli are evident in three different clinical contexts: (1) isolated glomerulocystic kidney disease (GCKD); (2) glomerulocystic kidneys associated with heritable malformation syndromes, such as tuberous sclerosis, Meckel syndrome, medullary cystic kidney disease (MCKD2), orofaciodigital syndrome type I, trisomies (9, 13, 18), the short-rib polydactyly syndromes, and Zellweger cerebrohepatorenal syndrome; and (3) glomerular cysts present in dysplastic kidneys.[39]

Isolated GCKD can occur as a sporadic condition, a familial disorder, or as the infantile manifestation of ADPKD. Pathologically, the kidney architecture is normal, with no dysplastic elements in the cortex and no evidence of urinary tract obstruction. Cystic dilation predominantly involves the Bowman space and initial proximal tubule; it is defined as a twofold to threefold dilation of Bowman space versus the normal glomerular dimension. Glomerular cysts can be distributed from the subcapsular zone to the inner cortex. The typical ultrasound pattern in GCKD involves increased echogenicity of the renal cortex with minute cysts, smaller than those evident in ADPKD. Young infants with either familial or sporadic forms of GCKD may also have renal medullary dysplasia and biliary dysgenesis.[39]

Glomerulocystic kidney disease is usually transmitted as an autosomal dominant trait. It is often discovered in infants with a familial history of ADPKD. In these infants, the kidneys are bilaterally

enlarged and diffusely cystic. In non–ADPKD-associated GCKD families, the kidneys are typically normal in size, although on occasion, enlarged kidneys are observed. Several sporadic cases of nonsyndromal GCKD also have been described, suggesting either new, spontaneous mutations or a recessively transmitted disorder.[39]

Familial hypoplastic GCKD (MIM 137920) appears to be a distinct form of GCKD. The kidneys are smaller than normal and often associated with medullocalyceal abnormalities. The disease is pleiotropic among affected family members, with variable associations of hypoplastic GCKD, gynecologic abnormalities, and maturity-onset diabetes of the young type 5 (MODY5), and results from mutations in *TCF2,* the gene encoding hepatocyte nuclear factor 1β (HNF-1β).[76]

ACQUIRED CYSTIC DISEASE

Hypokalemic Cystic Disease

Renal cysts are often seen in association with chronic hypokalemia caused by primary hyperaldosteronism or other renal potassium-wasting disorders. Almost 50% of patients with idiopathic adrenal hyperplasia and 60% of those with adrenal tumors have been found to have renal cysts distributed primarily in the renal medulla. These cysts typically regress after adrenalectomy.[77]

Hilar Cysts

Hilar cysts are spherical accumulations of clear, fat droplet–containing fluid within the renal sinus. These cystic structures are not lined by epithelia. They are most often seen in debilitated patients and may represent atrophy of the renal sinus fat.

Perinephric Pseudocysts

Perinephric pseudocysts are also unlined cavities. They typically occur under the renal capsule or in the perirenal fascia as a result of urine extravasation from a renal cyst after traumatic or spontaneous rupture, or as the posterior extension of a pancreatic pseudocyst. Surgical intervention is indicated for associated urinary tract obstruction. Otherwise, treatment is directed to the underlying cause.

Acquired Cystic Disease in Renal Failure

Acquired cystic disease is a significant complication of prolonged renal failure. It should be considered in the differential diagnosis of cystic disease presenting with longstanding chronic renal impairment (see Table 47-4). Acquired renal cystic disease is discussed further in Chapter 89.

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CHAPTER 48

Alport and Other Familial Glomerular Syndromes

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ALPORT SYNDROME

Definition

Alport syndrome (AS) is a generalized, inherited disorder of basement membranes caused by mutations affecting specific proteins of the type IV (basement membrane) collagen family. The major features of AS are hematuria, progressive nephritis with proteinuria and declining renal function, sensorineural deafness, and ocular abnormalities. The course of AS is gender dependent; affected males typically have severe disease, whereas the manifestations of AS in women tend to be relatively mild. In 1902, Guthrie[1] provided the first description of familial hematuria. Later studies of Guthrie's family by Hurst[2] and Alport[3] revealed the progressive nature of the nephropathy, its association with deafness, and the poorer prognosis in affected males. In the 1970s, the glomerular basement membrane (GBM) was recognized as the site of the primary abnormality in AS.[4-6] Indirect evidence of abnormalities in type IV collagen[7,8] was followed by mapping of the major AS locus to the X chromosome,[9] cloning of a new type IV collagen gene *(COL4A5)* and its assignment to the same X-chromosomal region,[10] and identification of the first *COL4A5* mutations in patients with X-linked AS.[11]

Etiology and Pathogenesis

Type IV Collagen

Type IV collagen is a major constituent of basement membranes. The type IV collagen family of proteins comprises six isomeric chains, designated α1(IV) to α6(IV). Each of these chains has a major collagenous domain of about 1400 residues containing the repetitive triplet sequence glycine (Gly)–X–Y, in which X and Y represent a variety of other amino acids; a C-terminal noncollagenous (NC1) domain of about 230 residues; and a noncollagenous N-terminal sequence of 15 to 20 residues.

Each type IV collagen molecule is a heterotrimer composed of three α chains. Formation of these heterotrimers is initiated by C-terminal NC1 domain interactions, accompanied by folding of the collagenous domains into triple helices. There is evidence for at least three types of type IV collagen heterotrimer: $\alpha1(IV)_2$–α2(IV); α3(IV)–α4(IV)–α5(IV); and $\alpha5(IV)_2$–α6(IV). Type IV collagen triple helices form open, nonfibrillar networks that associate with laminin assemblies through interactions mediated by nidogen to form basement membranes.

The six type IV collagen genes are arranged in pairs on three chromosomes (Fig. 48-1). The 5′ ends of each gene pair are adjacent to each other, separated by sequences of varying length that contain motifs involved in the regulation of transcriptional activity.

There are several distinct type IV collagen networks in basement membranes: a ubiquitous network comprising the α1(IV) and α2(IV) chains; and other networks, restricted in distribution, composed of α3(IV), α4(IV), and α5(IV) chains, or α5(IV) and α6(IV) chains. GBM contains separate α1–α2(IV) and α3–α4–α5(IV) networks, whereas epidermal basement membranes (EBMs) contain separate networks of α1–α2(IV) chains and α5–α6(IV) chains. A network composed of α1, α2, α5, and α6(IV) chains has been described in smooth muscle basement membranes.[12] These various networks likely have different physical and functional characteristics and interact differently with other matrix components and adjacent cells.

Genetics

Three forms of AS have been established on a molecular genetic basis: an X-linked form resulting from mutations at the *COL4A5* locus, primarily affecting the α5(IV) chain; an autosomal recessive form arising from mutations at the *COL4A3* locus or the *COL4A4* locus, affecting the α3(IV) and α4(IV) chains, respectively, and an autosomal dominant form from heterozygous mutations in *COL4A3* or *COL4A4* (Table 48-1).

X-Linked Alport Syndrome X-linked Alport syndrome (XLAS) is the predominant form of the disease, accounting for about 80% of patients. Several hundred *COL4A5* mutations have been described, mostly missense mutations, splice-site mutations, and deletions of fewer than 10 base pairs.[13,14] A common missense mutation involves replacement of a glycine residue in the collagenous domain of the α5(IV) chain by another amino acid. Such mutations are thought to interfere with the normal folding of the α5(IV) chain into triple helices with other α(IV) chains.

Male patients with *COL4A5* deletions consistently progress to end-stage renal disease (ESRD) during the second or third decade of life and have deafness.[15] This phenotype is associated with most of the missense, nonsense, and splicing mutations of *COL4A5* described so far. Several missense mutations of *COL4A5* have been associated with late-onset (after the third decade) ESRD and with late development of deafness or normal hearing. The severity of disease in a female heterozygous for a *COL4A5* mutation probably depends primarily on the relative activities of the mutant and normal X chromosomes in renal, cochlear, and ocular tissues.

Autosomal Recessive Alport Syndrome Autosomal recessive Alport syndrome (ARAS) arises from mutations affecting both alleles of *COL4A3* or *COL4A4*.[15,16] ARAS should be suspected when an individual exhibits the typical clinicopathologic features of the disease but lacks a positive family history, especially when a young female has findings indicative of severe disease, such as deafness, nephrotic syndrome, and impaired renal function, However, sporadic cases of AS may represent *de novo* mutations at the *COL4A5* locus or a germ-line *COL4A5* mutation in the proband's mother. Most patients with ARAS develop ESRD and deafness before age 30 years, regardless of gender.

Autosomal Dominant Alport Syndrome Heterozygous mutations in *COL4A3* or *COL4A4* typically result in asymptomatic hematuria.[16,17] In some families, however, these mutations may also be associated with progressive nephropathy, that is, autosomal dominant Alport syndrome (ADAS).[18,19] ADAS patients tend to have a slower course to ESRD than those with XLAS or ARAS.[20]

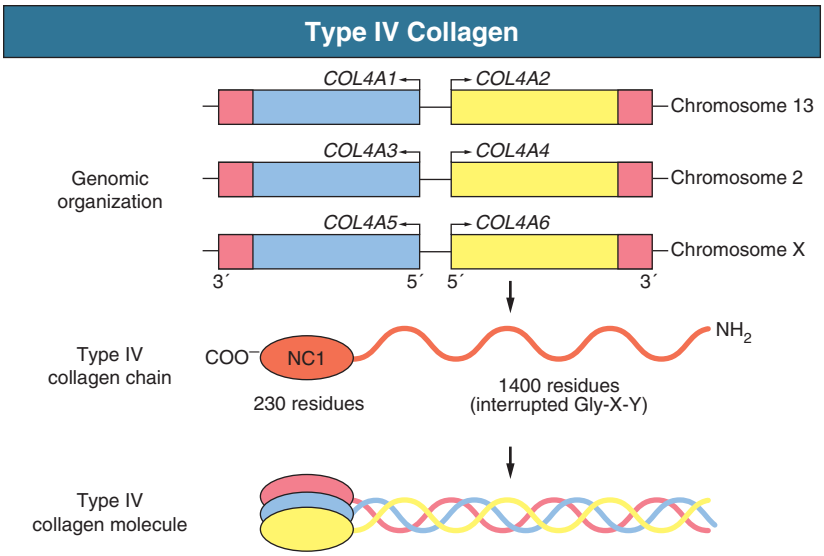

Figure 48-1 Genomic organization of type IV collagen genes. Each type IV collagen chain is synthesized from one of the pairs of type IV collagen genes. Each type IV collagen molecule is a heterotrimer of three type IV collagen chains (see also Fig. 48-4).

Molecular Genetics of Alport Syndrome

Inheritance	Affected Locus	Gene Product
X-linked (XLAS)	*COL4A5*	α5(IV)
X-linked + leiomyomatosis	*COL4A5* + *COL4A6*	α5(IV) + α6(IV)
Autosomal recessive (ARAS)	*COL4A3* *COL4A4*	α3(IV) α4(IV)
Autosomal dominant	*COL4A3* *COL4A4*	α3(IV) α4(IV)

Table 48-1 Molecular genetics of Alport syndrome.

Type IV Collagen in Alport Basement Membranes

The GBMs and tubular basement membranes of males with XLAS usually fail to stain for the α3(IV), α4(IV), and α5(IV) chains but do express the α1(IV) and α2(IV) chains[21] (Fig. 48-2). Women with XLAS frequently exhibit mosaicism of GBM expression of the α3(IV), α4(IV), and α5(IV) chains, whereas expression of the α1(IV) and α2(IV) chains is preserved. Most males with XLAS show no EBM expression of α5(IV), whereas female heterozygotes frequently display mosaicism (Fig. 48-3). Lens capsules of some males with XLAS do not express the α3(IV), α4(IV), or α5(IV) chains, whereas expression of these chains appears normal in other patients.

In most patients with ARAS, GBM shows no expression of the α3(IV), α4(IV), or α5(IV) chains, but α5(IV) and α6(IV) are expressed in Bowman capsule, distal tubular basement membrane, and EBM[20] (Fig. 48-4). Therefore, XLAS and ARAS may be differentiated by immunohistochemical analysis. Basement membrane expression of type IV collagen α chains appears to be normal in patients with ADAS.

These observations indicate that a mutation affecting one of the chains involved in the α3–α4–α5(IV) network can prevent GBM expression not only of that chain but also of the other two chains. Most observational and experimental evidence supports the hypothesis that these effects reflect post-translational events. Some mutant chains are unable to participate in the formation of trimers; as a result, the normal chains that are prevented from forming trimers undergo degradation. Other mutations may allow formation of abnormal trimers that are degraded before deposition in basement membranes can occur (Fig. 48-5).

Clinical Manifestations

Renal Defects

Hematuria is the cardinal finding of AS. Affected males have persistent microhematuria. Many also have episodic gross hematuria, precipitated by upper respiratory infections, usually during the first two decades of life. Hematuria has been discovered in the first year of life in affected boys, in whom it is probably present from birth. Boys who are free of hematuria during the first 10 years of life are unlikely to be affected.

More than 90% of females with XLAS have persistent or intermittent microhematuria, but about 7% of obligate heterozygotes never manifest hematuria.[21] Hematuria appears to be persistent in both males and females with ARAS. About 50% of carriers of *COL4A3* or *COL4A4* mutations have hematuria.[16,17]

Proteinuria is usually absent early in life but develops eventually in all males with XLAS and in both males and females with ARAS. Proteinuria increases progressively with age and may result in the nephrotic syndrome. Proteinuria develops eventually in most heterozygous females.[22] Hypertension also increases in incidence and severity with age. Similar to proteinuria, hypertension is more likely to occur in affected males than in affected females with XLAS, but there are no gender differences in the hypertension frequency in ARAS.

End-stage renal disease develops in all affected males with XLAS, at a rate determined primarily by the nature of the underlying *COL4A5* mutation.[15] Thus, the rate of progression is fairly constant among affected males within a particular family, but there is significant interkindred variability. Significant intrakindred variability in the rate of progression to ESRD has been reported in some families with missense *COL4A5* mutations.

Progression to ESRD in females with XLAS was considered an unusual event until a 2003 European study of several hundred XLAS females found that 12% developed ESRD before age 40 (vs. 90% of XLAS males), increasing to 30% by age 60 and 40% by 80.[22] The risk for ESRD was significantly increased in heterozygotes with proteinuria. The outcome of XLAS in females is presumed to depend on the relative activities of the normal and mutant X chromosomes, but this has yet to be proved. Gross hematuria in childhood, nephrotic syndrome, and the finding of diffuse GBM thickening by electron microscopy are risk factors for chronic kidney disease (CKD) in affected females.[23] Sensorineural deafness and anterior lenticonus are also indicative of an unfavorable outcome in affected women. Both

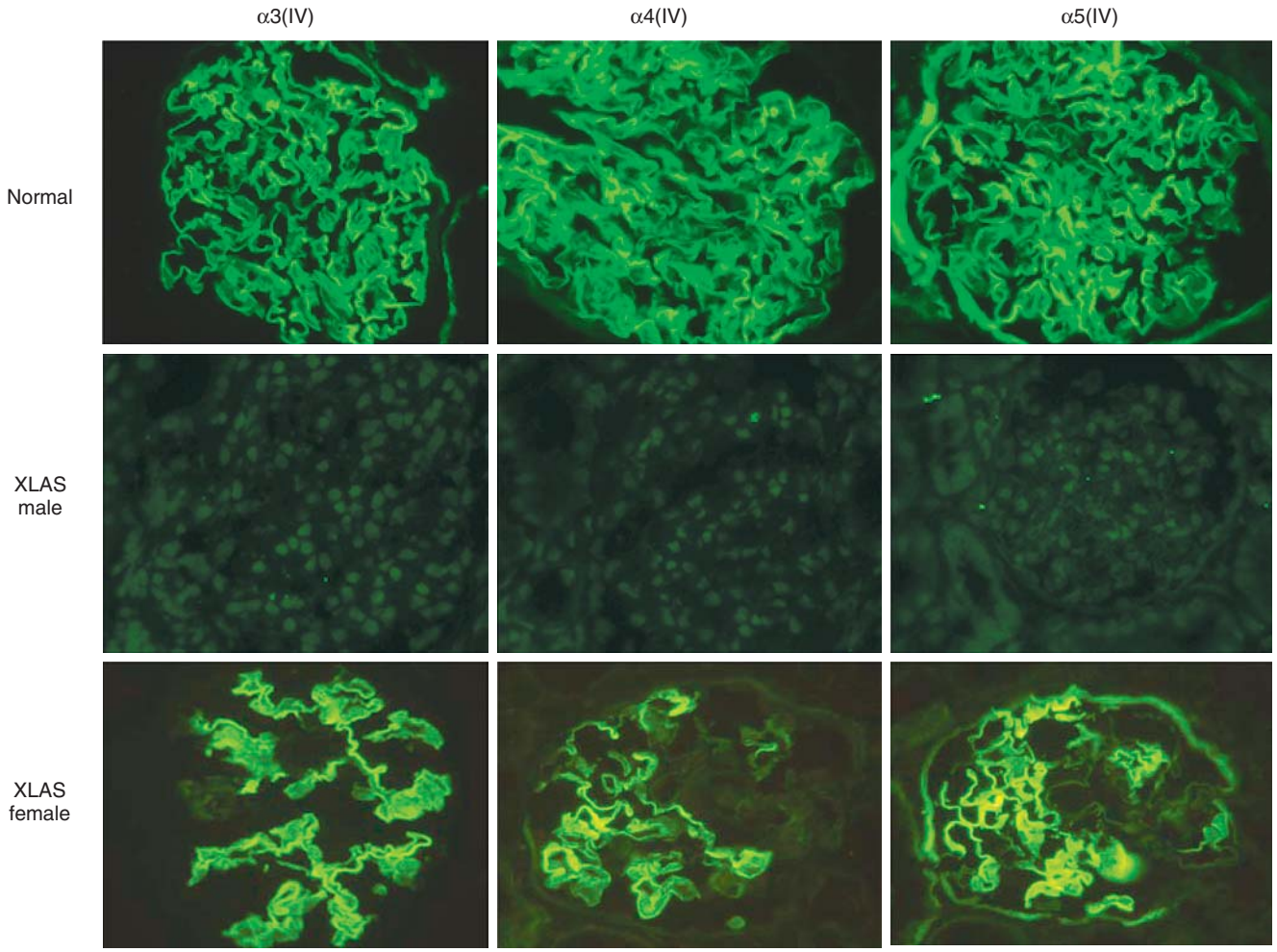

Figure 48-2 Immunohistochemistry of glomerular basement membrane (GBM) in X-linked Alport syndrome (XLAS). In a normal individual *(top row)*, GBM stains strongly for the α3(IV), α4(IV), and α5(IV) chains of type IV collagen. Staining of GBM of an affected male is negative for each of these chains *(middle row)*, whereas an affected female shows mosaic immunoreactivity *(bottom row)*.

males and females with ARAS appear likely to progress to ESRD during the second or third decade of life.

Cochlear Defects

Deafness is frequently but not universally associated with the Alport renal lesion, occurring in about 80% of males and 25% to 30% of females with AS.[15,22] In some families with Alport nephropathy and apparently normal hearing, deafness may occur late and may be very slowly progressive.

Hearing loss in AS is never congenital and usually becomes apparent by late childhood to early adolescence in boys with XLAS and in both boys and girls with ARAS. Hearing impairment in members of families with AS is always accompanied by evidence of renal involvement. There is no convincing evidence that deaf males lacking renal disease can transmit AS to their offspring. In its early stages, the hearing deficit is detectable only by audiometry, with bilateral reduction in sensitivity to tones in the range 2000 to 8000 Hz. In affected males, the deficit extends progressively to other frequencies, including those of conversational speech.

Ocular Defects

Ocular defects occur in 30% to 40% of XLAS males and in about 15% of XLAS females.[15,22] *Anterior lenticonus,* which is virtually pathognomonic of AS, occurs in about 15% of XLAS males and is almost entirely restricted to AS families with progression to ESRD before age 30 years and deafness.[15] Anterior lenticonus is absent at birth, usually appearing during the second to third decade of life, and is bilateral in 75% of patients (Fig. 48-6, *A*). The spectrum and frequencies of ocular lesions appear to be similar in XLAS and ARAS.[24]

Another common ocular manifestation of AS is a maculopathy, which consists of whitish or yellowish flecks or granulations in a perimacular distribution and occurs in 15% to 30% of patients (Fig. 48-6, *B*). The maculopathy does not appear to be associated with any visual abnormalities.

Corneal endothelial vesicles (posterior polymorphous dystrophy) have been observed in AS and may indicate defects in Descemet membrane, the basement membrane underlying the corneal endothelium. Recurrent corneal erosion in AS has been attributed to alterations of the corneal EBM.

Leiomyomatosis

The association of AS with leiomyomatosis of the esophagus and tracheobronchial tree has been reported in about 30 families.[14] Affected females typically exhibit genital leiomyomas as well, with clitoral hypertrophy and variable involvement of the labia majora and uterus. Bilateral posterior subcapsular cataracts also occur frequently in affected individuals. Symptoms usually appear in late

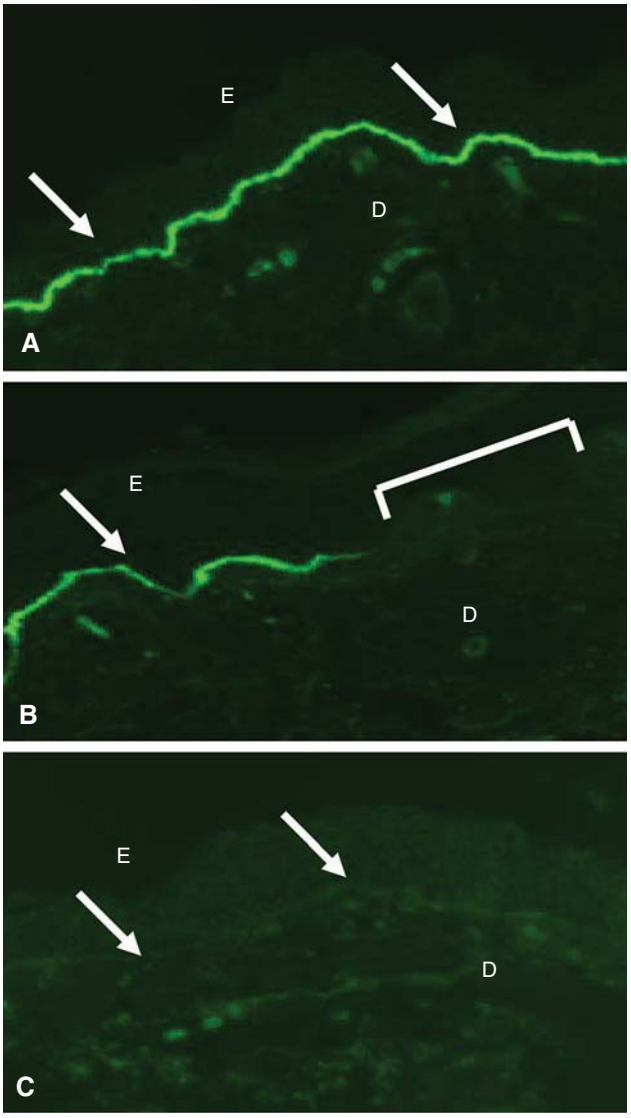

Figure 48-3 Immunohistochemistry of epidermal basement membrane (EBM) in X-linked Alport syndrome. A, In a normal male, EBM shows strong staining for α5(IV) at the dermoepidermal junction *(arrows)* between dermis *(D)* and epidermis *(E)*. **B,** In an affected female, EBM shows mosaic staining *(arrow);* the *white bracket* identifies a length of EBM negative for α5(IV). **C,** In affected males, staining of EBM *(arrows)* for α5(IV) is absent.

childhood and include dysphagia, postprandial vomiting, retrosternal or epigastric pain, recurrent bronchitis, dyspnea, cough, and stridor. All patients with AS–diffuse leiomyomatosis complex have been found to have deletions that encompass the 5′ ends of *COL4A5* and *COL4A6*.

Hematologic Defects

An autosomal dominant syndrome of hereditary nephritis, deafness, and megathrombocytopenia called Epstein syndrome has been described in a small number of families. Families with Fechtner syndrome exhibit these features as well as leukocyte inclusions (May-Hegglin anomaly). Both Epstein and Fechtner syndrome arise from mutations in nonmuscle myosin heavy-chain IIA.[25] Basement membranes of these patients do not exhibit abnormalities in expression of type IV collagen α chains. Therefore, Epstein and Fechtner syndromes are best considered distinct forms of hereditary nephritis rather than variants of AS.

Arterial Abnormalities

Aneurysmal dilation of the thoracic and abdominal aorta and smaller arterial vessels has been described in a small number of males with Alport syndrome.[26]

Pathology

There are no pathognomonic lesions by light microscopy or direct immunofluorescence in AS. In affected males, biopsies obtained before 5 years of age typically show no light microscopy changes. Mesangial hypercellularity and matrix expansion are typically observed in older children and adolescents. Glomeruli of affected males eventually show focal segment glomerulosclerosis, and interstitial fibrosis and tubular atrophy are often found in affected boys older than 10. Light microscopy findings in affected females correlate with proteinuria and kidney function; an affected female of any age who has isolated hematuria is likely to have little or no abnormality by light microscopy. Indirect immunofluorescence of type IV collagen α-chain expression in renal or skin basement membranes can be diagnostic (see earlier discussion) and is increasingly available in specialized laboratories around the world.

Electron microscopy (EM) frequently reveals diagnostic abnormalities. The cardinal fine structural feature of the kidney that occurs in most patients with AS is the variable thickening, thinning, basket weaving, and lamellation of the GBM (Fig. 48-7). The thick segments measure up to 1200 nm in depth, usually have irregular outer and inner contours, and are found more frequently in males than in females. The lamina densa is transformed into a heterogeneous network of membranous strands, which enclose clear electron-lucent areas that may contain round granules of variable density measuring 20 to 90 nm in diameter. There are variable degrees of epithelial foot process fusion.

Not all Alport kindreds demonstrate these characteristic ultrastructural features. Thick, thin, normal, and nonspecifically altered GBMs have all been described. Affected young males, heterozygous females at any age, and, on occasion, affected adult males may have diffusely attenuated GBM measuring as little as 100 nm or less in thickness rather than the pathognomonic lesion. Although diffuse attenuation of GBM has been considered the hallmark of thin basement membrane nephropathy, some patients with this abnormality are members of kindreds with a history of progression to renal failure. Therefore, the significance of an ultrastructural finding of thin GBM must be considered in the context of the family history, basement membrane expression of type IV collagen α chains, and if available, molecular genetic information.

Diagnosis and Differential Diagnosis

Figure 48-8 summarizes the evaluation of patients with hematuria and a positive family history. AS should be included in the initial differential diagnosis of patients with persistent microhematuria after excluding structural abnormalities of the kidneys or urinary tract. The presence on EM of diffuse thickening and multilamellation of the GBM predicts a progressive nephropathy, regardless of family history. However, in a patient with a negative family history, EM cannot differentiate *de novo* XLAS from ARAS. In some patients, the biopsy findings may be ambiguous, particularly in females and young patients of either gender. Furthermore, families with progressive nephritis and *COL4A5* mutations in association with GBM thinning have been described, indicating that the classic Alport GBM lesion is not present in all Alport kindreds.

It is not unusual to see a patient with hematuria or to discover that multiple relatives also have hematuria, although none has ever

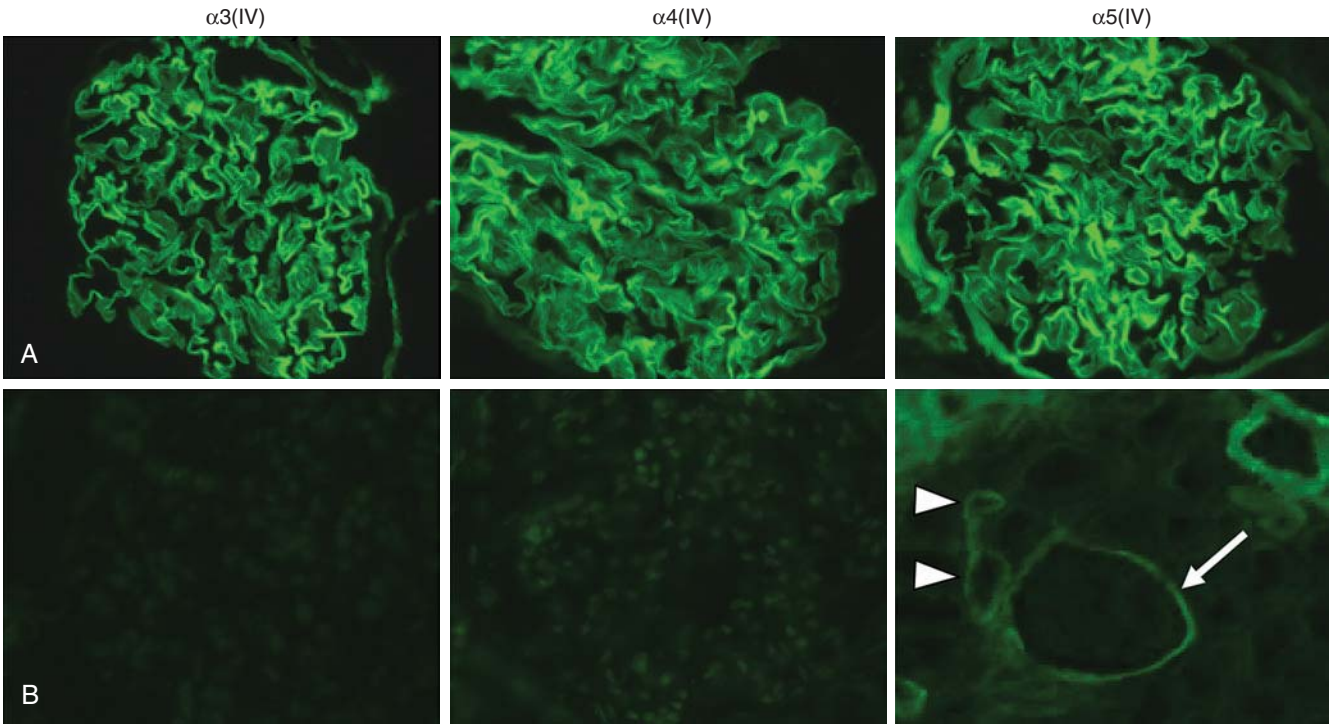

Figure 48-4 Immunohistochemistry of kidney in patient with autosomal recessive Alport syndrome. A, Normal glomerular basement membrane (GBM) and Bowman capsule staining for α3(IV), α4(IV), and α5(IV). **B,** Patient shows no GBM staining, but it is present in Bowman capsule *(arrow)* and distal tubular basement membranes *(arrowheads)*.

undergone kidney biopsy. Who should undergo biopsy in such cases? The natural history of the AS renal lesion suggests that older, male subjects are more likely to exhibit diagnostic ultrastructural GBM abnormalities. In families with a firm diagnosis of AS established, evaluation of individuals with newly recognized hematuria can be limited to ultrasound of the kidneys and urinary tract to exclude coincidental tumor or structural anomalies of the urinary tract.

Absence of the α3, α4, and α5 chains of type IV collagen from GBM and distal tubular basement membrane has not been described in any condition other than AS, making this a diagnostic finding on kidney biopsy (Table 48-2). Examination of skin biopsy specimens by immunofluorescence for expression of α5(IV) in the EBM may be informative, but apparently normal expression of type IV collagen α chains in basement membranes does not exclude the diagnosis of AS. Mosaic expression of α5(IV) is common in heterozygous females. Although mosaic expression of α5(IV) is diagnostic of the carrier state, a normal result does not exclude heterozygosity. A female member of an Alport kindred who does not have hematuria may still be a carrier, but is less likely to exhibit detectable mosaicism than a female with hematuria.

A firm histologic diagnosis of AS cannot always be established, or it may not be possible to determine the mode of transmission, despite careful evaluation of the pedigree and application of the full range of histologic methods. In these situations, genetic analysis may provide information essential for determining prognosis and guiding genetic counseling. Genetic analysis for AS is becoming increasingly available as a clinical assay in commercial laboratories. A current list of laboratories offering molecular genetic diagnosis of Alport syndrome can be found at genereviews.org.

Glomerular diseases that typically occur sporadically may on occasion be heritable and should be considered in the differential diagnosis. These include focal segmental glomerulosclerosis, membranous nephropathy, membranoproliferative glomerulonephritis, IgA nephropathy, and C3 glomerulopathy.

Natural History

Microhematuria, the first and invariable renal manifestation of AS, probably reflects GBM thinning and a tendency to develop focal ruptures because of defective expression of the α3–α4–α5(IV) network. Anterior lenticonus most likely results from the inability of the abnormal lens capsule to maintain the normal conformation of the lens. Ultrastructural studies of Alport cochleae suggest that the hearing deficit may be attributable to a defect in adherence of the organ of Corti to the basilar membrane.[27]

In its early stages, AS is clinically and often histologically indistinguishable from thin basement membrane nephropathy, which typically has a benign outcome. GBM attenuation is therefore an insufficient explanation for the divergent natural histories of the two conditions. What factors initiate and drive the progression of Alport nephropathy to ESRD? Reduction in the quantity of α3(IV), α4(IV), and α5(IV) chains in GBM, as likely occurs in thin basement membrane nephropathy, probably has consequences different from complete loss of these chains, as occurs in most males with XLAS and most patients with ARAS. There is increasing information about the molecular events that occur consequent to the loss of the α3(IV)–α4(IV)–α5(IV) network. In the GBM, the normal transition from the $\alpha1(IV)_2$–$\alpha2(IV)_1$ network of nascent glomeruli to the α3(IV)–α4(IV)–α5(IV) network of mature glomeruli fails to occur, and α1(IV) and α2(IV) chains accumulate in Alport glomeruli as the disease progresses.[28,29] Alport GBM shows overexpression of other matrix proteins that are normally absent from GBM or present in scant quantities, including type V collagen, type VI collagen, laminin α2 chain, and fibronectin. These alterations in GBM composition are unique to AS.[28,30] Both glomerular endothelial cells and podocytes

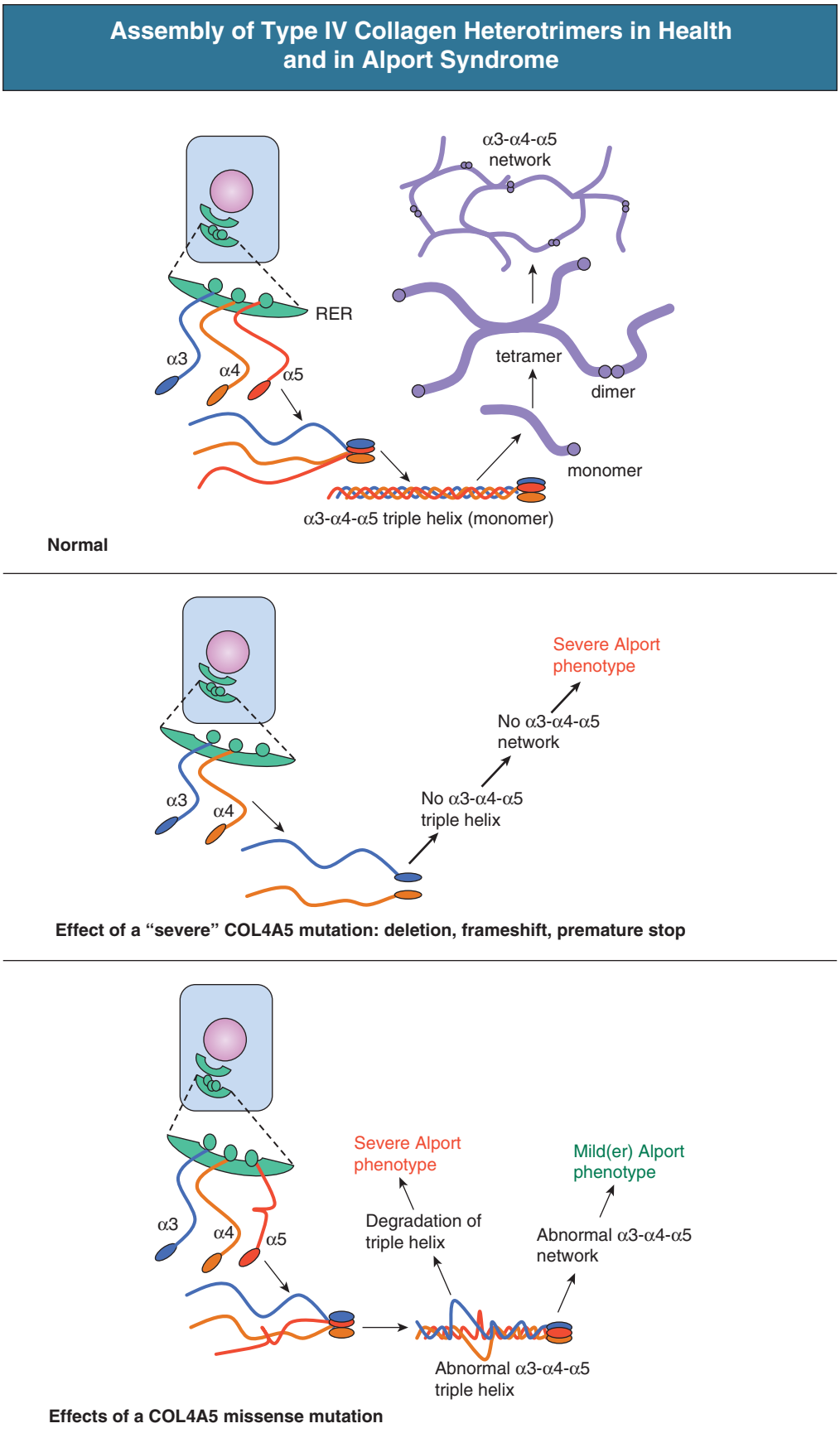

Figure 48-5 **Assembly of type IV collagen heterotrimers in health and in Alport syndrome.** *RER,* Rough endoplasmic reticulum.

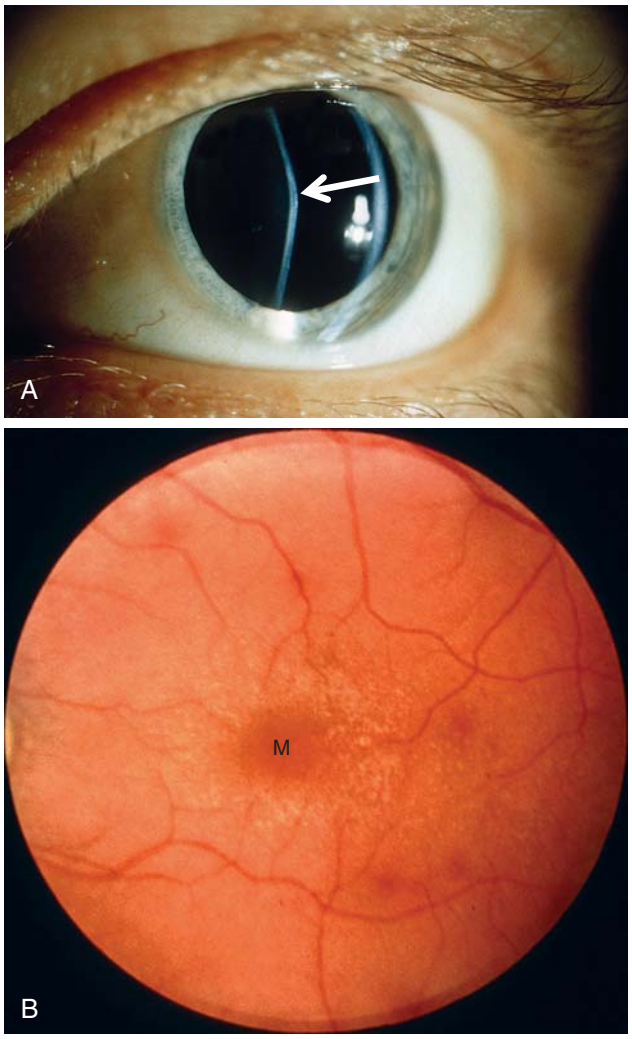

Figure 48-6 Ocular abnormalities in Alport syndrome. A, Anterior lenticonus shown by slit-lamp ophthalmoscopy. The anterior surface of the lens is cone shaped (arrow marks apex of the cone), rather than the normal smooth ellipse. **B,** Perimacular flecks. Note the white flecks surrounding the macula *(M)*. *(From reference 62.)*

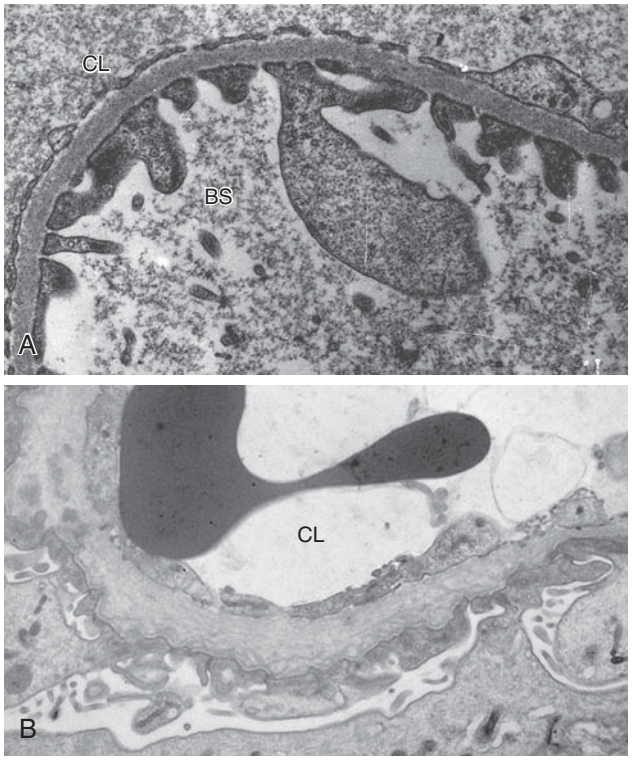

Figure 48-7 Renal biopsy in Alport syndrome. A, Normal glomerular capillary wall; *BS,* Bowman space. **B,** Glomerular capillary wall from a patient with Alport syndrome, at the same magnification; *CL,* capillary lumen. Note the thickening of the glomerular basement membrane (GBM), the splitting of the lamina densa into multiple strands, and the marked irregularity of the epithelial aspect of the GBM in the patient with Alport syndrome.

appear to contribute to the accumulation of these proteins in Alport GBM. Alterations in glomerular extracellular matrix are accompanied by changes in glomerular cell behavior, including expression of transforming growth factor β1, integrins, and matrix metalloproteinases.[31] Activation of fibrogenic pathways in the renal interstitium presumably represents a downstream consequence of glomerular disease.

Treatment

Current clinical practice recommendations for delaying ESRD in AS patients focus on the early introduction of inhibitors of the renin-angiotensin system (RAS) to suppress urinary protein excretion.[32,33] The focus on RAS inhibition is based on experimental and clinical evidence as well as practical considerations. Angiotensin-converting enzyme (ACE) inhibition lengthens survival in mice with ARAS.[33] When ACE inhibition in Alport mice is begun before the onset of proteinuria, the duration of survival is doubled, a therapeutic result thus far not exceeded by any other intervention. ACE inhibition begun after the onset of proteinuria also improves survival in Alport mice, to a lesser but still significant degree. The effect of ramipril on survival was superior to that of candesartan in a murine comparison study.[34]

Analysis of retrospective data collected by the European Alport Registry indicates that ACE inhibitor therapy initiated while glomerular filtration rate (GFR) is still normal delays ESRD by years.[35] This effect has also been shown in pairs of affected brothers discordant for ACE inhibitor therapy.[35] ACE inhibition, angiotensin receptor blockade, and aldosterone inhibition have been shown to reduce proteinuria in children with Alport syndrome, in both uncontrolled and controlled studies.[36] The effect of losartan on proteinuria was greater than the effect of amlodipine.[36] As shown in the ESCAPE trial, ACE inhibitors can be used safely in children with CKD, at doses that achieve suppression of urinary protein excretion.[37] RAS antagonists, especially ACE inhibitors, are relatively inexpensive and widely available. In theory, any child in the world with AS should be able to receive treatment with an ACE inhibitor. This cannot be said for other treatments, such as stem cell therapy, which have shown early promise in murine AS models.[38]

Consensus recommendations for the management of AS children include (1) early screening for hematuria in at-risk children; (2) regular determination of urinary albumin and protein excretion on diagnosis; and (3) initiation of angiotensin blockade once overt proteinuria develops. The goal of blockade is to reduce the urine protein-creatinine (PC) ratio by 50% in children with a ratio of 0.2 to 1 mg/mg, or to less than 0.5 mg/mg in those with a ratio greater than 2 mg/mg.[32] A randomized trial examining the effect of angiotensin blockade on the transitions from isolated hematuria to microalbuminuria to overt proteinuria is underway in Europe (EARLY PRO-TECT). Future clinical trials comparing angiotensin blockade to other therapies, alone or in combination, will be needed to identify the most effective approaches to delaying and preventing ESRD in patients with Alport syndrome.

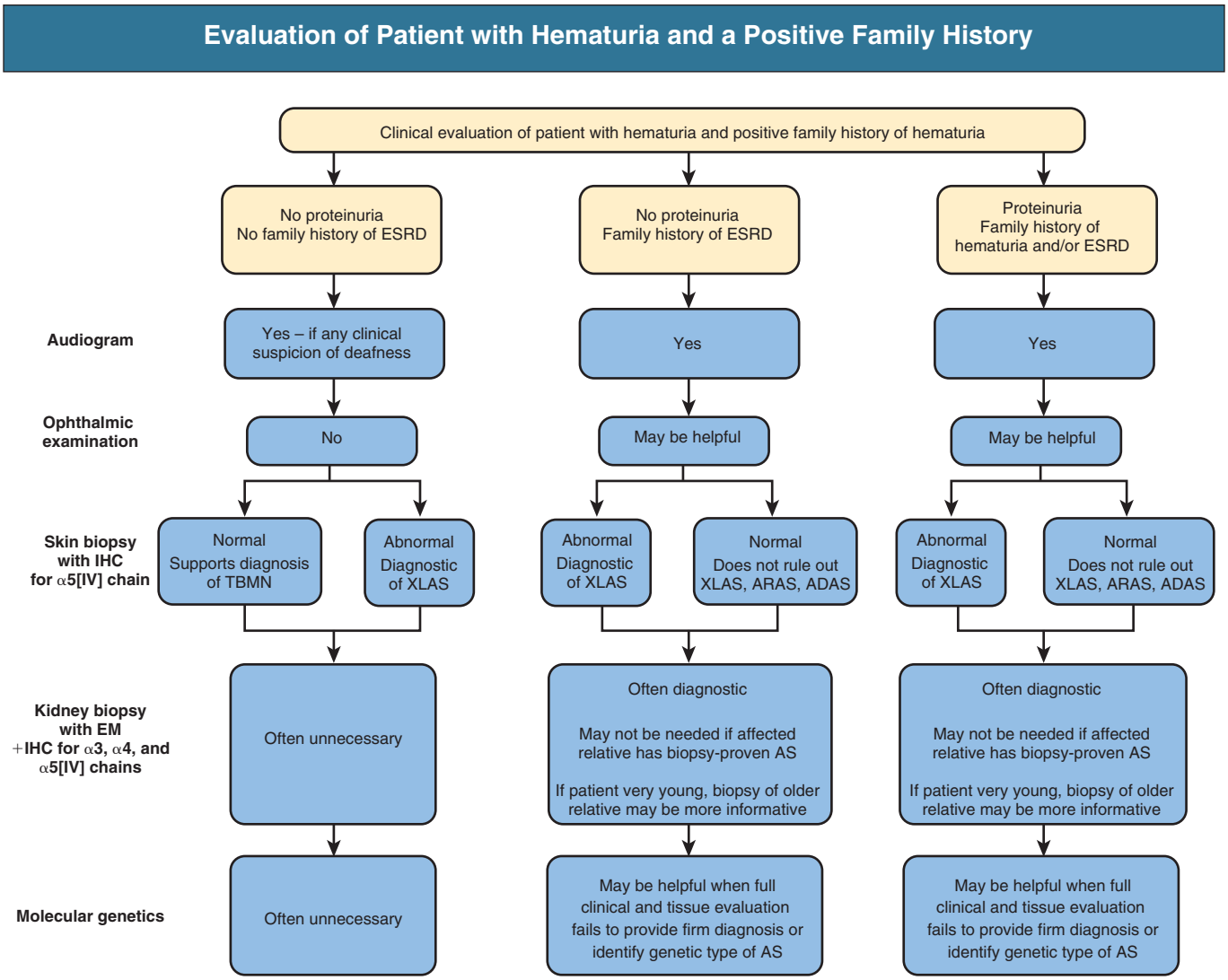

Figure 48-8 Evaluation of patient with hematuria and positive family history. *ADAS,* Autosomal dominant Alport syndrome; *ARAS,* autosomal recessive Alport syndrome; *AS,* Alport syndrome; *EM,* electron microscopy; *ESRD,* end-stage renal disease; *IHC,* immunohistochemistry; *TBMN,* thin basement membrane nephropathy; *XLAS,* X-linked Alport syndrome.

Transplantation

At present, renal transplantation is the only available treatment for AS. Graft survival in patients with familial nephritis is equivalent to that in patients with other diagnoses. However, anti-GBM glomerulonephritis involving the renal allograft is a rare but dramatic manifestation of AS, occurring in 2% to 3% of male AS patients who undergo transplantation (see Chapter 24).

Are women who are heterozygous for *COL4A5* mutations suitable kidney donors? Clearly, those with proteinuria, hypertension, or reduced GFR should not donate, nor should the woman with hearing loss. For heterozygotes with hematuria but normal renal function and hearing, no long-term follow-up information is available on the impact of uninephrectomy in such women. Given the recent finding that 30% to 40% of heterozygous women may eventually develop ESRD, however, the risk that a heterozygous donor will ultimately develop significant renal impairment must be higher than for the usual kidney donor. However, a common clinical scenario is a mother choosing to donate to her son with AS, and the choices of the whole family should be considered.

THIN BASEMENT MEMBRANE NEPHROPATHY: FAMILIAL AND SPORADIC

Definition

Isolated glomerular hematuria may occur as a familial or sporadic condition and is often associated with a renal biopsy finding of excessively thin GBM. The term *benign familial hematuria* was used in the past to describe disease kindreds in whom multiple individuals in several generations have isolated hematuria without progression to ESRD. More recently, thin basement membrane nephropathy (TBMN) has been used to identify both familial and sporadic isolated hematuria associated with attenuated GBM. It is likely that several disorders that differ at the molecular level are associated with GBM thinning, and in some patients, it is probably a normal variant. In general, this discussion applies to both familial and sporadic TBMN.

Similar to Alport syndrome, familial TBMN is an inherited GBM disorder manifested by chronic hematuria, but it differs clinically from AS in several important respects: (1) extrarenal abnormalities

Immunostaining for Type IV Collagen in Alport Syndrome				
Type IV Collagen Group	**Glomerular Basement Membranes**	**Bowman Capsules**	**Distal Tubular Basement Membrane**	**Epidermal Basement Membrane**
Normal (Males and Females)				
α3(IV)	Present	Present	Present	Absent
α4(IV)	Present	Present	Present	Absent
α5(IV)	Present	Present	Present	Present
X-Linked (Males)*				
α3(IV)	Absent	Absent	Absent	Absent
α4(IV)	Absent	Absent	Absent	Absent
α5(IV)	Absent	Absent	Absent	Absent
X-Linked (Females)†				
α3(IV)	Mosaic			Absent
α4(IV)	Mosaic			Absent
α5(IV)	Mosaic			Mosaic
Autosomal Recessive (Males and Females)*				
α3(IV)	Absent	Absent	Absent	Absent
α4(IV)	Absent	Absent	Absent	Absent
α5(IV)	Absent	Present	Present	Present

Table 48-2 Immunostaining for type IV collagen in Alport syndrome. *In some Alport kindreds, staining of basement membranes for type IV collagen chains is entirely normal. Therefore, a normal result does not exclude a diagnosis of X-linked Alport syndrome. †Some heterozygous females have normal basement membrane immunoreactivity for type IV collagen chains. Therefore, a normal result does not exclude the carrier state.

are rare; (2) proteinuria, hypertension, and progression to ESRD are unusual, seen in less than 10% of affected individuals, and extremely unusual before age 40; (3) gender differences in expression of TBMN are not apparent; and (4) transmission is autosomal dominant. TBMN and early AS may be difficult to differentiate histologically because diffuse GBM attenuation is characteristic of both. However, the GBM of patients with TBMN remains attenuated over time, rather than undergoing the progressive thickening and multilamellation that occurs in AS.

Etiology and Pathogenesis

Although TBMN is an autosomal dominant condition, a negative family history may not be reliable because patients are frequently unaware that they have relatives with hematuria. Familial TBMN has been localized to *COL4A3* or *COL4A4* in numerous kindreds.[39,40] Of heterozygous carriers of a *COL4A3* or *COL4A4* mutation, 50% or more have hematuria.[16,17] However, linkage to *COL4A3* and *COL4A4* has been excluded in other families with isolated hematuria, indicating that TBMN is a genetically heterogeneous condition.

Immunohistologic studies of type IV collagen in GBM of patients with TBMN have found no abnormalities in the distribution of any of the six α chains. Immunohistologic evaluation of GBM type IV collagen may therefore be useful in the differentiation of TBMN from AS (see later discussion).

Clinical Manifestations

An estimated 20% to 25% of patients referred to a nephrologist for evaluation of persistent hematuria will prove to have thin GBM on renal biopsy. Individuals with TBMN typically have persistent microhematuria that is first detected in childhood. In some patients, microhematuria is intermittent and may not be detected until adulthood. Episodic macroscopic hematuria, often in association with upper respiratory infections, is not unusual. The hematuria of TBMN appears to be lifelong.

Overt proteinuria and hypertension are unusual in TBMN but have been reported. Some of these patients may have actually had AS, in which the predominant abnormality of GBM was attenuation rather than thickening and multilamellation. Other glomerular disorders, such as IgA nephropathy and focal or global glomerulosclerosis, may occur concurrently with TBMN.

Pathology

Light and immunofluorescence microscopy are unremarkable in typical cases of TBMN. Most patients exhibit diffuse thinning of the whole GBM and of the lamina densa (Fig. 48-9). GBM width is age and gender dependent in normal individuals. Both the lamina densa and the GBM increase rapidly in thickness between birth and 2 years of age, followed by gradual thickening into adulthood. GBM thickness in adult men (373 ±42 nm) exceeds that in adult women (326 ±45 nm).[41] Each EM laboratory should establish a consistent technique for measuring GBM thickness and determine its own reference range for GBM width to make comparisons with published data meaningful. Typically, a value of 250 nm will accurately separate adults with normal GBM from those with TBMN. For children, the cutoff is in the range of 200 to 250 nm. Intraglomerular variability in GBM width is minimal in patients with TBMN.

Diagnosis and Differential Diagnosis

If the family history indicates autosomal dominant transmission of isolated hematuria without deafness or ocular abnormalities, if there is no family history of CKD, and if kidney and urinary tract imaging studies are normal, a presumptive diagnosis of TBMN can often be made without kidney biopsy (see Fig. 48-7). When family history is negative or unknown or there are atypical coexisting features, such

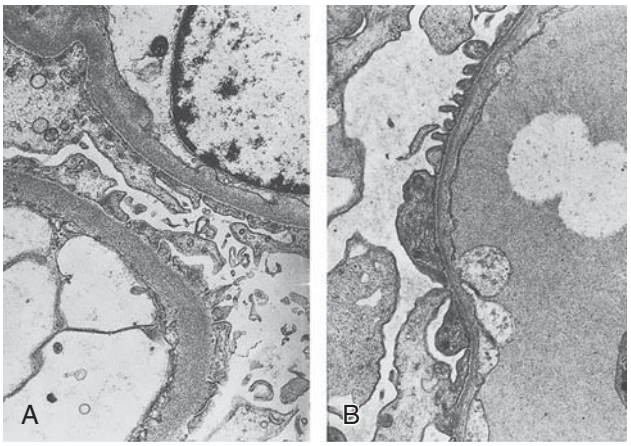

Figure 48-9 Thin basement membrane nephropathy. Electron micrographs of renal biopsy specimens. **A,** Normal glomerular capillary wall. **B,** Thin basement membrane nephropathy at the same magnification. Note the diffuse and uniform attenuation of the GBM and the lamina densa. *(From reference 63.)*

as proteinuria and deafness, renal biopsy may be very informative. A finding of thin GBM may be further characterized by examining the distribution of type IV collagen α chains in the kidney. Normal distribution of these chains provides supportive but not conclusive evidence for a diagnosis of TBMN. Marked variability in GBM width within a glomerulus in a patient with persistent microhematuria should raise suspicion of AS, although focal lamina densa splitting has been described in TBMN. Genetic analysis may confirm a heterozygous mutation in *COL4A3* or *COL4A4*.

Treatment

Patients with TBMN should be reassured but not lost to follow-up examination. The risk for chronic renal impairment is small (likely <5%) but real. Urinalysis and measurement of blood pressure and renal function are recommended every 1 to 2 years.

FABRY DISEASE (ANDERSON-FABRY DISEASE)

Definition

Fabry disease comprises the clinical and the pathologic manifestations of hereditary deficiency of the enzyme α-galactosidase A (α-Gal A), resulting in the intracellular accumulation of neutral glycosphingolipids with terminal α-linked galactosyl moieties (Fig. 48-10). Anderson[42] and Fabry[43] each described the characteristic skin lesions of this condition in 1898 and noted the association of proteinuria with the skin lesion, for which Fabry coined the term *angiokeratoma corporis diffusum*.

Etiology and Pathogenesis

More than 100 mutations causing Fabry disease have been identified in the gene for α-Gal A, which is located on the X chromosome. Most of the described mutations are associated with the classic Fabry phenotype, in which there is multisystem involvement. Certain missense mutations have been identified in patients with a mild phenotype limited to cardiac abnormalities.[44]

Deficiency of α-Gal A leads to progressive intracellular accumulation of neutral glycosphingolipids, particularly those with

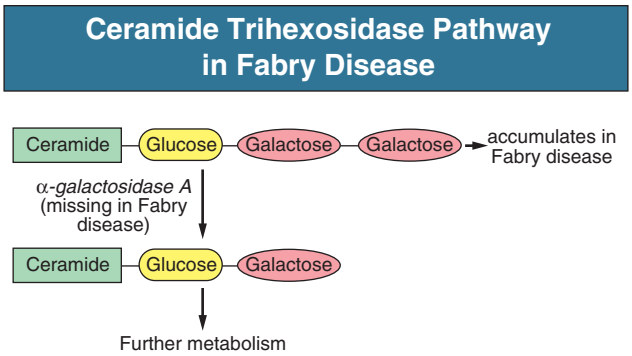

Figure 48-10 Ceramide trihexosidase pathway in Fabry disease. α-Galactosidase A deficiency leads to tissue accumulation of trihexosylceramide.

α-galactosyl moieties, the most abundant of which is globotriaosylceramide (Gb3). Glycosphingolipids are normal constituents of the plasma membrane, the membranes of intracellular organelles, and circulate in association with apolipoproteins. The glycosphingolipids that accumulate in Fabry disease are identical to those found in normal tissue. All tissues except red blood cells accumulate Gb3, with the highest concentrations found in the diseased kidney.

Clinical Manifestations and Pathology

Classic Fabry disease is a multisystem disorder, with prominent and potentially devastating involvement of the kidneys, heart, and peripheral and central nervous system. As expected for an X-linked disorder, severe clinical manifestations occur in hemizygous males, whereas heterozygous females exhibit a variable but typically less severe course. In affected males, the initial features of the disease are seen in childhood and early adolescence and consist of paresthesias and pain in the hands and feet with episodic pain crises. The course of the disease is variable but usually leads to ESRD in the third to sixth decade. Myocardial or cerebral infarctions are typical terminal events. Severe Fabry disease in a female reflects extensive inactivation of the X chromosome carrying the normal α-Gal A allele.

Renal Defects

Although the earliest manifestation of renal involvement is a concentrating defect, the nephropathy of Fabry disease typically manifests as mild to moderate proteinuria, sometimes with microhematuria, beginning in the third decade. Nephrotic syndrome is unusual. Urinary oval fat bodies, with a Maltese cross configuration when viewed with a polarizing microscope, are a result of the large amounts of glycosphingolipid in the urine (see Chapter 4, Fig. 4-2, *B*). Deterioration of renal function is gradual, with hypertension and ESRD developing by the fourth or fifth decade of life. Heterozygous women typically display mild renal involvement but may develop ESRD.

Light microscopy shows striking glomerular changes with additional abnormalities of tubular epithelium and vessels (Fig. 48-11). Glomerular visceral epithelial cells are enlarged and packed with small, clear vacuoles, which represent glycosphingolipid material that has been extracted during processing. Vacuoles may also be seen in parietal epithelial cells and the epithelial cells of the distal convoluted tubule and loop of Henle, but only rarely in mesangial cells, glomerular endothelial cells, or proximal tubular epithelial cells. There is progressive segmental and global glomerulosclerosis. Vacuoles are also observed in endothelial cells and smooth muscle cells of arterioles and arteries.

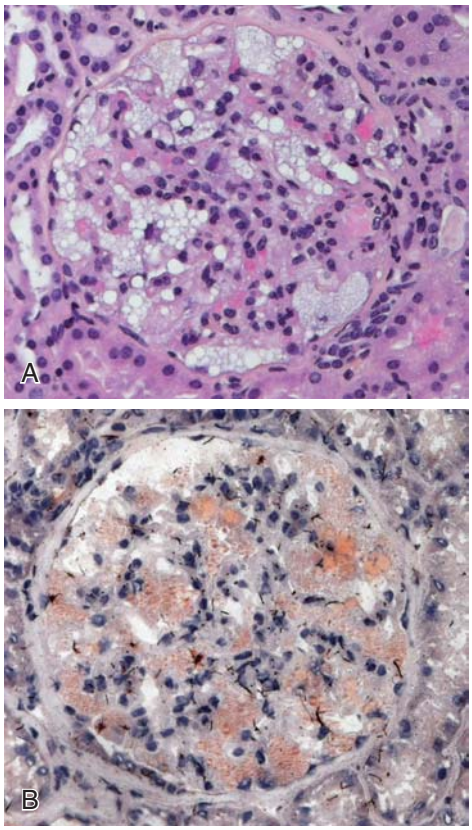

Figure 48-11 Light microscopy of a renal biopsy specimen in Fabry disease. Glomerular epithelial cell glycosphingolipid deposition demonstrated by **A,** vacuolation on hematoxylin-eosin staining (magnification ×20), and **B,** oil red O staining (×20). *(Courtesy Dr. Paolo Menè and Dr. Antonella Stoppacciaro, University of Rome.)*

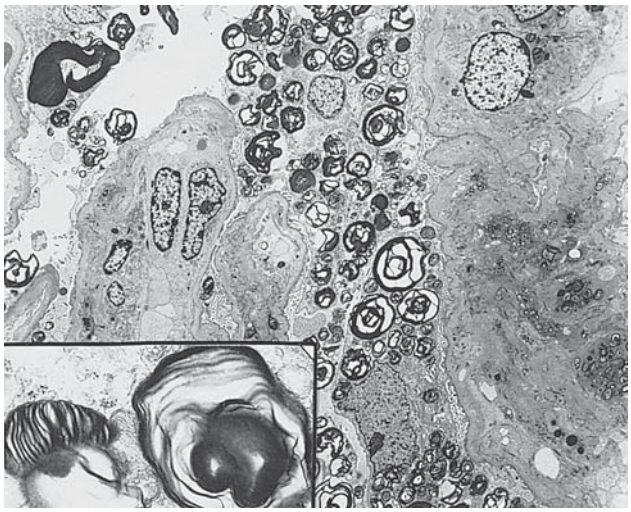

Figure 48-12 Electron micrograph of a renal biopsy specimen in Fabry disease. Glycosphingolipid is deposited in cytoplasmic vacuoles in glomerular visceral epithelial cells. *Inset,* Cytoplasmic vacuoles contain electron-dense material in parallel arrays (zebra bodies) and in concentric whorls (myelin figures). *(Courtesy Dr. J. Carlos Manivel.)*

On EM, there are abundant inclusions within lysosomes, particularly within visceral epithelial cells (Fig. 48-12). The inclusions (myelin figures) are typically round, comprising concentric layers of dense material separated by clear spaces. The layers may be arranged in parallel (zebra bodies). Detachment of visceral epithelial cells from the underlying basement membrane may be observed. Inclusions are also observed in heterozygous females, although usually in smaller numbers than in affected males. Typical inclusions may be noted in excreted renal tubular cells.

Figure 48-13 Angiokeratoma in Fabry disease. Note the multiple periumbilical angiokeratomas. *(Courtesy Dr. S. Waldek.)*

The progression of Fabry nephropathy to ESRD probably reflects two parallel processes. Visceral epithelial cell dysfunction, which results in proteinuria, is followed by visceral epithelial cell detachment and necrosis, leading to capillary loop collapse and segmental sclerosis. Simultaneously, progressive impairment of arteriolar flow may develop, as enlarging endothelial cells impinge on vascular lumina, resulting in ischemic glomerular damage.

Heart Defects

Glycosphingolipid accumulation in coronary arterial endothelial cells and in the myocardium results in coronary artery narrowing, which may lead to angina, myocardial infarction, or congestive heart failure. Arrhythmias and valvular lesions have been identified. Certain missense mutations affecting α-Gal A may present as isolated left ventricular hypertrophy (LVH).[44]

Nervous System

Autonomic dysfunction is a prominent feature of Fabry disease, typically manifested by hypohidrosis, acral paresthesias, and altered intestinal motility. Cerebrovascular symptoms tend to appear during the fourth decade and include hemiparesis, vertigo, diplopia, dysarthria, nystagmus, nausea and vomiting, headache, ataxia, and memory loss. The vertebrobasilar circulation is preferentially involved. Symptoms are often recurrent. Life-threatening intracerebral hemorrhage and infarction are not unusual. Dementia arising from glycosphingolipid accumulation in small cerebral blood vessels has also been described.

Skin

Angiokeratomas usually appear during the second decade of life, presenting as dark-red macules or papules of variable size (Fig. 48-13). Typical locations include the lower trunk, buttocks, hips, genitalia, and upper thighs. The number of lesions varies from none up to 40. On histologic examination, angiokeratomas consist of dilated small veins in the upper dermis, covered by hyperkeratotic epidermis. Telangiectasias may be noted, especially behind the ears.

Eyes

Characteristic corneal opacities are common in both men and women with Fabry disease. These lesions, termed *verticillata,* are

identified by slit-lamp examination and are whorls of whitish discoloration that radiate from the center of the cornea. Cataracts and dilated conjunctival or retinal vessels may be observed.

Lungs

Dyspnea and cough are common in men with Fabry disease, often with airflow limitation on spirometry. This may be a consequence of fixed narrowing of the airways caused by glycosphingolipid accumulation.

Diagnosis

Diagnosis of affected males can usually be made clinically, with the additional information from slit-lamp eye examination. The diagnosis should be confirmed by demonstrating decreased or absent α-Gal A activity in serum, leukocytes, cultured skin fibroblasts, or tissue. Atypical variants may have enzyme activity up to 35% of normal. Heterozygous females have intermediate levels of α-Gal A activity, but values may be in the low-normal range, making measurement of enzyme activity an insensitive way of diagnosing carriers. Alternatives include careful slit-lamp eye examination, measurement of urinary ceramide digalactoside and trihexoside, and molecular techniques. Current information on laboratories offering sequencing of the α-Gal gene can be obtained at gene reviews.org. Identification of carriers is particularly relevant when family members are being considered as living kidney donors.

Fabry disease should be considered in patients with unexplained ESRD,[45] especially if LVH is present or there is a history of stroke.[46]

Treatment

Until recently, clinicians could offer little beyond palliative, symptomatic care, but the introduction of enzyme replacement therapy with recombinant human α-Gal A (agalsidase) has transformed the treatment of Fabry disease. Randomized clinical trials showed that agalsidase administration during 5 to 6 months resulted in reduced plasma and urine Gb3; amelioration of neuropathic pain; enhanced quality of life; clearing of Gb3 deposits from kidney, heart, and skin; and improved cerebral blood flow.[47,48] A multicenter longitudinal study showed that agalsidase stabilized renal function in patients with mild to moderate renal impairment at baseline and reduced left ventricular mass in those with LVH at baseline during 1 to 2 years of treatment.[49] However, the impact of enzyme replacement therapy on long-term renal outcome is still unclear.[50,51] Addition of ACE inhibitor and/or angiotensin receptor blocker (ARB) therapy to enzyme replacement can result in sustained reductions in proteinuria.[52] In patients with ESRD, agalsidase infusion may be combined with hemodialysis, because there is little clearance of the enzyme by dialysis.[53] Agalsidase therapy has been recommended for all affected males and symptomatic carrier females, but the drug is prohibitively expensive in many parts of the world.[54] An alternative treatment approach based on chemical "chaperones" is under investigation.[55,56]

Renal transplantation is an effective treatment of advanced Fabry nephropathy but does not ameliorate the extrarenal manifestations. Transplanted kidneys from deceased donors or unaffected living donors may develop glycosphingolipid inclusions, but these are generally infrequent and clinically insignificant. Fabry heterozygotes should not become kidney donors. Coronary artery and cerebrovascular disease are the major causes of mortality in patients with Fabry disease who have undergone renal transplantation. Renal allograft recipients with Fabry disease are candidates for agalsidase treatment.[54]

Fabry Disease in Childhood

Because it is often not appreciated that the signs and symptoms of Fabry disease, particularly pain crises, acroparesthesias, angiokeratomas, and corneal opacities, typically have their onset in childhood, the diagnosis is frequently delayed until well into adult life.[57] Symptomatic children with Fabry disease are potential candidates for agalsidase therapy.

NAIL-PATELLA SYNDROME

Definition

Nail-patella syndrome (NPS) is an autosomal dominant condition characterized by hypoplasia or absence of the patellae, dystrophic nails, dysplasia of the elbows and iliac horns, and renal disease.

Etiology and Pathogenesis

The NPS locus was identified in 1998 as the LIM homeodomain transcription factor *LMX1B*.[58,59] A variety of mutations in *LMX1B* have been found in NPS patients, including missense, splicing, insertion or deletion, and nonsense alterations. The results of *in vitro* studies of the transcriptional effects of mixing wild-type and mutant *LMX1B* suggest that NPS results from haploinsufficiency of *LMX1B*, rather than a dominant-negative effect.[60] Although *LMX1B* appears to be important for normal limb and kidney development, the precise mechanisms for the renal effects of *LMX1B* mutations remain under investigation.

Clinical Manifestations

Renal Defects

Clinically apparent renal disease occurs in less than half of NPS patients. The nephropathy is usually benign, with about a 10% risk for progression to ESRD. The clinical signs of NPS nephropathy appear in adolescence or young adulthood and typically include microscopic hematuria and mild proteinuria, although some patients develop nephrotic syndrome and mild hypertension. The severity of the renal manifestations may differ substantially in related individuals.

Skeletal Defects

The patellae are absent or hypoplastic in more than 90% of patients with NPS and may be associated with effusions and osteoarthritis of the knees (Fig. 48-14). In about 80% of patients, osseous processes project posteriorly from the iliac wings (iliac horns), which is pathognomonic (Fig. 48-15). Anomalies of the elbows include aplasia, hypoplasia, and posterior processes at the distal end of the humeri.

Nails

Nail abnormalities occur in about 90% of patients and are typically bilateral and symmetric. Fingernails are affected more often than toenails. The nails may be absent or dystrophic with discoloration, koilonychia, longitudinal ridges, or triangular lunulae.

Pathology

The only specific features of the NPS renal lesion are ultrastructural; EM shows multiple irregular lucencies of the GBM, giving it a moth-eaten appearance (Fig. 48-16). Such lucencies may also be observed in the mesangium. These lucent areas sometimes contain cross-banded collagen fibrils, which are more easily observed after staining with phosphotungstic acid (Fig. 48-17). The fibrils, which are type

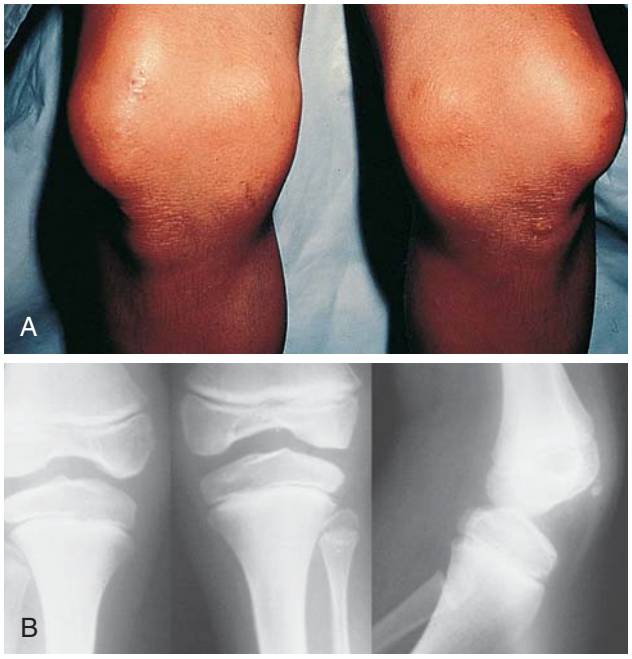

Figure 48-14 Nail-patella syndrome. Clinical (**A**) and radiologic (**B**) appearance of absence of the patellae. *(Courtesy Dr. R. Vernier.)*

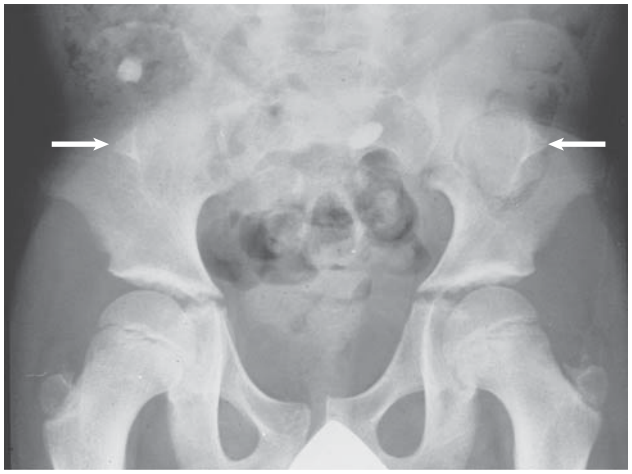

Figure 48-15 Nail-patella syndrome. Iliac horns *(arrows). (Courtesy Dr. R. Vernier.)*

III collagen,[61] tend to be arranged in clusters, and the surrounding GBM is often thickened. This may be observed in the kidneys in the absence of clinically evident renal disease, but fibrils have not been found in extraglomerular basement membranes. Cross-banded fibrils of type III collagen have been seen in GBM of patients with glomerular disease who lack nail or skeletal abnormalities, sometimes as a familial condition with autosomal recessive inheritance (collagen III glomerulopathy; see Chapter 28). It is uncertain whether there is a pathogenetic relationship between collagen type III glomerulopathy and NPS.

Treatment

No specific therapy is available for the nephropathy of NPS. There has been no reported recurrence in transplanted kidneys. Because nail-patella syndrome is an autosomal dominant disorder, careful evaluation of potential living related kidney donors for features of NPS is essential.

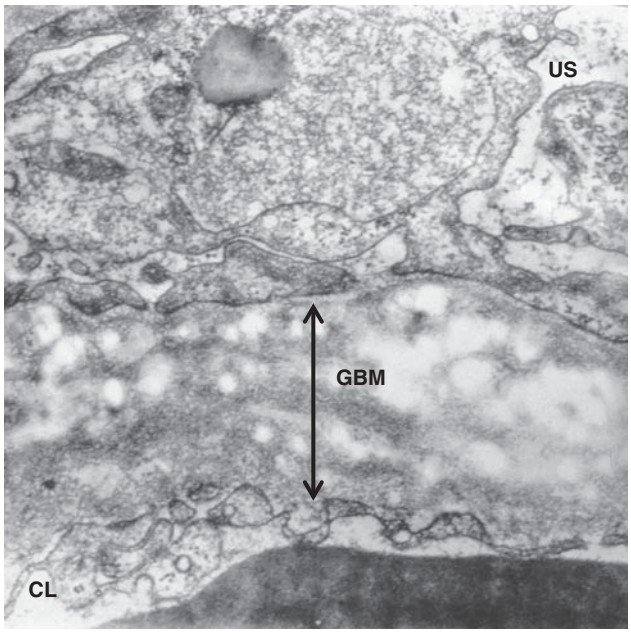

Figure 48-16 Electron micrograph of renal biopsy specimen in nail-patella syndrome. The GBM appears moth-eaten on routine staining; *CL,* capillary lumen; *US,* urinary space. *(Courtesy Dr. R. Vernier.)*

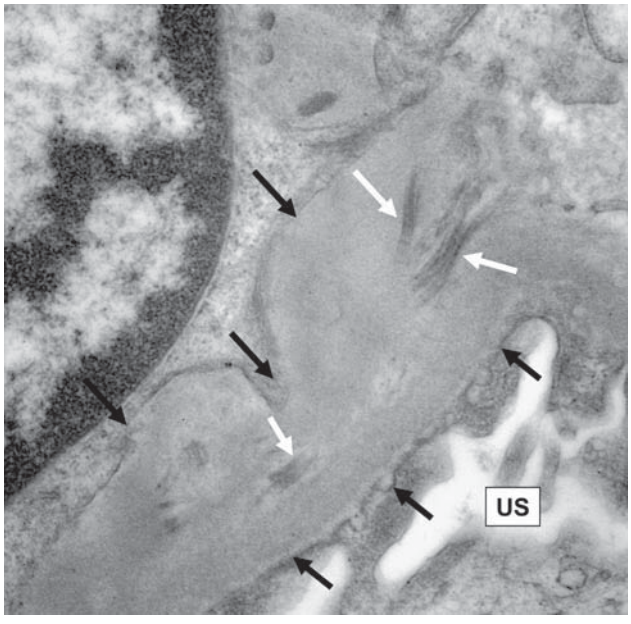

Figure 48-17 Electron micrograph of renal biopsy specimen in nail-patella syndrome. *Black arrows* show margins of irregular glomerular basement membrane. Staining with phosphotungstic acid reveals fibrillar collagen *(white arrows). US,* Urinary space.

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CHAPTER 49

Inherited Disorders of Sodium and Water Handling

Peter Gross and Peter Heduschka

Glomerular filtration yields about 150 liters of water, 21,000 mmol of sodium (Na^+), and 750 mmol of potassium (K^+) in a healthy individual in 24 hours, yet only minute fractions of these quantities are excreted eventually as urine. This remarkable volume reduction is accomplished by highly active tubular transport. Inherited defects of tubular transport proteins may thus lead to major fluid and electrolyte derangements. This chapter describes disorders arising in the thick ascending limb of Henle loop and thereafter; proximal tubular disorders are described in Chapter 50 and disturbances of acidification in Chapter 12.

Genetic studies have unraveled the molecular basis of most of the inherited tubular disorders, establishing specific diagnoses more clearly and explaining the corresponding pathogenesis more reliably than previously possible. It is hoped that improved therapies will be developed in time. Diagnostic genetic testing is available for a number of the disorders discussed in this chapter (see www.genetests.org).

PHYSIOLOGY OF SODIUM AND WATER REABSORPTION

Sodium Reabsorption

In all tubular epithelial cells, a basolateral energy requiring Na^+,K^+–adenosine triphosphatase (ATPase) will ensure that intracellular Na^+ is kept at low levels while K^+ is high. The resulting concentration gradients of Na^+ across the apical cell membrane drive passive Na^+ reabsorption from the tubular lumen to the cell interior. Apical Na^+ channels and transport proteins serve to regulate the Na^+ reabsorption, and the proteins involved differ from one tubular segment to the next.

In the proximal tubule, an apical Na^+-hydrogen (H^+) exchange protein (NHE3) facilitates most of the Na^+ reabsorption. It is inhibitable by acetazolamide. The thick ascending limb (TAL) of Henle loop has an apical Na^+-K^+-$2Cl^-$ cotransporter (NKCC2) that can be blocked by furosemide and bumetanide. For efficient Na^+ reabsorption by NKCC2, K^+ must be returned through the renal outer medulla K^+ channel (ROMK) from the cell to the low K^+ tubular fluid (Fig. 49-1). It is also important that sodium transport by this segment is dependent on a basolateral chloride (Cl^-) channel (ClC-Kb) and an accessory protein of ClC-Kb called *barttin* (see Fig. 49-1).

The distal convoluted tubule reabsorbs Na^+ by a unique apical Na^+-Cl^- cotransporter (NCCT). The protein is specifically inhibited by thiazides (Fig. 49-2). A basolateral ClC-Kb chloride channel is also necessary for efficient sodium reabsorption.

In the collecting duct, the apical epithelial sodium channel (ENaC) regulates Na^+ reabsorption. Amiloride and triamterene specifically block ENaC, whereas the mineralocorticoid aldosterone upregulates ENaC (Fig. 49-3). Figure 49-4 provides an overview of tubular proteins of Na^+ reabsorption and their corresponding inheritable disorders (see also Chapters 2 and 7).

Water Reabsorption

In most nephron segments, water follows sodium chloride (NaCl, salt) passively through aquaporins, the constitutively open water transport proteins in apical and basolateral tubular cell membranes. The collecting duct is different, however, and is equipped with apical aquaporin 2 (AQP2), the sole water channel in the kidney that can be regulated on a short-term basis by vasopressin. In this way, the collecting duct provides for eventual fine-tuning of water reabsorption or excretion (Fig. 49-5; see also Chapters 2 and 8).

DISORDERS OF SODIUM HANDLING

Figure 49-6 provides an overview of inherited disorders of Na^+ transport. On clinical grounds, four different phenotypes can broadly be distinguished, as follows:

1. Hypokalemia and normal blood pressure (Bartter syndrome, Gitelman syndrome).
2. Hypokalemia and high blood pressure (Liddle syndrome, apparent mineralocorticoid excess, glucocorticoid-remediable hyperaldosteronism, adrenal 17α-hydroxylase deficiency, adrenal 11β-hydroxylase deficiency).
3. Hyperkalemia and normal blood pressure (pseudohypoaldosteronism, adrenal 21-hydroxylase deficiency, adrenal aldosterone synthase deficiency).
4. Hyperkalemia and high blood pressure (Gordon syndrome).

Some of the disorders are caused by mutated renal transport proteins (e.g., Gitelman syndrome). In others, the genetic defect resides in the adrenals, and the changes in adrenal mineralocorticoids and glucocorticoids create the renal phenotype.

CONDITIONS WITH HYPOKALEMIA, METABOLIC ALKALOSIS, AND NORMAL BLOOD PRESSURE

Bartter Syndrome

Bartter syndrome is rare and is manifests in childhood or in the perinatal period with severe hypokalemia, metabolic alkalosis, and low-normal blood pressure (BP), all of which are caused by tubular wasting of Na^+ and Cl^-.[1] In contrast, Gitelman syndrome is mostly a disorder of adults, and hypomagnesemia is a defining feature.[2]

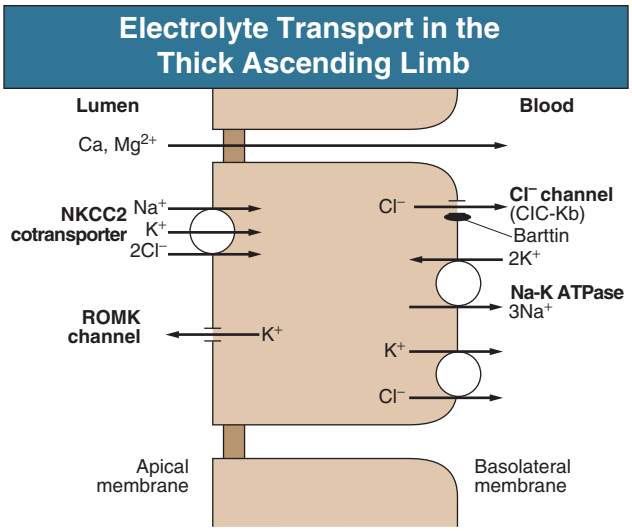

Figure 49-1 Electrolyte transport in thick ascending limb of the loop of Henle. The furosemide-sensitive Na^+-K^+-$2Cl^-$ *(NKCC2)* cotransporter is driven by low intracellular Na^+ and Cl^- concentrations produced by the Na^+,K^+-ATPase pump, the K^+-Cl^- cotransporter, and the basolateral Cl^- channel (ClC-Kb). The β subunit (barttin) is crucial for normal functioning of the ClC-Kb channels. Apical K^+ recycling through the low-conductance, ATP-sensitive renal outer medullary K^+ *(ROMK)* channel ensures the efficient functioning of the NKCC2 cotransporter.

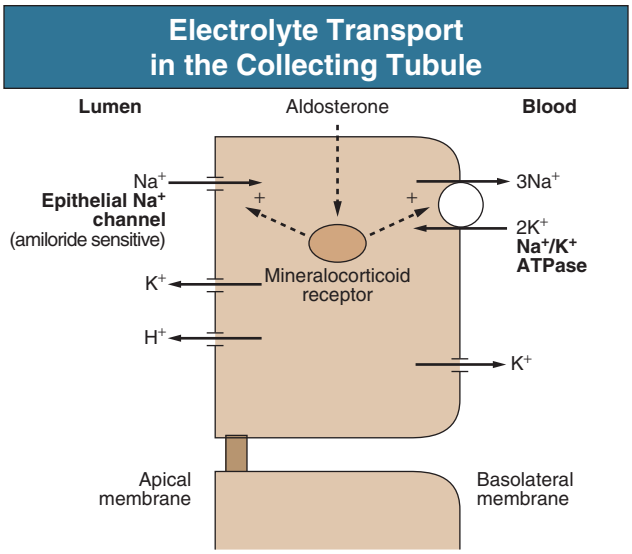

Figure 49-3 Electrolyte transport in principal cell of the collecting tubule. Reabsorption of Na^+ occurs through the amiloride-sensitive epithelial Na^+ channel (ENaC). Its uptake is coupled to K^+ and H^+ secretion. Aldosterone increases the activity of ENaC and Na^+,K^+-ATPase, which increases Na^+ reabsorption and K^+ and H^+ secretion, resulting in hypokalemic alkalosis. Cortisol is also a ligand for the mineralocorticoid receptor but is normally removed by oxidation by 11β-hydroxysteroid dehydrogenase to cortisone.

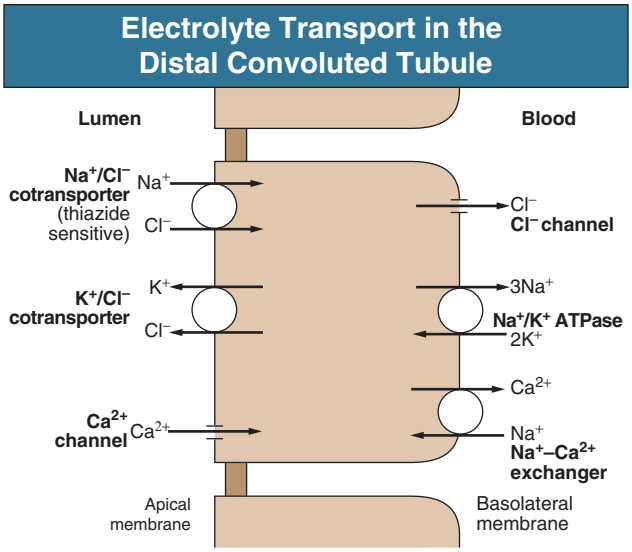

Figure 49-2 Electrolyte transport in the distal convoluted tubule. Reabsorption of Na^+ and Cl^- occurs across the apical membrane by the thiazide-sensitive Na^+-Cl^- cotransporter (NCCT), and these ions leave the cell through the Cl^- channels and through the Na^+,K^+-ATPase pump. Calcium ions enter the cell through the Ca^{2+} channels and exit through the Na^+-Ca^{2+} exchanger.

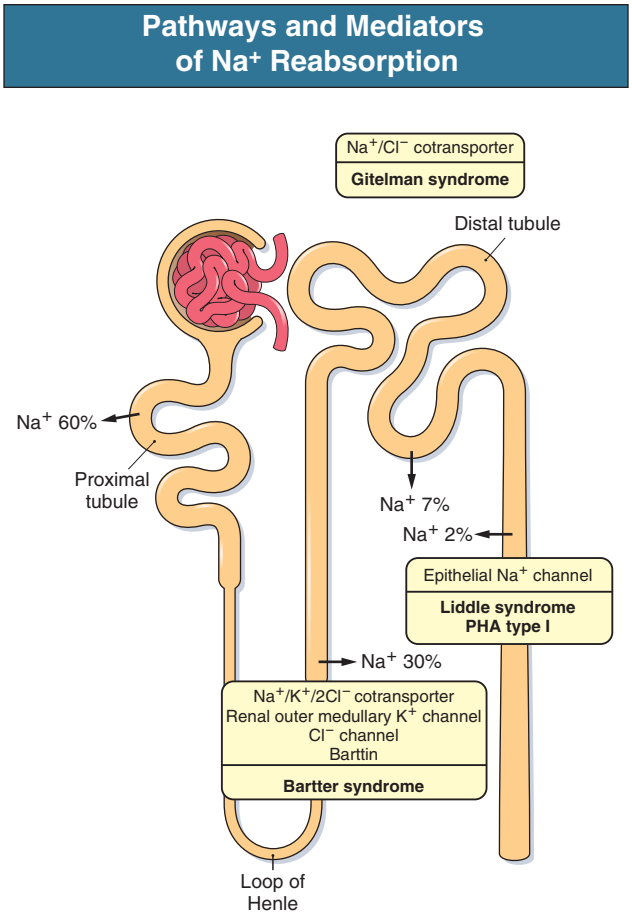

Figure 49-4 Pathways and mediators involved in Na^+ reabsorption. Almost 60% of the filtered Na^+ is reabsorbed in the proximal tubule. The distal portions of the nephron reabsorb the remainder. The chief mediators involved in Na^+ reabsorption and disorders resulting from their mutations are shown in boxes. *PHA,* Pseudohypoaldosteronism.

Pathogenesis

Bartter syndrome is caused by TAL dysfunction and by inactivating mutations of each of its major transport proteins: NKCC2 for Bartter syndrome type 1; ROMK for type 2; ClC-Kb, type 3; and barttin, type 4[3-6] (Table 49-1; see also Fig. 49-1). The pathogenic consequences of these mutations are broadly similar in all four varieties, except that the more severe phenotypes (types 1, 2, and 4) are manifested earlier in life.

Loss of function of any one of the four transport proteins will impair NaCl reabsorption by the TAL, increasing the delivery of salt

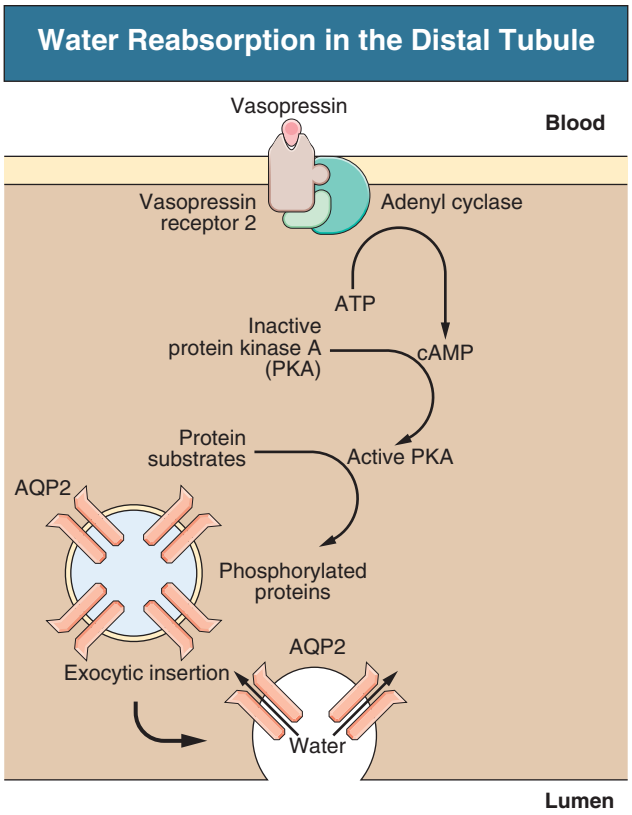

Figure 49-5 Water reabsorption in the distal tubule. The aquaporin AQP2, which is exclusively present in the principal cells of the collecting tubules and ducts, is the chief vasopressin-regulated water channel. Activation of cAMP-dependent protein kinase A mediates protein phosphorylation that triggers exocytic insertion of AQP2 channels into the apical membrane. These channels increase the water permeability of the apical membrane, facilitating water transport.

to the distal nephron. NaCl reabsorption is stimulated in those segments, but compensates only partly for the salt wasting; it is associated with distal secretion of K^+ and H^+. The net loss of NaCl from the nephron will cause plasma volume contraction, low-normal BP, and secondary hyperaldosteronism. The loss of K^+ and H^+ will be followed by severe hypokalemia and metabolic alkalosis. Hypokalemia and increased angiotensin II (Ang II) also stimulate prostaglandin E_2 (PGE_2) production.

Reduced Cl^- absorption in the loop of Henle inhibits voltage-driven paracellular absorption of Ca^{2+}, causing hypercalciuria, an

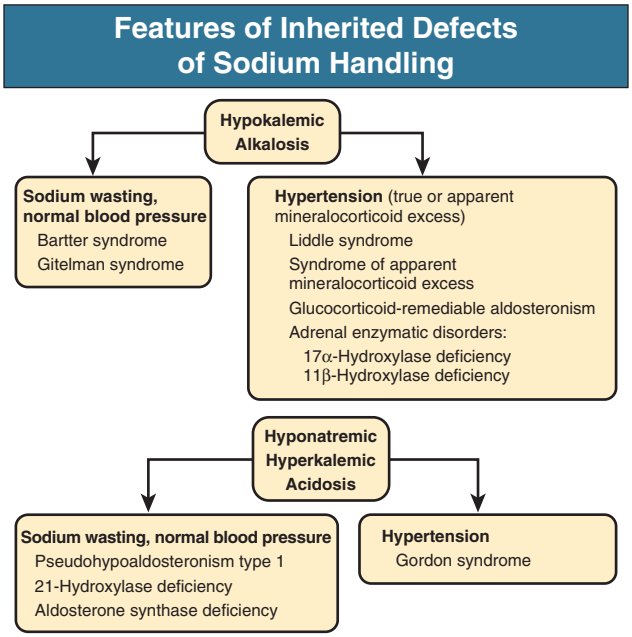

Figure 49-6 Features of inherited defects of sodium handling.

Inherited Single Gene Defects of Sodium and Water Handling

Syndrome	Inheritance	Gene Localization	Gene Product
Neonatal Bartter syndrome	AR	15q	Na-K-2Cl cotransporter *NKCC2*
Neonatal Bartter syndrome	AR	11q	Renal potassium channel *ROMK*
Classic Bartter syndrome	AR	1p	Renal chloride channel *CIC-Kb*
Bartter syndrome with deafness	AR	1p	β subunit of CIC-Kb *Barttin*
Gitelman syndrome	AR	16q	NaCl cotransporter *NCCT*
Liddle syndrome	AD	16p	Epithelial sodium channel *ENaC*
Syndrome of apparent mineralocorticoid excess	AR	16q	11β-hydroxysteroid dehydrogenase type II
Glucocorticoid-remediable aldosteronism	AD	8q	Aldosterone synthase *CYP11B2*
Pseudohypoaldosteronism type I	AD AR	4p 12p, 16p	Mineralocorticoid receptor *ENaC*
Gordon syndrome	AD AD AD	12p 17q 1q	WNK1 WNK4 Not identified
Congenital adrenal hyperplasia	AR AR AR	6p 8q 10q	21-hydroxylase 11β-hydroxylase 17α-hydroxylase
Nephrogenic diabetes insipidus	X-linked AR	Xq 12q	AVP receptor 2 Aquaporin 2

Table 49-1 Inherited single-gene defects of sodium and water handling. *AD,* Autosomal dominant; *AR,* autosomal recessive; *AVP,* arginine vasopressin.

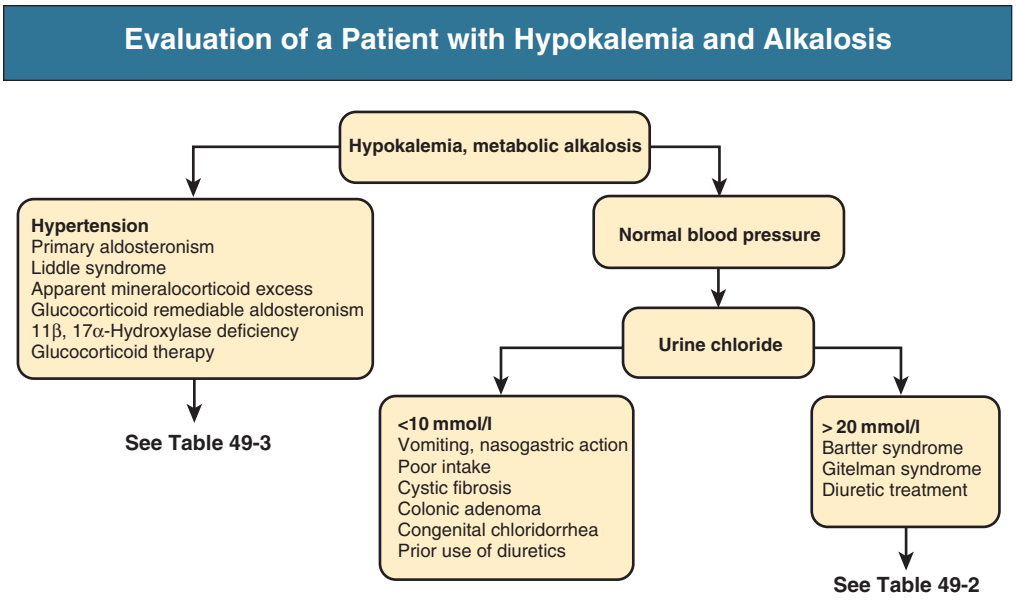

Figure 49-7 Evaluation of a patient with hypokalemia and metabolic alkalosis.

important feature of Bartter syndrome that may be associated with nephrocalcinosis.

Inactivating mutations of barttin also cause deafness because barttin-dependent chloride transport is crucial to endolymph production in the inner ear.[6] In some individuals with mutation of ClC-Kb (type 3), there is a mixed Bartter and Gitelman syndrome.[7] In these patients, the features of Bartter syndrome are associated with hypomagnesemia and hypocalciuria. Age at presentation is 1 month to 29 years. This mixed syndrome may be explained by the overlapping distribution of ClC-Kb, which is also expressed in the distal tubule, the site affected in Gitelman syndrome.[7] Finally, gain-of-function mutations in the extracellular calcium ion–sensing receptor also cause a Bartter-like syndrome.[8] The receptor is normally expressed in TAL, and its activation inhibits salt reabsorption similar to furosemide; also, this syndrome is associated with hypocalcemia.[8]

Clinical Manifestations

Bartter syndrome from mutations in NKCC2, ROMK, or barttin has a more severe phenotype than that caused by mutations of ClC-Kb. The more severe phenotype typically presents in the perinatal period and is called *antenatal* Bartter syndrome. The milder variety is called *classic* Bartter syndrome.

The clinical features of antenatal Bartter syndrome include hypokalemia and metabolic alkalosis in a newborn with vomiting and failure to thrive. There may also be a history of polyhydramnios and premature delivery. Polyuria, hypercalciuria, and high urinary chloride concentrations are characteristic. Nephrocalcinosis may manifest later in life. A prenatal diagnosis of Bartter syndrome may be made by demonstration of high Cl^- concentrations in amniotic fluid.

Patients with classic Bartter syndrome develop normally during the first 2 to 5 years of life. Thereafter, vomiting, polyuria, recurrent episodes of dehydration, and fever may become apparent. Carpopedal spasms and fatigue are common. Many children show developmental delay. The BP is low normal. The laboratory features are comparable to those described previously, but nephrocalcinosis is usually absent.

Diagnosis

A newborn or a young child with vomiting, dehydration, low-normal BP, severe hypokalemia, and metabolic alkalosis is likely to have Bartter syndrome if there is high urinary Cl^- and K^+. The suspected diagnosis will receive further support if supplements of K^+ and Cl^- are inefficient in correcting the severe hypokalemia and BP. Diuretics will not be found in the urine. Hypomagnesemia and hypocalciuria are absent. Secondary hyperaldosteronism is a regular feature. In questionable cases, genotyping should be used to confirm the diagnosis.

Differential Diagnosis

In syndromes of chronic severe hypokalemia with metabolic alkalosis, the differential diagnosis may be facilitated greatly by taking into consideration the associated BP and the urinary chloride concentration (Fig. 49-7).

Hypertension indicates disorders related to hyperaldosteronism. If Bartter syndrome is associated with a normal or low-normal BP, however, extrarenal or renal Cl^- and Na^+ losses are the cause. Extrarenal loss of sodium occurs in diarrhea, vomiting, or burns and is characterized by very low Cl^- concentrations in the urine, often 1 mmol/l. By contrast, renal loss of salt with high urinary Cl^- and Na^+ is typical of Bartter syndrome, Gitelman syndrome, and diuretic use. The absence of hypomagnesemia and hypocalciuria will then argue against Gitelman syndrome (Table 49-2). Genotyping is recommended to diagnose overlap of Bartter and Gitelman syndromes.

Treatment

Patients with the neonatal form of Bartter syndrome have marked fluid and electrolyte disturbances that need to be corrected carefully. Saline infusion may be required in the neonatal period. Potassium chloride supplementation is always necessary.[9] Addition of spironolactone or triamterene may be useful in correcting hypokalemia, but the effect of these drugs is usually transient. Angiotensin-converting enzyme (ACE) inhibitors have been used for correction of hypokalemia, with conflicting results. Magnesium deficiency may aggravate renal K^+ wasting and, if present, should be corrected.

The efficacy of long-term treatment with prostaglandin synthase inhibitors, such as indomethacin (1 to 3 mg/kg/24 h) or ibuprofen, is well established.[9] These act by reducing cortical perfusion and decreasing delivery of Na^+ and Cl^- to the distal nephron, ameliorating many of the features of the disease. The amplifying effect of prostaglandins on the renal tubules is also neutralized. Treatment

Features Differentiating Bartter and Gitelman Syndrome

Feature	Bartter Syndrome		Gitelman Syndrome
	Neonatal	*Classic*	
Age at onset	Neonatal period	Infancy/ childhood	Childhood/ later
Maternal hydramnios	Common	Rare	Absent
Polyuria, polydipsia	Marked	Present	Rare
Dehydration	Present	Often present	Absent
Tetany	Absent	Rare	Present
Growth retardation	Present	Present	Absent
Urinary calcium	Very high	Normal or high	Low
Nephrocalcinosis	Present	Rare	Absent
Serum magnesium	Normal	Occasionally low	Low
Urine prostaglandins (PGE_2)	Very high	High or normal	Normal
Response to PG synthetase inhibitors* (e.g., indomethacin)	Good	Good	Rare

Table 49-2 Features differentiating Bartter and Gitelman syndromes. In addition to these clinical and laboratory features, molecular diagnosis is now possible; *PGE_2*, prostaglandin E_2. *Improvement of hypokalemia and renal salt wasting.

results in reduction of polyuria and polydipsia, restitution of normal growth and activity, and correction of hypokalemia, although serum K^+ rarely exceeds 3.5 mmol/l. Plasma levels of renin and aldosterone decrease to the normal range.

Outcome

If not treated, Bartter patients may succumb to episodes of dehydration, electrolyte disturbance, or intercurrent infection. With appropriate therapy, most children improve clinically and show catch-up growth; pubertal and mental developments are usually normal. Lifelong therapy is needed. Chronic tubulointerstitial nephropathy caused by persistent hypokalemia, hypercalciuria, and nephrocalcinosis may lead to progressive decline in renal function. There are anecdotal reports of renal transplantation in patients with end-stage renal disease (ESRD). The biochemical parameters return to normal after transplantation.

Gitelman Syndrome

Gitelman syndrome is an autosomal recessive condition also characterized by hypokalemic metabolic alkalosis, but with hypocalciuria and hypomagnesemia.

Pathogenesis

The similarity between the features of Gitelman syndrome and those caused by thiazide administration originally suggested that the defect might be in the distal convoluted tubule. The condition has now been linked to inactivating mutations in the gene for NCCT (see Figs. 49-2 and 49-4).[10] Loss of NCCT function results in Na^+ and Cl^- wasting from this segment, leading to hypovolemia with secondary activation of the renin-aldosterone system. However, the resulting increase in collecting tubule Na^+ reabsorption is counterbalanced by K^+ and H^+ excretion, causing hypokalemic alkalosis. The distal convoluted tubule normally reabsorbs only 7% to 8% of the filtered Na^+ and Cl^- load. The degree of volume contraction, the stimulation of the renin-angiotensin system, and the amount of K^+ loss are therefore not substantial enough to stimulate PGE_2 production.

The hypocalciuria may be caused by enhanced proximal tubular calcium reabsorption, secondary to plasma volume contraction. The renal magnesium wasting is caused by downregulation of the epithelial magnesium channel TRPM6 in distal convoluted tubules.

Clinical Manifestations and Diagnosis

The prevalence of Gitelman syndrome is estimated at approximately 1:40,000 in Caucasian populations. The severity of symptoms varies widely. More severely affected patients complain of generalized and muscle weakness, inability to work for extended periods, salt craving, and a preference for licorice. Cardiac disturbances, muscle cramps, and tetany are only exceptionally present. Chondrocalcinosis of the knees does occur later in life, a result of hypomagnesemia. Laboratory evaluation will show moderate hypomagnesemia, severe hypokalemia, hypocalciuria, high urinary chloride concentration, and absence of thiazides from the urine. BP will be in the low-normal range. These findings establish the diagnosis. Genotyping should be performed in questionable or incomplete syndromes.

Treatment

There is no consensus on the best mode of treatment for Gitelman syndrome. Magnesium at 5 to 15 mmol/day (e.g., as magnesium oxide or aspartate) and potassium supplements are usually given to improve muscle weakness or cramps. However, dosing may be limited by diarrhea and abdominal discomfort. In exceptional cases, parenteral Mg^{2+} has been infused. Indomethacin, cyclooxygenase-2 (COX-2) inhibitors, and spironolactone are usually not helpful. The long-term prognosis for cardiac and renal function as well as for general health is good.

CONDITIONS WITH HYPOKALEMIA, METABOLIC ALKALOSIS, AND HYPERTENSION

Conditions with hypokalemia, metabolic alkalosis, and hypertension all have true or apparent mineralocorticoid excess.

Liddle Syndrome (Pseudohyperaldosteronism)

Liddle syndrome is an autosomal dominant syndrome of hypertension and variable degrees of hypokalemic metabolic alkalosis. The patients resemble those with primary hyperaldosteronism, but levels of mineralocorticoid hormones are not increased. Renin and aldosterone are suppressed, and there is no response to spironolactone or epleronone.[11] However, triamterene and amiloride, which are aldosterone-independent inhibitors of distal Na^+ transport, correct hypertension, renal K^+ loss, and hypokalemia.[12]

Pathogenesis

Liddle syndrome is related to mutations of the β or γ subunit of the collecting duct ENaC.[13] The mutations result in truncations of the cytoplasmic C-terminal tail of the affected subunits. Collecting duct sodium reabsorption depends on the channel density present in the apical cell membrane. Channel density is regulated by removal of ENaC from the cell membrane, ubiquitination, and degradation. In Liddle syndrome, the mutated ENaC protein cannot be recognized by NEDD4, a ubiquitin ligase protein; thus the channels remain in the cell membrane for prolonged periods.[12] This action results in enhanced sodium reabsorption, hypertension, and hypokalemic alkalosis (see Fig. 49-3).

Features of Liddle Syndrome, Apparent Mineralocorticoid Excess, and Glucocorticoid-Remediable Aldosteronism			
Feature	**Liddle Syndrome**	**AME**	**GRA**
Inheritance	Autosomal dominant	Autosomal recessive	Autosomal dominant
Chief features	Significant hypertension, polyuria, growth retardation	Low birth weight, early-onset hypertension, polyuria, growth retardation	Significant hypertension, hemorrhagic stroke
Plasma aldosterone	Reduced	Reduced	Elevated
Plasma renin activity	Reduced	Reduced	Reduced
Urinary mineralocorticoid metabolites	Normal	Elevated ratios of THF + allo-THF to THE; free cortisol to cortisone	Elevated cortisol C-18 oxidation products
Response of the Hypertension to:			
Glucocorticoids	No	Satisfactory	Satisfactory
Triamterene	Satisfactory	Satisfactory	Satisfactory
Spironolactone	No	Satisfactory	Satisfactory

Table 49-3 Features of Liddle syndrome, apparent mineralocorticoid excess (AME), and glucocorticoid-remediable aldosteronism (GRA). These syndromes are all characterized by hypokalemia, metabolic alkalosis, and hypertension; *THE,* tetrahydrocortisone; *THF,* tetrahydrocortisol.

Clinical Manifestations and Diagnosis

Liddle syndrome is a rare disorder of hypertension in teenage children[12] that is associated with hypokalemic metabolic alkalosis and low blood levels of renin and aldosterone. The original patient developed renal failure from an unknown cause and eventually underwent transplantation.[14] Thereafter, her BP normalized, and renin and aldosterone responded normally to provocative measures.

This condition should be differentiated from primary hyperaldosteronism, apparent mineralocorticoid excess, and glucocorticoid-remediable aldosteronism (Table 49-3), as well as 11β-hydroxylase (steroid 11β-monooxygenase) or 17α-hydroxylase (steroid 17α-monooxygenase) deficiency. Activating mutations of the mineralocorticoid receptor (MR) have been reported and should also be differentiated.[15]

Treatment

Therapy consists of Na^+ restriction and K^+ supplements. Triamterene directly inhibits apical Na^+ channels, resulting in increased urinary Na^+ and decreased K^+ excretion and resolution of hypertension. Amiloride usually normalizes the BP and K^+ levels. However, most patients with Liddle syndrome continue to have growth restriction. Because the pathogenetic disorder is not correctable with age, lifelong therapy is required.

Apparent Mineralocorticoid Excess

Pathogenesis

Apparent mineralocorticoid excess (AME) is an autosomal recessive condition resulting from deficiency of the type II (renal and placental) isoform of the enzyme 11β-hydroxysteroid dehydrogenase. Clinical features of AME closely mimic those of Liddle syndrome.[16]

In normal conditions, aldosterone is the principal mineralocorticoid regulating electrolyte and water balance, through its effects on distal renal tubules and cortical collecting ducts. After binding to the MR, aldosterone increases synthesis of various proteins, chiefly Na^+,K^+-ATPase on the basolateral surface and ENaC on the apical surface. These proteins increase Na^+ reabsorption and K^+ secretion in the distal tubules (see Fig. 49-3). Cortisol is also a ligand for the MR and shows potent sodium-retaining activity. Cortisol is, however, normally metabolized by 11β-hydroxysteroid dehydrogenase to cortisone, which lacks such an action.

Loss-of-function mutations in the gene encoding 11β-hydroxysteroid dehydrogenase have been detected in patients with the inherited form of AME.[17,18] As a consequence, in the kidney, intracellular metabolic clearance of cortisol is severely impaired. The accumulation of cortisol causes nonspecific MR stimulation, followed by increased Na^+ reabsorption with K^+ and H^+ secretion. 11β-Hydroxysteroid dehydrogenase is also expressed in the placenta; The enzyme's reduced activity might be related to the low birth weight characteristic of AME patients. Carbenoxolone and glycyrrhizic acid (found in licorice compounds) are potent inhibitors of this enzyme. Consumption of these agents may be associated with features similar to AME.

Clinical Manifestations and Diagnosis

Apparent mineralocorticoid excess is characterized by an onset of hypertension in childhood, hypokalemia, metabolic alkalosis, very low plasma levels of renin and aldosterone, and increased metabolites of cortisol in the urine. There may be a history of low birth weight and subsequent failure to thrive.

The diagnosis of AME is made by finding, on gas chromatography or mass spectroscopy, elevated urinary levels of hydrogenated metabolites of cortisol (tetrahydrocortisol plus allotetrahydrocortisol) compared with cortisone (tetrahydrocortisone). The ratio of urinary free cortisol to cortisone is also increased.[19] Heterozygotes may occasionally show hypertension, normal serum K^+, suppressed plasma renin and aldosterone, and moderately elevated urinary cortisol to cortisone metabolite ratio. A variant of AME, called AME type 2, has similar clinical features but a milder urinary steroid profile.[20]

Treatment

Treatment with oral dexamethasone (0.75 to 5 mg/day) suppresses cortisol secretion, resulting in reduced Na^+ reabsorption and amelioration of hypertension and hypokalemia. Urinary concentrations of metabolites of cortisol and cortisone are only moderately affected. As in Liddle syndrome, patients with AME respond to treatment with K^+ supplements combined with triamterene or amiloride. Spironolactone is effective in AME patients, although not in those with Liddle syndrome. Mineralocorticoid blockade is preferred as long-term therapy, to avoid adverse effects of dexamethasone.

Renal transplantation is followed by normalization of cortisol metabolism, biochemical abnormalities, and hypertension.[21]

Glucocorticoid-Remediable Aldosteronism

Glucocorticoid-remediable aldosteronism (GRA) appears to be the most common monogenic form of human hypertension. It is an autosomal dominant condition. Patients present with typical features of primary hyperaldosteronism: hypertension, suppressed plasma renin activity, and hypokalemia. Unlike primary hyperaldosteronism (due to aldosterone-producing adrenal adenoma), hypersecretion of aldosterone in GRA can be reversed by the administration of corticosteroids. Affected individuals have early-onset hypertension. There is a high prevalence of hemorrhagic stroke, largely as a result of ruptured intracranial aneurysms. Hypokalemia is typically mild but becomes more pronounced if diuretics are given. Serum potassium levels may occasionally be normal.

Pathogenesis

Patients with GRA have adrenocorticotropic hormone (ACTH)–sensitive aldosterone production occurring in the zona fasciculata of the adrenal gland, which is usually responsible only for cortisol synthesis. Normal individuals synthesize aldosterone in the zona glomerulosa. The two isoenzymes of 11β-hydroxylase involved in the biosynthesis of aldosterone and cortisol are steroid 11β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2), respectively (Fig. 49-8). The genes for these isoenzymes are located close to each other on the long arm of chromosome 8. Unequal meiotic crossovers may produce hybrid genes by fusion of the promoter end of *CYP11B1* with the coding sequence of *CYP11B2,* so that *CYP11B2* encoding aldosterone synthase is inappropriately regulated by ACTH, as is *CYP11B1*.[16] Abnormal expression of this chimeric gene in the adrenal zona fasciculata has been shown by *in situ* hybridization.

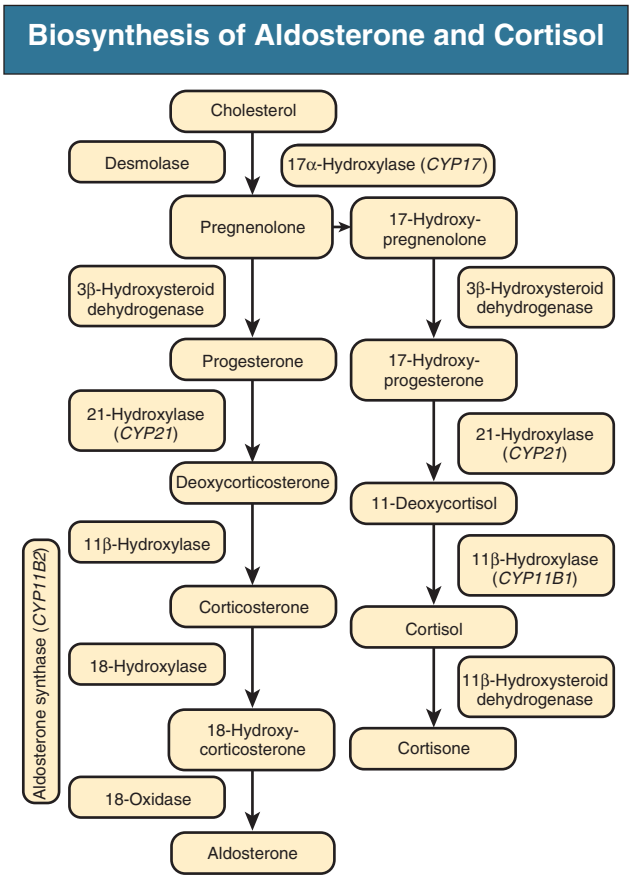

Figure 49-8 Biosynthesis of aldosterone and cortisol. Although cortisol and aldosterone both require 11β-hydroxylation of precursors, these steps are catalyzed by different isoenzymes: steroid 11β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2), respectively. Aldosterone synthase also mediates two further conversions. Common enzyme deficiencies leading to derangement in sodium and water balance are shown. Cortisol is converted peripherally by 11β-hydroxysteroid dehydrogenase to cortisone.

Diagnosis

Patients with GRA are often misdiagnosed as having primary hypertension. Hypertensive patients with early-onset hypertension, early cerebral hemorrhage (<40 years), hypokalemia before or after diuretic therapy, and refractoriness to standard antihypertensive medication are candidates for GRA testing. Similar to other genetic forms of hypertension (Liddle syndrome, AME, Gordon syndrome), plasma renin activity is low. Although the mean aldosterone levels are high, determination of serum aldosterone has poor sensitivity as a screening test. In GRA, the aldosterone-renin ratio is elevated (>300), whereas in primary hypertension, AME, and Liddle syndrome, it is not increased.

The biochemical hallmark of GRA is overproduction and excretion of cortisol C-18 oxidation products, reflecting the action of aldosterone synthase on cortisol in the zona fasciculata. Large amounts of the so-called hybrid steroids (18-hydroxycortisol and 18-oxocortisol) can be found in the urine by specialized steroid laboratories.

Dexamethasone leads to suppression of blood aldosterone levels. When 0.5 mg of dexamethasone is given every 6 hours for 2 days, it suppresses aldosterone to undetectable levels (<4 ng/dl).

Direct screening for the hybrid gene *CYP11B1/CYP11B2* can also be performed and confirms the diagnosis[22] (test can be obtained at www.brighamandwomens.org/Departments_and_Services/medicine/services/endocrine/Services/gra/default.aspx).

Treatment

Treatment with low-dose corticosteroid is effective in GRA patients. Typically, 0.125 to 0.25 mg of dexamethasone or 2.5 to 5 mg of prednisolone is administered at bedtime. Therapeutic goals are normotension and normalization of biochemical markers (urinary 18-oxosteroid, serum aldosterone). MR antagonists (spironolactone, eplerenone) and ENaC antagonists such as amiloride and triamterene are also useful treatments. Antihypertensive therapy with β-blockers and ACE inhibitors is less likely to be effective.

Incomplete Phenotypes

Occasional patients with Liddle syndrome, AME, or GRA either do not express the complete phenotype or have mild clinical or biochemical features and are considered to have primary hypertension. Poor BP control with conventional therapy should suggest an alternative diagnosis. Hypokalemia may not be a feature at presentation but develops with diuretic treatment. These conditions should be considered in patients with early-onset hypertension, failure to thrive, or a strong family history. The response to specific treatment with potassium-sparing diuretics or corticosteroids may suggest the diagnosis.

Adrenal Enzymatic Disorders

Inherited deficiency of 11β- or 17α-hydroxylase also causes mineralocorticoid excess with hypertension and hypokalemic metabolic alkalosis (see Fig. 49-8).

Deficiency of 17α-hydroxylase (CYP17) impairs normal production of cortisol and adrenal androgens, resulting in pseudohermaphroditism in genetic males and primary amenorrhea in females.

Features of Renal-limited and Multisystem Forms of Pseudohypoaldosteronism Type I		
Feature	**Renal-Limited Form**	**Multisystem Form**
Underlying defect	Mineralocorticoid receptor	Epithelial sodium channel
Affected organs	Kidney only	Kidney, sweat, salivary glands, distal colon
Inheritance	Autosomal dominant	Autosomal recessive
Salt wasting	Variable	Severe
Blood renin, aldosterone	Very high	Very high aldosterone
Sweat, salivary Na^+	Normal	High
Clinical features	Salt wasting variable, during stress	Severe salt wasting, hyperkalemia, severe skin infections, respiratory infections (mimics cystic fibrosis)
Treatment	Sodium chloride supplements for 1-3 years Carbenoxolone is effective in some patients (creates situation similar to AME)	Lifelong sodium chloride supplements; strict potassium restriction; prophylactic antibiotics if recurrent skin sepsis; no response to carbenoxolone
Prognosis	Improvement usually by 6-8 years, need for salt supplement diminishes	Improvement rare with age

Table 49-4 Features of renal-limited and multisystem forms of pseudohypoaldosteronism type 1. *AME,* Apparent mineralocorticoid excess.

Cortisol deficiency results in increased ACTH secretion, low levels of renin and aldosterone, hypokalemia, metabolic alkalosis, and hypertension. Diagnosis is confirmed by finding excessive levels of deoxycorticosterone and corticosterone in the urine. Administration of corticosteroids corrects the mineralocorticoid excess state.

Deficiency of 11β-hydroxylase (CYP11B1) also impairs cortisol production but results in excessive androgens. Genetic females show pseudohermaphroditism, whereas males have virilization. The cortisol deficiency results in high blood levels of ACTH, deoxycortisol, and deoxycorticosterone; corticosterone levels are normal. Hypokalemia is variable. Diagnosis is confirmed by measurement of high levels of tetrahydro-11-deoxycortisol in the urine. Hypokalemia is variable. Treatment with corticosteroids corrects hypertension and hypokalemia; renin levels increase, but aldosterone remains low because of the biosynthetic defect.

CONDITIONS WITH HYPONATREMIA, HYPERKALEMIA, METABOLIC ACIDOSIS, AND NORMAL BLOOD PRESSURE

Conditions with hyponatremia, hyperkalemia, metabolic acidosis, and normal BP have features of mineralocorticoid deficiency either because of a synthetic defect or because of end-organ resistance.

Pseudohypoaldosteronism

Pseudohypoaldosteronism (PHA) is a state of renal tubular (and other tissue) unresponsiveness to the action of aldosterone.[23] Symptoms start in early infancy with marked salt wasting and failure to thrive.

Type 1 PHA includes at least two major entities, with either renal or multiple target organ defects; the renal form is more common. The inheritance of renal-limited PHA type 1 is autosomal dominant but may be sporadic. Loss-of-function mutations of the gene for the mineralocorticoid receptor (located on 4p) have been identified.[24] Multiple end-organ (multisystem) PHA type 1 is a severe autosomal recessive disorder with multiple target organ resistance to the action of mineralocorticoids and is associated with inactivating mutations of α, β, or γ subunits of ENaC.[25] Table 49-4 compares the features of the two major PHA type 1 forms.

Aldosterone Biosynthetic Defects

Patients with defects in aldosterone biosynthesis show salt wasting with hyponatremia, hyperkalemia, hypovolemia, and elevated plasma renin activity.[26] The enzymes cholesterol desmolase, 3β-hydroxysteroid dehydrogenase, and 21-hydroxylase are required for synthesis of cholesterol and aldosterone, whereas aldosterone synthase is selectively responsible for aldosterone production in the adrenal cortex (see Fig. 49-8). Table 49-5 compares characteristics of diseases with aldosterone biosynthetic defects.

Deficiency of 21-Hydroxylase

Mutations in the gene encoding 21-hydroxylase (*CYP21*) result in two major forms of the disease: a virilizing form and the more common salt-wasting type.[27] Patients with signs only of androgen excess are said to have the virilizing form. Female infants show varying degrees of pseudohermaphroditism, whereas affected males have normal or precocious sexual development. Patients with the salt-wasting type present with hyponatremia, hyperkalemia, and moderate to severe volume depletion.

The diagnosis of 21-hydroxylase deficiency should be suspected in any newborn with genital ambiguity, salt wasting, or hypotension. Blood levels of progesterone, 17-hydroxyprogesterone, and dehydroepiandrosterone are raised several-fold above normal.

Patients with electrolyte imbalance and shock require resuscitation with intravenous fluids and salt supplements. Replacement therapy with oral hydrocortisone and 9α-fludrocortisone is required long term. Some amelioration of the tendency to salt wasting may be seen with age because of the ability of children to regulate their dietary salt intake and maturation of proximal tubular function.

Reconstructive genital surgery may be required in females with genital ambiguity. Fetal DNA analysis and demonstration of elevated 17-hydroxyprogesterone in amniotic fluid allow prenatal detection of affected female infants. Treatment of the mother with dexamethasone from early in gestation reduces virilization of genitalia of the affected female fetus.

Aldosterone Biosynthetic Defects				
Defective Enzyme	**21-Hydroxylase**	**3β-Hydroxysteroid Dehydrogenase**	**Cholesterol Desmolase**	**Aldosterone Synthase**
Incidence	Most common (1:11,000-23,000 births)	Rare	Rare	Rare
Aldosterone	Deficient	Deficient	Deficient	Deficient
Cortisol production	Deficient	Deficient	Deficient	Normal cortisol
ACTH	Loss of feedback inhibition	Loss of feedback inhibition	Loss of feedback inhibition	Normal feedback inhibition
Adrenal hyperplasia	Yes	Yes	Yes	No
Genital ambiguity	In females	In females	In females	No
Clinical features	Children with failure to thrive; hyponatremia, hyperkalemia, acidosis, and hypotension			
Elevated metabolites	17-Hydroxyprogesterone	Dehydroepiandrosterone		Corticosterone
Therapy	Oral hydrocortisone and 9α-fludrocortisone			9α-Fludrocortisone

Table 49-5 Characteristics of diseases with aldosterone biosynthetic defects. *ACTH,* Adrenocorticotropic hormone.

A CONDITION WITH HYPERKALEMIA, METABOLIC ACIDOSIS, AND HYPERTENSION

Pseudohypoaldosteronism Type 2 (Gordon Syndrome)

The clinical inverse of Gitelman syndrome, Gordon syndrome is an autosomal dominant condition characterized by hypertension, hyperkalemia, and mild hyperchloremic metabolic acidosis.

Pathogenesis

Two genes have been identified as responsible for PHA type 2.[28] The genes encode two members of the with-no-lysine kinase family: WNK1 and WNK4. The WNK kinases are both expressed in the kidney within the convoluted tubule and the collecting ducts. WNK4 acts as a negative regulator of thiazide-sensitive NCCT function (see Fig. 49-2), reducing cell surface expression of NCCT. WNK4 also downregulates ROMK and epithelial chloride flux. Mutations in *WNK4* are missense and cause loss of function, so that WNK4 loses its ability to suppress NCCT and ROMK. Transporter overactivity consequently leads to Na^+ and K^+ retention. WNK1 prevents WNK4 from interacting with NCCT. Mutations in *WNK1* are intronic deletions that increase WNK1 expression. WNKs are intriguing targets for novel antihypertensive agents.

Clinical Manifestations and Diagnosis

Hyperkalemia may be present from birth, but as in GRA, hypertension may not be manifested until later in life. Patients show hyperchloremic metabolic acidosis; plasma renin and aldosterone are reduced to variable degrees.

Treatment

As specific inhibitors of the NCCT, thiazides are able to correct completely the clinical and biochemical features of Gordon syndrome.

NEPHROGENIC DIABETES INSIPIDUS

Congenital nephrogenic diabetes insipidus (NDI) is a rare polyuric disorder identified by the failure to concentrate urine despite normal or elevated levels of vasopressin. Glomerular filtration rate (GFR) and solute excretion rate are normal. Congenital NDI is caused by mutations in key proteins controlling water reabsorption in the distal tubule (see Fig. 49-5). Acquired diabetes insipidus is much more common, and its diagnosis and management are discussed in Chapter 8.

Pathogenesis

More than 90% of patients have X-linked recessive NDI with mutations in *AVPR2,* the gene at Xq28 coding for the arginine vasopressin receptor (AVPR). Mutant proteins are conformationally different, resulting in intracellular trapping of the receptor, which is retained in the endoplasmic reticulum. On occasion, the receptor may be expressed on the cell surface but is unable to bind vasopressin or to trigger an appropriate cyclic adenosine monophosphate (cAMP) response.[29] In less than 10% of the families, congenital NDI has an autosomal recessive inheritance, and mutations have been identified in the gene for aquaporin 2 located on chromosome 12q13. Similar to X-linked NDI, most autosomal recessive *AQP2* mutations are held back in the endoplasmic reticulum. A rare autosomal dominant form of NDI, also caused by mutation in *AQP2,* has been reported. These mutations lead to mistransporting of AQP2 mutant proteins to the basolateral membrane instead of the apical membrane.[30] Reduced expression of AQP2 may result in acquired NDI secondary to lithium or demeclocycline therapy.

Clinical Features

Manifestations of congenital NDI appear within the first weeks of life. Males with *AVPR2* mutations have marked polyuria and excessive thirst, which is often not recognized in early infancy. Unless the condition is suspected early, children have recurrent episodes of severe hypernatremic dehydration, occasionally complicated by convulsions.[31] Delayed development and mental retardation are possible consequences of these episodes. Cranial computed tomography may occasionally show dystrophic calcification in the basal ganglia and the cerebral cortex.

A reduced intake of calories because of the large quantities of water that are ingested leads to growth failure beginning in early childhood. Increased urine volumes may result in dilation of the lower urinary tract. Renal cortical damage from recurrent episodes of severe dehydration may result in impairment of renal function. Heterozygous females may show variable degrees of polyuria and

polydipsia. The onset and severity of clinical features of autosomal recessive NDI are similar to those of the X-linked form.

Diagnosis

Episodes of dehydration are marked by hypernatremia, hyperchloremia, and occasionally elevated levels of urea and creatinine. Polyuria with low urine osmolality (<200 mOsm/kg) and hypernatremia with plasma Na^+ concentration above 150 mmol/l and plasma osmolality above 300 mOsm/kg are highly suggestive of either vasopressin deficiency (central diabetes insipidus) or resistance to its action (NDI). Central diabetes insipidus is more common than NDI. Primary polydipsia resembles true diabetes insipidus in that compulsive water drinking results in polyuria with low urine osmolality; however, the plasma osmolality in primary polydipsia is normal or borderline low.

To confirm the lack of renal concentrating ability and to distinguish NDI from central diabetes insipidus and primary polydipsia, a vasopressin test is performed. Desamino-8-D-arginine vasopressin (DDAVP) is administered nasally (5 to 10 μg in neonates and infants, 20 μg in children) or by an intramuscular injection (0.4 to 1.0 μg in infants and young children, 2 μg in older children). Hourly urine collection is done during the next 6 hours. After administration of DDAVP, patients with NDI fail to show a rise of urine osmolality, from 200 to 300 mOsm/kg (normal, >800 mOsm/kg). Those with central diabetes insipidus and primary polydipsia concentrate urine appropriately.

Persistence of polyuria for years may result in a washout of the medullary countercurrent concentration mechanism. Several days of treatment with DDAVP may be required to elicit an appropriate response in these patients. In patients in whom primary polydipsia is strongly suspected, supervised reduction of fluid intake during several days may restore normal sensitivity to DDAVP.

Differential Diagnosis

Patients with central diabetes insipidus show hypernatremia with inappropriately dilute urine, no primary renal disease, and a rise in urine osmolality after administration of vasopressin or its analogues. Central diabetes insipidus usually results from posterior pituitary neuronal damage, which may be secondary to tumors (craniopharyngioma, optic glioma, metastasis), Langerhans cell histiocytosis, trauma (e.g., fracture of base of skull), or infections (meningitis, encephalitis). Deficiency of vasopressin may also be familial, with an autosomal dominant inheritance. Mutations of *AVP-NPII,* the gene for vasopressin–neurophysin II, have been reported.[32] The onset of vasopressin deficiency in the familial form may not be apparent until after the first few years of life. Central diabetes insipidus may also occur with the autosomal recessive syndrome of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (DIDMOAD, or Wolfram syndrome), which is autosomal recessive.

Many patients with central diabetes insipidus or NDI have a partial defect in vasopressin secretion or action. They are therefore able to concentrate urine to varying degrees after DDAVP administration, making precise diagnosis difficult. Measurement of plasma vasopressin in relation to plasma osmolality after an osmotic stimulus, such as fluid restriction, allows differentiation in these patients. Patients with severe or partial central diabetes insipidus always show subnormal vasopressin levels relative to plasma osmolality. In contrast, the values from patients with NDI or psychogenic polydipsia are always within or above the normal range.

Magnetic resonance imaging of the brain produces a bright spot on T1-weighted images of the posterior pituitary in normal individuals and also those with NDI or primary polydipsia. This signal is absent in most patients with central diabetes insipidus.

The differential response of clotting factors and urine osmolality to DDAVP is useful in differentiating X-linked (*AVPR2* abnormalities) from autosomal recessive (*AQP2* mutations) NDI. Patients with *AQP2* abnormalities show normal increases in factor VIII and von Willebrand factor after DDAVP infusion; this response is absent in those with an *AVPR2* defect.[31,33] Sequencing of *AVPR2* and *AQP2* is useful in identification of the molecular defect underlying NDI. Congenital NDI should also be differentiated from acquired forms of NDI (see Chapter 8).

Treatment

Appropriate management of patients with NDI prevents episodes of dehydration, allowing normal physical growth and development. Patients must have adequate water intake to prevent dehydration. The renal solute load is minimized by restriction of dietary protein and salt intake. Adequate energy and nutrients, depending on the age, should be provided to promote normal growth and development.

Thiazide diuretics, such as hydrochlorothiazide (1 to 2 mg/kg every 12 hours), when combined with reduction of salt intake, are effective in reducing urine output. Thiazides inhibit salt reabsorption in distal convoluted tubules, which leads to mild volume depletion. Hypovolemia stimulates fluid reabsorption in the proximal tubules, thereby diminishing water delivery to the collecting ducts. The antipolyuric effect can be enhanced by combination therapy with amiloride (0.1 to 0.2 mg/kg every 8 to 12 hours).

Because prostaglandins normally antagonize the action of vasopressin, prostaglandin synthase inhibitors are also effective in reducing urine volume and free water clearance. Not all nonsteroidal anti-inflammatory drugs are equally potent in inhibiting renal prostaglandin synthesis. Indomethacin (1 mg/kg every 12 hours) is used most often but may reduce GFR and cause gastrointestinal side effects.

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CHAPTER 50

Fanconi Syndrome and Other Proximal Tubule Disorders

John W. Foreman

The proximal tubule is responsible for the reabsorption of the bulk of a number of solutes, including glucose, amino acids, bicarbonate, and phosphate. This chapter describes a number of disorders, mainly heritable, that affect proximal tubule reabsorption, although Chapters 10 and 12 discuss discuss familial forms of hyperphosphaturia and renal tubular acidosis, respectively.

Most nonelectrolyte solutes are reabsorbed in the proximal tubule through specific transport proteins that cotransport them in conjunction with sodium (Fig. 50-1). The driving force for this solute transport is the electrochemical gradient for sodium entry maintained by the enzyme Na^+,K^+-ATPase. Most disorders of isolated solute reabsorption are related to defects in specific transport proteins, whereas disorders affecting multiple solutes, such as Fanconi syndrome, are probably secondary to defects in energy generation, Na^+,K^+-ATPase activity, or dysfunction of cellular organelles involved with membrane protein recycling.

FANCONI SYNDROME

Definition

In the 1930s, de Toni, Debré, and coworkers and Fanconi independently described several children with the combination of renal rickets, glycosuria, and hypophosphatemia. Fanconi syndrome now refers to a global dysfunction of the proximal tubule leading to excessive urinary excretion of amino acids, glucose, phosphate, bicarbonate, uric acid, and other solutes handled by this nephron segment. These losses lead to the clinical problems of acidosis, dehydration, electrolyte imbalance, rickets, osteomalacia, and growth failure. Numerous inherited or acquired disorders are associated with Fanconi syndrome (Box 50-1).

Etiology and Pathogenesis

The sequence of events leading to Fanconi syndrome is incompletely defined and probably varies with each cause. Possible mechanisms include widespread abnormality of most or all of the proximal tubule carriers, such as a defect in sodium binding to the carrier or insertion of the carrier into the brush border membrane, "leaky" brush border membrane or tight junctions, inhibited or abnormal Na^+,K^+-ATPase pump, or impaired mitochondrial energy generation (Fig. 50-1). An abnormality in energy generation has been implicated in a number of disorders, including hereditary fructose intolerance, galactosemia, mitochondrial cytopathies, and heavy metal poisoning, as well as in a number of experimental models of Fanconi syndrome. Abnormal subcellular organelle function, such as the lysosome in cystinosis or the megalin-cubilin endocytic pathway in Dent disease, is also a cause of Fanconi syndrome (Fig. 50-2).

In adults, the most common causes of persistent Fanconi syndrome are an endogenous or exogenous toxin such as a heavy metal, a medication, and a dysproteinemia. In children, the most common persistent cause is an inborn error of metabolism, such as cystinosis. Specific causes of Fanconi syndrome are discussed after a general description of the clinical manifestations and treatment of the syndrome.

Clinical Manifestations

Fanconi syndrome gives rise to a number of clinical abnormalities (Box 50-2).

Aminoaciduria

Aminoaciduria is a cardinal feature of Fanconi syndrome. Virtually every amino acid is found in excess in the urine, thus the term *generalized aminoaciduria.* There are no clinical consequences, however, because the losses are trivial, 0.5 to 1 g/day, in relation to the dietary intake.

Glycosuria

Glycosuria secondary to proximal tubule dysfunction is another of the cardinal features of Fanconi syndrome and results from impaired tubular reabsorption of glucose. It is often one of the first diagnostic clues. As with aminoaciduria, glycosuria rarely causes symptoms, such as weight loss or hypoglycemia.

Hypophosphatemia

Hypophosphatemia, secondary to impairment in phosphate reabsorption, is a common finding in Fanconi syndrome. Assessment of tubular phosphate handling can be made by measuring the maximum phosphate reabsorption in relation to the glomerular filtration rate (TmP/GFR) on fasting urine and blood samples. Elevated parathyroid hormone (PTH) and low vitamin D levels also may play a role in the phosphaturia of Fanconi syndrome, although these hormonal abnormalities are not always present. A few patients have impaired conversion of 25-hydroxyvitamin D to 1,25-hydroxyvitamin D; metabolic acidosis, another feature of Fanconi syndrome, may also impair this conversion. Another mechanism for the hypophosphatemia is impairment of the megalin-dependent reabsorption and degradation of filtered PTH.[1] Unabsorbed PTH then binds to receptors in more distal portions of the proximal tubule, leading to increased endocytosis of apical phosphate transporters and increased phosphaturia. The hypophosphatemia, especially if accompanied by hyperparathyroidism and low 1,25-hydroxyvitamin D levels, often leads to significant bone disease, presenting with pain, fractures, rickets, or growth failure.

Hyperchloremic Metabolic Acidosis

Hyperchloremic metabolic acidosis, another feature of Fanconi syndrome, is a result of impaired bicarbonate reabsorption by the proximal tubule (proximal or type 2 renal tubular acidosis; see

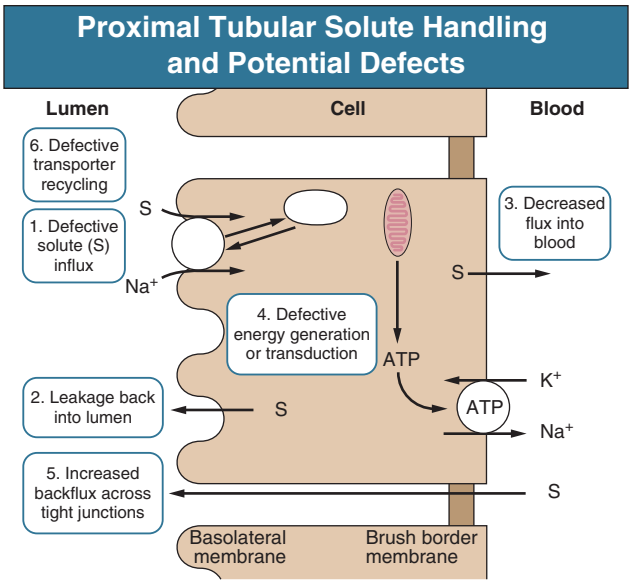

Figure 50-1 Defects and potential defects in proximal tubular solute handling. Solute uptake by the brush border membrane from the lumen is coupled to Na^+ influx. The favorable electrochemical driving force for luminal Na^+ is maintained by the Na^+,K^+-ATPase pump. Transported solute is then either used by the cell or returned to the blood across the basolateral membrane. Fanconi syndrome could arise because of a defect in one of six areas as shown. *ATP,* Adenosine triphosphate.

Causes of Fanconi Syndrome

Inherited Causes

Cystinosis
Galactosemia
Hereditary fructose intolerance
Tyrosinemia
Wilson disease
Lowe syndrome
Dent disease
Glycogenosis
Mitochondrial cytopathies
Idiopathic

Acquired Causes*

Drugs: *cisplatin, ifosfamide, tenofovir, cidofovir, adefovir,* didanosine, gentamicin, azathioprine, valproic acid (sodium valproate), suramin, streptozocin (streptozotocin), ranitidine
Dysproteinemias: *multiple myeloma, Sjögren syndrome, light-chain proteinuria, amyloidosis*
Heavy metal poisoning: lead, cadmium
Other poisonings: Chinese herbal medicine, glue sniffing
Other: nephrotic syndrome, renal transplantation, acute tubular necrosis

Box 50-1 Causes of Fanconi syndrome. *More common acquired causes are shown in italics.

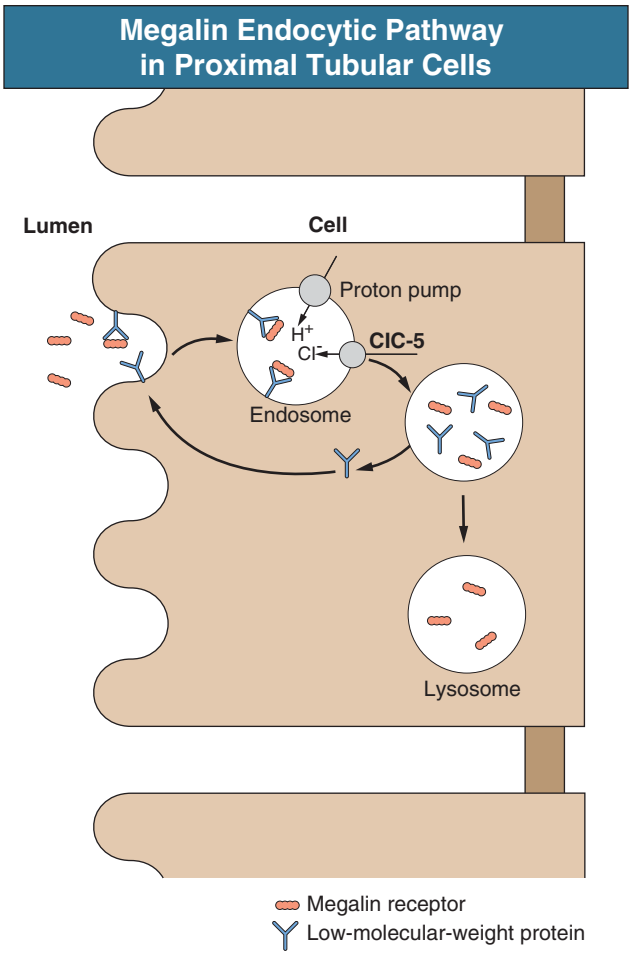

Figure 50-2 Megalin-cubilin endocytic pathway in proximal tubular cells. Low-molecular-weight proteins in the luminal fluid bind to the megalin-cubilin complex and are endocytosed. The recycling of megalin and further catabolism of these proteins depend on acidification of the vesicle by a proton pump. The ClC-5 chloride channel provides an electrical shunt for efficient functioning of the proton pump. This endocytosis pathway plays a role in membrane transporter recycling, and disruption of this pathway interferes with absorption of other luminal solutes.

Features of Fanconi Syndrome

Metabolic Abnormalities

Glycosuria
Hyperaminoaciduria
Hypophosphatemia
Acidosis
Hypokalemia
Hypouricemia
Hypocarnitinemia

Clinical Features

Rickets, osteomalacia
Growth retardation
Polyuria
Dehydration
Proteinuria

Box 50-2 Features of Fanconi syndrome.

Chapter 12). This impaired reabsorption can lead to the loss of more than 30% of the normal filtered load of bicarbonate. As the serum bicarbonate concentration ($[HCO_3^-]$) falls, the filtered load falls, and excretion drops such that the serum $[HCO_3^-]$ usually remains between 12 and 18 mmol/l. On occasion, there is an associated defect in distal acidification, usually in association with longstanding hypokalemia or nephrocalcinosis. Ammoniagenesis is usually normal or increased because of the hypokalemia and acidosis, unless there is an associated impairment in GFR.

Natriuresis and Kaliuresis

Natriuresis and kaliuresis are common in Fanconi syndrome and can give rise to significant, even life-threatening problems. These electrolyte losses are in part related to impaired bicarbonate reabsorption, with the subsequent urinary excretion of sodium and potassium ions with the bicarbonate. In some cases, sodium and potassium losses are so great that metabolic alkalosis and hyperaldosteronism result, simulating Bartter syndrome despite the lowered bicarbonate threshold. The clearance of potassium may be twice that of the GFR, and the resulting severe hypokalemia can cause sudden death.

Polyuria and Polydipsia

Polyuria, polydipsia, and frequent bouts of severe dehydration are common symptoms in young patients with Fanconi syndrome. The polyuria is mainly related to the osmotic diuresis from the excessive urinary solute losses; but some patients have an associated concentrating defect, especially those with prolonged hypokalemia.

Growth Retardation

Growth retardation in children with Fanconi syndrome is multifactorial. Hypophosphatemia, disordered vitamin D metabolism, and acidosis contribute to growth failure, as do chronic hypokalemia and extracellular volume contraction. Glycosuria and aminoaciduria probably do not play a role. However, even with correction of all these metabolic abnormalities, most patients fail to grow, especially those with cystinosis.

Hypouricemia

Hypouricemia, caused by impairment in renal handling of uric acid, is often present in Fanconi syndrome, especially in adults. Urolithiasis from the uricosuria has only rarely been reported, probably because the urine flow and pH are increased, inhibiting uric acid crystallization.

Proteinuria

Proteinuria is usually minimal, except when Fanconi syndrome develops in association with the nephrotic syndrome. Typically, only low-molecular-weight proteins (<30,000 daltons) are excreted, such as vitamin D and A–binding proteins, enzymes, immunoglobulin light chains, and hormones.

Treatment of Fanconi Syndrome

Therapy, whenever possible, should be directed at the underlying causes of Fanconi syndrome (see later discussion). This includes avoidance of the offending nutrient in galactosemia, hereditary fructose intolerance, or tyrosinemia; treatment of Wilson disease with penicillamine and other copper chelators; or treatment of heavy metal intoxication by chelation therapy. In these patients, resolution of Fanconi syndrome usually is complete.

In other patients with Fanconi syndrome, therapy is directed at the biochemical abnormalities secondary to the renal solute losses and at the bone disease often present in these patients. The proximal renal tubular acidosis (type 2 RTA) usually requires large doses of alkali for correction. Some patients benefit from hydrochlorothiazide to minimize the volume expansion associated with these large doses of alkali. Potassium supplementation usually is also needed, especially if there is a significant RTA. The use of potassium citrate, lactate, or acetate will correct not only the hypokalemia but also the acidosis. A few patients will require sodium supplementation along with potassium. Again, the use of a metabolizable anion will aid in the correction of the acidosis. Rarely, patients may need sodium chloride supplementation. Usually, these patients have alkalosis when untreated as a result of large urinary NaCl losses, which lead to volume contraction that overrides the RTA. Magnesium supplementation may be required. Adequate fluid intake is essential. Correction of hypokalemia and its effect on the concentrating ability of the distal tubule may lessen the polyuria.

Bone disease is multifactorial, including hypophosphatemia, urinary loss of vitamin D–binding protein and vitamin D, decreased synthesis of calcitriol in some patients, hypercalciuria, and chronic acidosis. Hypophosphatemia should be treated with 1 to 3 g/day of oral phosphate with the goal of normalizing serum phosphate levels. Many patients with Fanconi syndrome will require supplemental vitamin D for adequate treatment of the rickets and osteomalacia. It is unclear whether standard vitamin D (calciferol [ergocalciferol]) or a vitamin D metabolite is better for supplementation. Currently, most clinicians use a vitamin D metabolite, such as 1,25-dihydroxycholecalciferol (calcitriol). These metabolites obviate the concern of inadequate vitamin D hydroxylation by the proximal tubule mitochondria and reduce the risk for prolonged hypercalcemia because of their shorter half-life. Vitamin D therapy will also improve the hypophosphatemia and lessen the risk for hyperparathyroidism. Supplemental calcium is indicated in those with hypocalcemia after supplemental vitamin D is started. Hyperaminoaciduria, glycosuria, proteinuria, and hyperuricosuria usually do not lead to clinical difficulties and do not require specific treatment. Carnitine supplementation, to compensate for the urinary losses, may improve muscle function and lipid profiles, but the evidence is inconsistent.

INHERITED CAUSES OF FANCONI SYNDROME

Cystinosis

Definition

Cystinosis, or cystine storage disease, is characterized biochemically by excessive intracellular storage, particularly in lysosomes, of the amino acid cystine.[2] Three different types of cystinosis can be distinguished based on clinical course and age at onset and the intracellular cystine content. Benign or adult cystinosis is associated with cystine crystals in the cornea and bone marrow only, as well as the mildest elevation in intracellular cystine levels; no renal disease occurs. Infantile or nephropathic cystinosis is the most common form of cystinosis and is associated with the highest intracellular levels of cystine and the earliest onset of renal disease. In the intermediate or adolescent form, intracellular cystine levels are between those of the infantile and adult forms, with later onset of renal disease.

Etiology and Pathogenesis

Nephropathic cystinosis is transmitted as an autosomal recessive trait localized to the short arm of chromosome 17, with an estimated incidence of 1 in 200,000 live births. The *CTNS* gene codes for a lysosomal membrane protein, cystinosin, that mediates the transport of cystine from the lysosome.[3] The benign and intermediate forms

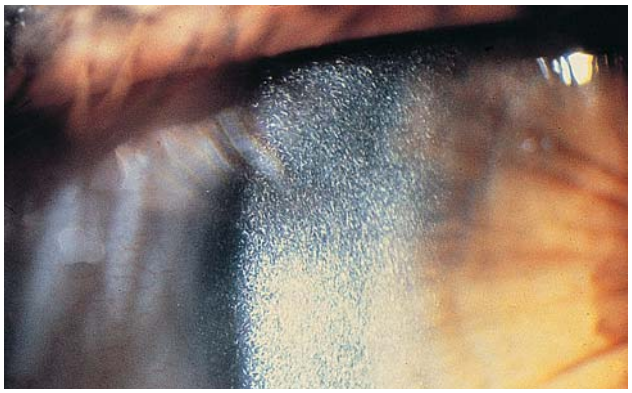

Figure 50-3 Corneal opacities in cystinosis. Tinsel-like refractile opacities in the cornea of a patient with cystinosis under slit-lamp examination. *(From reference 4.)*

of cystinosis are also associated with *CTNS* mutations but still have some functional transport protein, leading to lower intracellular cystine levels and slower onset of renal disease in the intermediate form and no renal disease in the benign form.

Clinical Manifestations

The first clinical symptoms and signs in nephropathic cystinosis are those of Fanconi syndrome and usually appear in the second half of the first year of life. Subtle abnormalities of tubular function can be demonstrated earlier in families with index cases, but there always is a delay between birth and the first symptoms. Rickets is common after the first year of life, along with growth failure. The growth failure occurs before the GFR declines and despite correction of electrolyte and mineral deficiencies. The GFR invariably declines and end-stage renal disease (ESRD) occurs by late childhood.

Nephrocalcinosis is relatively common, and a few patients have developed renal calculi. Photophobia is another common symptom that occurs by 3 years of age and is progressive. Older patients with cystinosis may develop visual impairment and blindness. Children with cystinosis usually have fair complexions and blond hair, but dark hair has been observed in some. Cystinosis has been observed in other ethnic groups but is less common than in Caucasians.

The diagnosis is based on the demonstration of elevated intracellular levels of cystine, usually in white blood cells or skin fibroblasts. Patients with nephropathic and intermediate cystinosis have intracellular cystine levels that exceed 2 nmol half-cystine per mg protein (normal <0.2 nmol half-cystine per mg protein). Heterozygotes for cystinosis will have levels that range from 0.2 to 1 nmol half-cystine/mg protein. A slit-lamp demonstration of corneal crystals strongly suggests the diagnosis[2] (Fig. 50-3). A prenatal diagnosis can be made with amniocytes or chorionic villi.

Common late complications of cystinosis include hypothyroidism, splenomegaly and hepatomegaly, decreased visual acuity, swallowing difficulties, pulmonary insufficiency, and corneal ulcerations.[5] Less frequently, older patients have developed insulin-dependent diabetes mellitus, myopathy, and progressive neurologic disorders. Decreased brain cortex has also been noted on imaging in some patients. Older patients may develop vascular calcification, especially of the coronary arteries, which can lead to myocardial ischemia.

Pathology

The morphologic features of the kidney in cystinosis vary with the stage. Early in the disease, cystine crystals are present in tubular epithelial cells, interstitial cells, and rarely glomerular epithelial cells[6,7] (Fig. 50-4, *A*). A swan-neck deformity or thinning of the first part of the proximal tubule is an early finding but is not unique to cystinosis. Later, there is pronounced tubular atrophy, interstitial fibrosis, and abundant crystal deposition with giant cell formation of the glomerular visceral epithelium, segmental sclerosis, and eventual glomerular obsolescence. Electron microscopy (EM) studies have demonstrated intracellular crystalline inclusions consistent with cystine (Fig. 50-4, *B*). Peculiar "dark cells," unique to the cystinotic kidney, have also been observed.

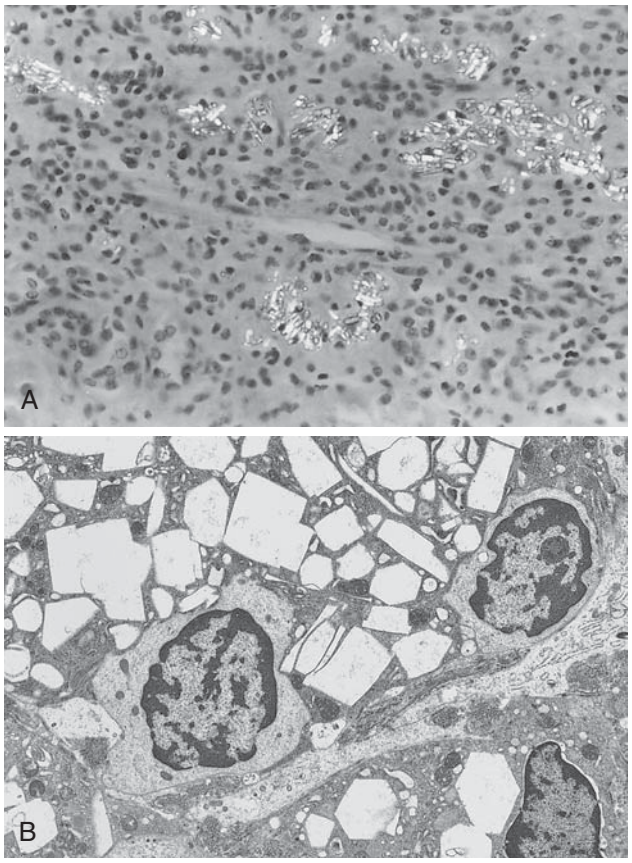

Figure 50-4 Cystine crystals in the kidney in cystinosis. A, Crystals are seen in photomicrograph of alcohol-fixed nephrectomy specimen, taken through incompletely crossed polarizing filters. Birefringent crystals are evident in tubular epithelial cells and free in the interstitium. **B,** Electron micrograph of a renal biopsy specimen shows hexagonal, rectangular, and needle-shaped crystals in macrophages within the interstitium. (Original magnification ×3000.) *(**A** from reference 6; **B** from reference 7.)*

Treatment

Nonspecific therapy for infantile cystinosis consists of vitamin D therapy and replacement of the urinary electrolyte losses, followed, in due course, by the management of the progressive renal failure (Table 50-1). Cysteamine therapy has now been shown to lower tissue cystine levels and slow the decline in GFR, especially in children with a normal serum creatinine concentration treated before 2 years of age[8] (Fig. 50-5). Cysteamine therapy also improves linear growth but not Fanconi syndrome. The most common problems associated with cysteamine therapy are nausea, vomiting, and a foul odor and taste. Treatment should begin with a low dose of cysteamine soon after the diagnosis is made, increased during 4 to 6 weeks to 60 to 90 mg/kg/day in four divided doses as close to every 6 hours as possible. Slowly increasing the dose minimizes the risk for neutropenia, rash, and arthritis. Leukocyte cystine levels should be checked every 3 to 4 months to monitor effectiveness and compliance, with the goal of achieving and maintaining a cystine level of

below 2.0 and preferably below 1.0 nmol half-cystine/mg protein. A long-acting formulation of cysteamine should be available soon that will allow twice-daily dosing. A 50-mM solution of cysteamine applied topically onto the eye has proved useful in depleting the cornea of cystine crystals, but it requires administration 6 to 12 times a day to be effective.

Treatment of ESRD in these children poses no greater problems than in other children. Successful renal transplantation reverses the renal failure and Fanconi syndrome but does not appear to improve the extrarenal manifestations of cystinosis. Cysteamine therapy should be continued after transplantation. Cystine does not accumulate in the transplanted kidney, except in infiltrating immunocytes.

Galactosemia

Etiology and Pathogenesis

Galactosemia is an autosomal recessively inherited disorder of galactose metabolism. It is most often the result of deficient activity of the enzyme galactose 1-phosphate uridyltransferase, the incidence of which is 1 in 62,000 live births.[9] Deficiency of this enzyme leads to the intracellular accumulation of galactose 1-phosphate, with damage to the liver, proximal renal tubule, ovary, brain, and lens. A less frequent cause of galactosemia is a deficiency of galactose kinase, which forms galactose 1-phosphate from galactose. Cataracts are the only manifestation of this form of galactosemia.

The pathogenesis of the symptoms of galactosemia is not clear. Accumulation of galactose 1-phosphate subsequent to the ingestion of galactose can inhibit a number of pathways for carbohydrate metabolism, and its level correlates somewhat with clinical symptoms. Defective galactosylation of proteins has also been postulated. Proposed as a pathogenetic mechanism, formation of galactitol from galactose by aldose reductase is probably responsible for the cataract formation.

Clinical Manifestations

Affected infants ingesting milk containing lactose, the most common source of galactose in the diet, rapidly develop vomiting, diarrhea, and failure to thrive. Jaundice from unconjugated hyperbilirubinemia is common, along with severe hemolysis. Continued intake of galactose leads to hepatomegaly and cirrhosis. Cataracts appear within days after birth, although at first they often are detectable only with a slit lamp. Mental retardation may develop within a few months. Fulminant *Escherichia coli* sepsis has been described in a number of infants, possibly a consequence of inhibited leukocyte bactericidal activity.

In addition to these clinical findings, galactose intake leads within days to hyperaminoaciduria and albuminuria. Increased urine sugar excretion is principally a result of galactosuria and not glycosuria. There seems to be little or no impairment in glucose handling by the renal tubule. Galactosemia should be suspected whenever there is a urinary reducing substance that does not react in a glucose oxidase test. The diagnosis can be confirmed by demonstration of deficient transferase activity in red blood cells, fibroblasts, leukocytes, or hepatocytes. Most infants with galactosemia are found through newborn metabolic screening.

Treatment

Galactosemia is treated by elimination of galactose from the diet. Acute symptoms and signs resolve in a few days. Cataracts will also regress to some extent. Even with early elimination of galactose, however, a common outcome in galactosemia is developmental delay, speech impairment, ovarian dysfunction, and growth retardation. Profound intellectual deficits are rare even in infants treated late.

Hereditary Fructose Intolerance

Etiology and Pathogenesis

Hereditary fructose intolerance is another disorder of carbohydrate metabolism associated with Fanconi syndrome.[10] Fructose intolerance is inherited as an autosomal recessive trait, with an estimated incidence of 1 in 20,000 live births. It is caused by a deficiency of the

Treatment of Cystinosis

Problem	Therapy
Removal of lysosomal cystine	Cysteamine, 0.235 g/m^2 q6h to maintain leukocyte cystine level <1 nmol half-cystine*/mg protein
Correction of Tubulopathy	
Dehydration	2-6 l/d fluid
Acidosis	2-15 mmol/kg/d K^+ citrate
Hypophosphatemia	1-4 g/d K^+ phosphate
Rickets	0.25-1 µg/d calcitriol
Adjunct therapies	NaCl, carnitine, indomethacin, hydrochlorothiazide
Later Therapies	
Growth failure	Growth hormone
Hypothyroidism	Thyroxine
Renal failure	Renal replacement therapy, ideally renal transplantation

Table 50-1 Treatment of cystinosis. *By convention, units are half-cystine because the cystine originally was converted to two cysteine molecules, or "broken in half," before measurement.

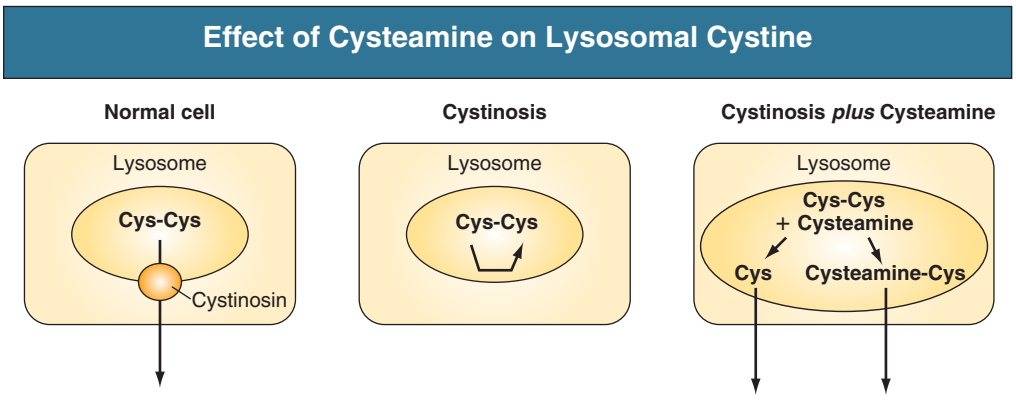

Figure 50-5 Effect of cysteamine on lysosomal cystine. In cystinosis, the transporter (cystinosin) for cystine *(Cys-Cys)* egress from the lysosome is defective. Cysteamine can easily enter the lysosome and combine with cystine, forming cysteine *(Cys)* and the mixed disulfide cysteamine-cysteine. Both these compounds can exit the lysosome through a transporter other than the cystine carrier.

B isoform of the enzyme fructose 1-phosphate aldolase, which cleaves fructose 1-phosphate into D-glyceraldehyde and dihydroxyacetone phosphate. Deficient activity of aldolase B leads to tissue accumulation of fructose 1-phosphate and reduced levels of adenosine triphosphate (ATP).

Clinical Manifestations

Symptoms of hereditary fructose intolerance appear at weaning when fruit, vegetables, and sweetened cereals that contain fructose or sucrose are introduced. Children with this disorder experience nausea, vomiting, and symptoms of hypoglycemia shortly after ingestion of fructose, sucrose, or sorbitol. These symptoms may progress to convulsions, coma, and even death, depending on the amount consumed. When they are exposed to fructose, infants may have a catastrophic illness, with severe dehydration, shock, acute liver impairment, bleeding, and acute kidney injury (AKI). Concomitant serum biochemical findings after fructose ingestion are decreased glucose, phosphate, and bicarbonate and increased uric acid and lactic acid. Chronic exposure to fructose leads to failure to thrive, hepatomegaly and fatty liver, jaundice, hepatic cirrhosis, and nephrocalcinosis. Children with hereditary fructose intolerance learn to avoid sweets.

Diagnosis

The diagnosis should be suspected when symptoms develop after the ingestion of fructose. This can be confirmed by assaying the activity of fructose 1-phosphate aldolase in a liver biopsy specimen and increasingly by genetic testing using leukocytes.

Treatment

Treatment of hereditary fructose intolerance involves strict avoidance of foods containing fructose and sucrose, but because most patients develop a strong aversion to such foods, this is usually easy. The greatest risk occurs during infancy, before those affected learn to avoid fructose.

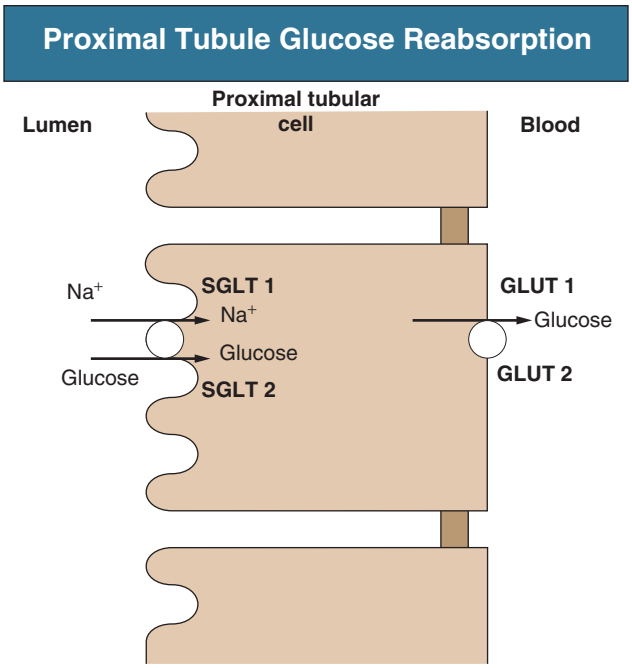

Figure 50-6 Proximal tubule glucose reabsorption. Glucose enters the proximal tubule cell coupled to Na^+ reabsorption from the lumen through a high-capacity, low-affinity transporter (SGLT2) in the early proximal tubule and a low-capacity, high-affinity transporter (SGLT1) in the late proximal tubule. Glucose exits the cell through the transporters GLUT1 and GLUT2 located in the late and early proximal tubule, respectively.

Glycogenosis

Most patients with glycogen storage disease and Fanconi syndrome have an autosomal recessive disorder characterized by heavy glycosuria and increased glycogen storage in the liver and kidney, known as the Fanconi-Bickel syndrome, or *glucose-losing syndrome,* because the glucose losses can be massive.[11] The defect is deficient activity of the sugar transporter GLUT2 (Fig. 50-6). GLUT2 facilitates sugar exit from the basolateral side of the proximal tubule and intestinal cell and sugar entry and exit from the hepatocyte and pancreatic β cell. A few patients with type I glycogen storage disease have mild Fanconi syndrome but not Fanconi-Bickel syndrome. The therapy for this disorder is directed at the renal solute losses, treatment of rickets (which can be severe), and frequent feeding to prevent ketosis. Uncooked cornstarch has been shown to lessen the hypoglycemia and to improve growth.

Tyrosinemia

Definition

Hereditary tyrosinemia type I, also known as *hepatorenal tyrosinemia,* is a defect of tyrosine metabolism affecting the liver, kidneys, and peripheral nerves.[12]

Etiology and Pathogenesis

The cause of hereditary tyrosinemia type I is a deficiency of fumarylacetoacetate hydrolase (FAH) activity; it is an autosomal recessive disorder. Decreased or absent FAH activity leads to accumulation of maleylacetoacetate (MAA) and fumarylacetoacetate (FAA) in affected tissues. These compounds can react with free sulfydryl groups, reduce intracellular levels of glutathione, and act as alkylating agents. MAA and FAA are not detectable in plasma or urine but are converted to succinylacetoacetate and succinylacetone. Succinylacetone is structurally similar to maleic acid, a compound that causes Fanconi syndrome experimentally in rats and may be the cause of Fanconi syndrome in humans affected with tyrosinemia.

Clinical Manifestations

The liver is the major organ affected, evident as early as the first month of life. Such infants usually have severe disease and die in the first year. All children with tyrosinemia will eventually develop macronodular cirrhosis, and many develop hepatocellular carcinoma. Acute, painful peripheral neuropathy and autonomic dysfunction can also occur. Proximal renal tubular dysfunction is evident in all patients with tyrosinemia, especially those presenting after infancy. Nephromegaly is very common, and nephrocalcinosis may be seen. Glomerulosclerosis and impaired GFR may be seen with time.

Diagnosis

The diagnosis should be suspected with elevated plasma tyrosine and methionine levels together with their *p*-hydroxy metabolites. The presence of succinylacetone in blood or urine is diagnostic of hereditary tyrosinemia type I.

Treatment

The institution of a diet low in phenylalanine and tyrosine dramatically improves the renal tubular dysfunction. Nitisinone, which inhibits the formation of MAA and FAA, dramatically improves the renal and hepatic dysfunction.[12] Liver transplantation has been successfully used to treat patients with severe liver failure and to prevent

the development of hepatocellular carcinoma. Liver transplantation leads to rapid correction of Fanconi syndrome.

Wilson Disease

Definition

Wilson disease is an inherited disorder of copper metabolism that affects numerous organ systems.[13,14] It has an overall incidence of 1 in 30,000 live births. About 40% of patients present with liver disease, 40% with extrapyramidal symptoms, and 20% with psychiatric or behavioral abnormalities.

Etiology and Pathogenesis

Wilson disease is caused by a defect in the P-type copper–transporting adenosine triphosphatase ATP7B, which is highly expressed in the liver, kidney, and placenta. It impairs biliary copper excretion and the incorporation of copper into ceruloplasmin. These abnormalities cause excessive intracellular accumulation of copper in the liver, with subsequent overflow into other tissues, such as brain, cornea, and renal proximal tubule.

Clinical Manifestations

Excessive storage of copper in the kidney leads to renal tubular dysfunction in most patients and full-blown Fanconi syndrome in some. Hematuria also has been noted. Renal plasma flow and GFR decrease as the disease progresses, but death from extrarenal causes occurs before the onset of renal failure. Fanconi syndrome usually appears before the onset of hepatic failure. Hypercalciuria with development of renal stones and nephrocalcinosis also have been reported. Besides proximal tubular dysfunction, abnormalities in distal tubular function, decreased concentrating ability, and distal renal tubular acidosis (type 1 RTA) have also been observed. Neurologic abnormalities, such as dysarthria and gait disturbances, may be the presenting symptom in young adults with Wilson disease. Kayser-Fleischer rings, dense brown copper deposits around the iris, may be visible but typically can be seen only with a slit lamp.

Pathology

Histologic examination of the kidney in untreated Wilson disease shows either no alteration on light microscopy or only some flattened proximal tubular cells without recognizable brush borders. EM shows loss of the brush border, disruption of the apical tubular network, electron-dense bodies probably representing metalloproteins in the subapical region of tubule cell cytoplasm, and cavitation of the mitochondria with disruption of the normal cristae pattern. Rubeanic acid staining shows intracytoplasmic copper granules. The copper content of kidney tissue is greatly elevated.

Diagnosis

The diagnosis of Wilson disease should be suspected in children and young adults with unexplained neurologic disease, chronic active hepatitis, acute hemolytic crisis, behavioral or psychiatric disturbances, or the appearance of Fanconi syndrome. In such patients, the presence of Kayser-Fleischer rings is an important clue in making the diagnosis. Serum ceruloplasmin levels are decreased in 96% of patients with Wilson disease. A greatly increased urinary copper level is also useful in making the diagnosis, especially if it increases significantly with D-penicillamine. Liver copper levels are increased in untreated patients. Mutational analysis is also available.

Treatment

Treatment with penicillamine, 1 to 1.5 g/day, reverses the renal dysfunction and may reverse the hepatic and neurologic disease, depending on the degree of damage before the onset of therapy. Recovery, however, is quite slow. Trientine can also chelate copper and is indicated in patients who cannot tolerate penicillamine. Tetrathiomolybdate is a potent agent in removing copper from the body and has been used in some patients with neurologic disease to prevent the immediate worsening of symptoms that can occur with penicillamine. Zinc salts, which induce intestinal metallothionein and blockade of intestinal absorption of copper, are useful in maintenance therapy. Liver transplantation has been successful in some patients but should be reserved for those with liver failure.

Lowe Syndrome

Lowe syndrome (oculocerebrorenal syndrome) is characterized by congenital cataracts and glaucoma, severe mental retardation, hypotonia with diminished to absent reflexes, and renal abnormalities.[15,16] Fanconi syndrome is followed by progressive renal impairment. ESRD usually does not occur until the third to fourth decade of life.

Lowe syndrome is transmitted as an X-linked recessive trait. Despite this inheritance pattern, Lowe syndrome has occurred in a few females. The defective gene codes for phosphatidyl inositol 4,5-bisphosphate 5-phosphatase, OCRL1, involved with cell trafficking and signaling.

Light microscopy of the kidney is normal early in the disorder, with endothelial cell swelling and thickening and splitting of the glomerular basement membrane seen by EM. In the proximal tubule cells, there is shortening of the brush border and enlargement of the mitochondria, with distortion and loss of the cristae. Only symptomatic treatment is available.

Dent Disease

Definition

Dent disease is an X-linked recessive disorder characterized by low-molecular-weight proteinuria, hypercalciuria, nephrolithiasis, nephrocalcinosis, and rickets.[17-19] Affected males often have aminoaciduria, phosphaturia, and glycosuria. Renal failure is common and may occur by late childhood. Hemizygous females usually have only proteinuria and mild hypercalciuria. X-linked recessive nephrolithiasis and X-linked recessive hypophosphatemic rickets have similar features, and most have a defect in the renal ClC-5 chloride channel. Dent disease type 2 is a clinically similar disease affecting males, but there is a mutation in the same gene that causes Lowe syndrome, although Dent type 2 patients do not have the brain or eye involvement seen in Lowe syndrome.[17]

Etiology and Pathogenesis

Most of these disorders are caused by a mutation in the *CLCN5* gene leading to inactive ClC-5 chloride channel function (see Fig. 50-2). The ClC-5 chloride channel spans the membrane of pre-endocytic vesicles just below the brush border of the proximal tubule. This channel plays a role in the acidification of these vesicles by a proton pump. Lack of this Cl^- channel interferes with protein reabsorption from the tubule through the megalin-cubilin receptor system and cell surface receptor recycling, which may explain the phosphaturia, glycosuria, and aminoaciduria.

The defective OCRL1 in Dent disease type 2 patients interferes with normal cell protein trafficking. The renal disease is similar to that seen in type 1 Dent disease. Although patients do not have the eye and brain disease seen in Lowe patients, a few Dent type 2 patients have a mild intellectual deficits, hypotonia, and subclinical cataracts.

Filtered PTH is also reabsorbed by the megalin-cubilin system for degradation in the lysosome. Decreased PTH reabsorption allows increased binding to luminal PTH receptors and increased endocytosis of luminal phosphate transporters, leading to increased phosphaturia.[1]

Mitochondrial Cytopathies

Definition

Mitochondrial cytopathies are a diverse group of diseases with abnormalities in mitochondrial DNA that lead to mitochondrial dysfunction in various tissues.[20]

Clinical Manifestations

Most of the mitochondrial cytopathies present with neurologic disorders such as myopathy, myoclonus, ataxia, seizures, external ophthalmoplegia, stroke-like episodes, and optic neuropathy. Other manifestations include retinitis pigmentosa, diabetes mellitus, exocrine pancreatic insufficiency, sideroblastic anemia, sensorineural hearing loss, pseudo-obstruction of the colon, hepatic disease, cardiac conduction disorders, and cardiomyopathy.

The most common renal manifestation associated with mitochondrial cytopathies is Fanconi syndrome, although a number of patients have been described with focal segmental glomerulosclerosis (FSGS) and corticosteroid-resistant nephrotic syndrome. All the patients with renal abnormalities have had extrarenal disorders, mainly neurologic disease. Most patients present in the first months of life and die soon afterward.

Diagnosis

A clue to mitochondrial cytopathies is elevated serum or cerebrospinal fluid lactate levels, especially in association with an altered lactate-pyruvate ratio, suggesting a defect in mitochondrial respiration. The presence of "ragged red fibers," a manifestation of abnormal mitochondria, in a muscle biopsy specimen is another clue, especially with large abnormal mitochondria on EM of muscle tissue.

Treatment

There is little to offer these patients in terms of definitive therapy. Low mitochondrial enzyme complex III activity can be treated with menadione or ubidecarenone. Deficient mitochondrial enzyme complex I activity may be treated with riboflavin and ubidecarenone. Ascorbic acid has been used to minimize oxygen free radical injury. High-lipid, low-carbohydrate diet has been tried in cytochrome *c* oxidase deficiency.

Idiopathic Fanconi Syndrome

A number of patients develop the complete Fanconi syndrome in the absence of any known cause. Traditionally called "adult" Fanconi syndrome because it was thought that only adults were affected, it is now clear that children may be affected, and a more proper designation is *idiopathic* Fanconi syndrome. Not all the features of Fanconi syndrome may be present when the patient is first seen, but do appear with time. Idiopathic Fanconi syndrome can be inherited in an autosomal dominant, autosomal recessive, or even X-linked pattern. However, most cases occur sporadically, with no evidence of genetic transmission. The prognosis is variable, and some patients develop chronic renal failure 10 to 30 years after onset of symptoms. A few patients have undergone renal transplantation; in some, Fanconi syndrome has recurred in the allograft without evidence of rejection, suggesting an extrarenal cause of the idiopathic form. In one family, the gene defect was localized to chromosome 15.[21]

Renal morphologic descriptions of such cases are scanty. In some reports, no abnormalities were found, and in others, tubular atrophy with interstitial fibrosis was interspersed with areas of tubular dilation. Greatly dilated proximal tubules with swollen epithelium and grossly enlarged mitochondria with displaced cristae have also been noted.

ACQUIRED CAUSES OF FANCONI SYNDROME

Numerous substances can injure the proximal renal tubule. Injury can range from an incomplete Fanconi syndrome to acute tubular necrosis or ESRD. The extent of the tubular damage varies depending on the type of toxin, amount ingested, and host. A careful history of possible toxin exposure and recent medications is important in patients with tubular dysfunction. Box 50-1 lists the more common causes of acquired Fanconi syndrome.

Heavy Metal Intoxication

A major cause of proximal tubular dysfunction is acute heavy metal intoxication, principally lead and cadmium. In lead poisoning, the renal tubular dysfunction, mainly aminoaciduria and mild glycosuria and phosphaturia, is usually overshadowed by the involvement of other organs, especially the central nervous system.[22] Fanconi syndrome associated with cadmium poisoning is associated with severe bone pain, giving rise to the name itai-itai ("ouch-ouch") disease for its occurrence in Japanese patients affected by industrial contamination of the soil.[23]

Tetracycline

Outdated tetracycline causes a reversible Fanconi syndrome even in therapeutic doses. Recovery is rapid when the degraded drug is stopped. The compound responsible for the tubule dysfunction is anhydro-4-tetracycline, formed from tetracycline by heat, moisture, and low pH.

Cancer Chemotherapy Agents

A number of cancer chemotherapy agents have been associated with Fanconi syndrome and renal tubular dysfunction, especially cisplatin and ifosfamide. Carboplatin has been associated with reduced GFR and magnesium wasting but not Fanconi syndrome. The nephrotoxicity of both cisplatin and ifosfamide is dose dependent and often irreversible. Besides the usual manifestations of Fanconi syndrome, cisplatin toxicity is characterized by hypomagnesemia, caused by hypermagnesuria, which can be extremely severe, persistent, and difficult to treat.[24] Ifosfamide is more often associated with hypophosphatemic rickets.[25] Chloroacetaldehyde, a metabolite of ifosfamide, appears experimentally to cause Fanconi syndrome. Both ifosfamide and cisplatin can cause an irreversible reduction in GFR.

Other Drugs and Toxins

Exposure to a wide range of toxins may give rise to Fanconi syndrome, often in association with a reduced GFR, including 6-mercaptopurine, toluene (glue sniffing), and Chinese herbal medicines containing *Aristolochia* species.[26] There have also been anecdotal reports associating Fanconi syndrome with valproic acid (valproate), suramin, cresol-based antiseptic (Lysol), gentamicin, and ranitidine. Antiviral medications, especially antiretroviral agents

such as tenofovir, are an increasingly common cause of Fanconi syndrome.[27]

Dysproteinemias

Dysproteinemia[28] from multiple myeloma, light-chain proteinuria,[29] Sjögren syndrome, and amyloidosis is sometimes associated with Fanconi syndrome, which appears to be correlated with urinary free light chains with specific physicochemical characteristics that crystallize within the tubular cells.

Glomerular Disease

Nephrotic syndrome has rarely been associated with Fanconi syndrome. Most of these patients have FSGS, and the occurrence of Fanconi syndrome heralds a poor prognosis.

After Acute Kidney Injury

Tubular dysfunction can occur during recovery from AKI from any cause, whether or not a known tubular toxin was originally implicated.

After Renal Transplantation

Fanconi syndrome has appeared rarely after renal transplantation. The pathogenesis probably is multifactorial, including sequelae of acute tubular necrosis, rejection, nephrotoxic drugs, ischemia from renal artery stenosis, and residual hyperparathyroidism.

FAMILIAL GLUCOSE-GALACTOSE MALABSORPTION AND HEREDITARY RENAL GLYCOSURIA

Definition

Renal glycosuria refers to the appearance of readily detectable glucose in the urine when the serum glucose concentration is in a normal range. When the serum glucose concentration is in a physiologic range, virtually all the filtered glucose is reabsorbed in the proximal tubule.[30] Filtered glucose enters the proximal tubule through two specific carriers (SGLT1 and SGLT2) coupled to sodium and exits the cell through the sugar transporters GLUT1 and GLUT2 (see Fig. 50-6). However, when the serum level exceeds the physiologic range, the filtered load exceeds the capacity of these carriers, and glucose begins to appear in the urine; this is termed the *renal threshold.*

Etiology and Pathogenesis

Familial glucose-galactose malabsorption is a rare autosomal disorder that is caused by mutations in the gene coding for the brush border sodium-glucose cotransporter SGLT1, which is found in the intestinal cell and the S_3 segment of the proximal renal tubule cell. The disorder is characterized by the neonatal onset of life-threatening diarrhea from the intestinal malabsorption of glucose and galactose, which resolves rapidly with the removal of glucose and galactose and its dipeptide, lactose, from the diet. These patients frequently also have a mild renal glycosuria.

Familial renal glycosuria occurs with an incidence of 1 in 20,000 live births and appears to be inherited as a codominant trait with variable penetrance.[31] This disorder is caused by mutations in the *SLC5A2* gene that codes for the SGLT2 glucose transporter found in the early portion of the proximal tubule. Inhibitors of SGLT2, which mimic this genetic defect, have been used recently in type 2 diabetes to lower hyperglycemia without causing weight gain or aggravating hyperinsulinism.

In the past, renal glycosuria was divided into three types based on the reabsorption patterns observed during glucose infusion studies, but this typing system has been questioned because clearance data suggest that patients with renal glycosuria have rates of glucose reabsorption that vary from virtually no reabsorption to near-normal rates, rather than three distinct types, probably reflecting different mutations in the *SLC5A2* gene.[31]

Natural History

Patients with familial glucose-galactose malabsorption appear to grow and develop normally with removal of the offending sugars from the diet. The clinical course of hereditary renal glycosuria is benign, except for a few patients with polyuria and salt wasting, and it is not a precursor to diabetes mellitus. Patients need to be aware of the condition in order not to receive unnecessary diagnostic investigations, or even treatment for presumed diabetes mellitus.

AMINOACIDURIAS

As with glucose, amino acids are almost completely reabsorbed in the proximal tubule by a series of specific carriers. Studies have described a number of inherited disorders resulting in the incomplete reabsorption of a specific amino acid or a group of amino acids[32,33] (Table 50-2).

Cystinuria

Definition

Cystinuria is characterized by the excessive urinary excretion of cystine and the dibasic amino acids ornithine, lysine, and arginine.[35]

Etiology and Pathogenesis

These four amino acids share a transport system on the brush border membrane of the proximal tubule. Because of the relative insolubility of cystine when its urine concentration exceeds 250 mg/l (1 mmol/l), patients with cystinuria have recurrent renal calculi.

Cystinuria is an autosomal recessive trait with a disease incidence of 1 in 15,000 births.[34] Initially, there appeared to be three genetic types on the basis of *in vitro* studies of intestinal transport and amino acid excretion in heterozygotes. More recently, two genes (*SLC3A1* coding for the protein rBAT and *SLC7A9* for the protein $b^{0,+}$AT) have been identified that are defective in cystinuria. *SLC3A1* heterozygotes have normal excretion rates for cystine. *SLC7A9* heterozygotes

Inherited Aminoacidurias

Disease	Clinical Findings	Urine Amino Acids
Cystinuria	Urolithiasis	Cystine, lysine, ornithine, arginine
Hartnup disease	Rash, neurologic disease	Neutral amino acids
Iminoglycinuria	None	Proline, hydroxyproline glycine
Lysinuric protein intolerance	Hyperammonemia, vomiting, diarrhea	Dibasic amino acids

Table 50-2 Inherited aminoacidurias.

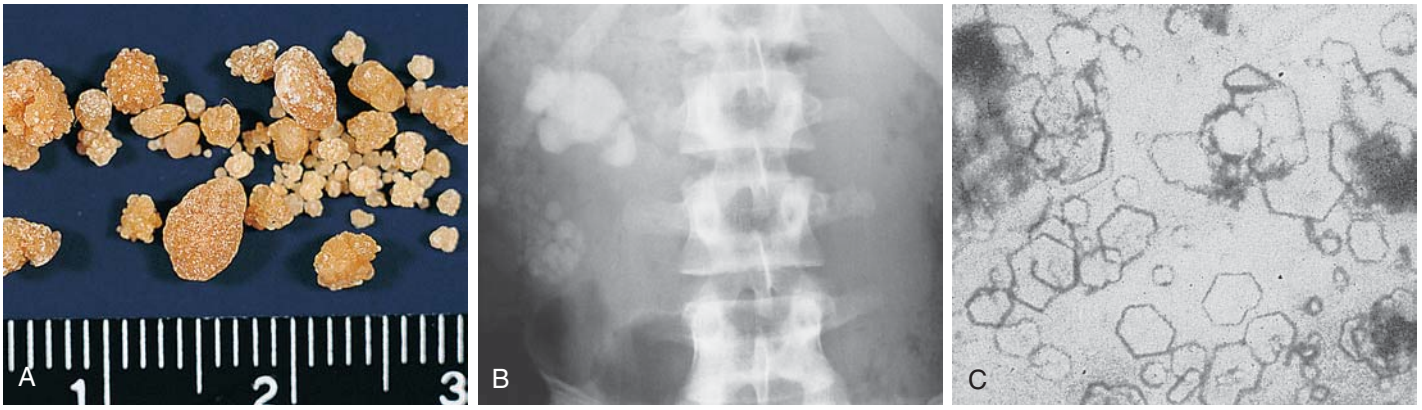

Figure 50-7 Cystinuria. A, Both rough and smooth cystine calculi. **B,** Plain radiograph of a cystine calculus in the right renal pelvis and further multiple parenchymal calculi. **C,** Urine microscopy showing characteristic flat hexagonal crystals (see also Fig. 4-4, *G*).

have cystine excretion rates that range from normal to almost that of homozygous patients. Based on these data, a newer classification proposed type A for mutations in both *SLC3A1* genes and type B for mutations in *SLC7A9*.[34] Type AB is compound heterozygote. Type A accounts for 38% of cystinuria patients, type B for 47%, and type AB for 14%.

Clinical Manifestations

Cystine stones (calculi) are typically yellow-brown (Fig. 50-7, *A*) and are radiopaque (Fig. 50-7, *B*). Cystine crystals appear as microscopic, flat hexagons in the urine (Fig. 50-7, *C*), and this is a clue to the diagnosis.

Diagnosis

Patients can be screened for cystinuria with the cyanide-nitroprusside test, but type B heterozygotes may also give a positive result. The definitive test is to quantify cystine and dibasic amino acid excretion in a 24-hour urine specimen. Homozygotes excrete more than 118 mmol cystine per mmol creatinine (250 mg/g).

Treatment

The aim of therapy in cystinuria is to lower the urine cystine concentration to below 300 mg/l (1.25 mmol/l). The first step is to increase fluid intake. However, because most patients with cystinuria excrete 0.5 to 1 g/day of cystine, a urine output of 2 to 4 l/day is needed to achieve this goal. Cystine solubility increases in alkaline urine, but the urine pH must be above 7.5 to be effective. In patients with recurrent stone disease, thiols, such as penicillamine, are extremely useful through the formation of a more soluble, mixed disulfide of the thiol and cysteine from cystine. Penicillamine should be started at 250 mg/day and gradually increased (maximum, 2 g/day) during 3 months to achieve a urine cystine concentration below 300 mg/l in conjunction with a high fluid intake. Tiopronin is equally effective and is better tolerated than penicillamine. Tiopronin should also be started at a low dose and slowly increased (maximum, 2 g/day). Captopril can be useful (an effect resulting from its thiol structure, not its angiotensin-converting enzyme inhibitor effect), but the dose range (75 to 150 mg/day) may be limited by its hypotensive effects.

Hartnup Disease

Hartnup disease is an autosomal recessive trait characterized by a neutral aminoaciduria that arises from a defect in a specific carrier for neutral amino acid transport present in both the intestine and the proximal renal tubule. The gene responsible for Hartnup disease is *SLC6A19*. It codes for the neutral amino acid transporter B^0AT1. From newborn screening programs, the genetic defect is more common than originally thought because most individuals with the aminoaciduria never manifest symptoms. Individuals who become symptomatic with Hartnup disease have pellagra-like clinical features, including a photosensitive dermatitis, ataxia, and psychotic behavior. These symptoms appear to be secondary to niacin deficiency partly caused by inadequate intestinal absorption of tryptophan, the precursor for niacin synthesis. However, most individuals who inherit the Hartnup transport defect do not have symptoms, so there must be other environmental or genetic factors that contribute to disease. Nicotinamide supplementation leads to clearing of the skin disease and occasionally some of the neurologic problems. The renal loss of neutral amino acids appears to have minimal clinical importance.

Iminoglycinuria

Iminoglycinuria is a benign heritable defect in the proximal tubule transporter PAT1, leading to incomplete reabsorption of proline, hydroxyproline, and glycine.

Lysinuric Protein Intolerance

Lysinuric protein intolerance is associated with recurrent bouts of hyperammonemia after a protein load, resulting from the decreased renal and intestinal dibasic amino acid transport.

Other Aminoacidurias

Rare individuals have been described with abnormalities in the excretion of other amino acids. These usually occur in association with mental retardation.

HEREDITARY DEFECTS IN URIC ACID HANDLING

Hereditary Renal Hypouricemia

Hereditary renal hypouricemia is a rare autosomal recessive disorder characterized by very low serum uric acid levels (<2.5 mg/dl; [<150 µmol/l] in adult men and <2.1 mg/dl [<124 µmol/l] in adult women) and increased uric acid clearance, ranging from 30% to 150% of the filtered load.[36] In the normal kidney, uric acid is both

reabsorbed and secreted in the proximal tubule by two different uric acid–anion exchange transporters and a voltage-sensitive pathway. In some patients, the defect is in the gene *SLC22A12* that codes for the protein URAT1; other patients have been found to have mutations in *SLC2A9 (GLUT9)*. Most patients do not have symptoms and are found incidentally when a low serum uric acid concentration is noted during routine serum chemistry evaluation. About one fourth of patients with renal hypouricemia have had renal stones, but only one third of these were uric acid stones. There may also be hypercalciuria, and a few patients have had exercise-induced AKI, thought to be caused by acute tubular injury by passage of uric acid "gravel" in association with volume depletion and reduced urine pH. Most patients require no treatment, but if forming uric acid stones, they should maintain a high fluid intake. Urine alkalinization and allopurinol can be used for patients with persistent uric acid stones.

Familial Juvenile Hyperuricemic Nephropathy and Medullary Cystic Kidney Disease Type 2

Familial juvenile hyperuricemic nephropathy (FJHN) is a rare autosomal dominant condition characterized by hyperuricemia associated with a tubular defect in uric acid excretion.[37] Children develop progressive chronic kidney disease (CKD) with interstitial fibrosis and glomerulosclerosis. The hyperuricemia is caused by renal underexcretion of uric acid. Diagnosis is suggested by a fractional excretion of uric acid of less than 5% (normal, 10% to 15%). Controversy exists as to whether lowering of serum uric acid slows the progression of CKD; the studies reporting benefit have usually involved starting of a xanthine oxidase inhibitor early in the course of the disease. Isosthenuria and hypertension are common, and some patients have renal salt wasting. Many of the features of FJHN are also seen in medullary cystic kidney disease type 2 (MCKD2).[38] Most of these patients have a defect in the gene *UMOD,* on chromosome 16p12, coding for the Tamm-Horsfall/uromodulin protein. This mutation may interfere with the function of the Na-K-2Cl transporter, leading to a secondary increase in proximal sodium and uric acid reabsorption. This mutation may also lead to deposition of abnormal protein in the endoplasmic reticulum and ultimately cell death.

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CHAPTER 51

Sickle Cell Disease

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DEFINITIONS

Sickle cell disease is an autosomal recessive inherited disorder that predominantly affects persons of African, Mediterranean, Indian, and Middle Eastern descent. The gene for sickle hemoglobin (hemoglobin S, or HbS) results in the replacement of the normal glutamine by valine in the sixth position of the β-globin subunit, thereby changing the configuration of the hemoglobin molecule and enhancing the aggregation of hemoglobin molecules during cellular or tissue hypoxia, dehydration, or oxidative stress. This aggregation decreases the pliability of the erythrocytes and may distort their shape to a characteristic crescent or sickle, resulting in their premature destruction (hemolysis) and frequent, widespread vaso-occlusive episodes with subsequent acute and chronic organ damage. Sickle cell anemia occurs in those homozygous for HbS or in heterozygotes when HbS coexists with another abnormal hemoglobin (e.g., hemoglobin C, β-thalassaemia chains). *Sickle cell trait* occurs in those heterozygous for HbS when the other hemoglobin molecule is normal.

Sickle cell nephropathy describes the structural and functional abnormalities of the kidney in sickle cell disease.

SICKLE CELL DISEASE

Epidemiology

Sickle cell disease was first recognized in West Africa. The high prevalence of HbS in this region probably represents a survival benefit because the presence of sickle cell trait protects against malaria. At present, sickle cell disease is a worldwide health problem because HbS has spread throughout Africa, around the Mediterranean, and to the Middle East and India as well as to the Caribbean, North America, and northern Europe. The prevalence of the sickle cell gene is about 8% in African Americans and about 25% in adult Nigerians and in some areas in equatorial Africa, Saudi Arabia, and India.

Restriction enzyme techniques have identified several HbS haplotypes, mutations of the HbS molecule, that have probably arisen independently of each other. There are four major types in Africa—the Benin, Senegal, Cameroon, and Bantu (or Central African Republic)—and one Asian haplotype. Variations in these haplotypes determine disease severity; for example, the Senegalese haplotype is associated with a higher hemoglobin F (HbF) concentration and has a better prognosis than others. In a sample population of Nigerians, Benin haplotype was detected in 92.3%.[1] Gender influences disease severity; female HbSS patients with Benin haplotype have a higher HbF level than male patients.

Pathogenesis

Genetics

Sickle cell disease comprises a group of heterogeneous disorders that share the presence of the gene for HbS, either homozygous (i.e., sickle cell anemia, HbSS) or double heterozygous (i.e., combination of HbS with another abnormal hemoglobin).[2,3] Sickle cell anemia is the most common form. The most common double heterozygous disorders are the combinations of HbS with hemoglobin C (HbSC) and with β-thalassemia (HbS-thal). Patients with HbS-thal may produce reduced amounts of normal β chains (HbS–β^{+}-thal), but not always (HbS–β^{0}-thal). Those with a sickle cell trait or carrier state are heterozygous for HbS only.

Pathophysiology

The driving pathophysiologic factor is HbS polymerization. The mutated β-globin chains of the HbS molecule tend to crystallize to a polymer nucleus in the deoxygenated state. Polymerization disrupts the architecture and changes the shape of the red blood cell (RBC), increases its rigidity, and causes sickling (Fig. 51-1). Polymerization is dynamic and depends on three independent variables: degree of cellular hypoxia, intracellular hemoglobin concentration, and presence or absence of HbF (fetal hemoglobin).[4] The main determinant of disease severity is the rate and extent of HbS polymerization, which drives the two major pathophysiologic processes: vaso-occlusion with ischemia-reperfusion injury and hemolytic anemia (Fig. 51-2).[5]

Vaso-occlusion occurs in all patients, often triggered by inflammation and typically found in clinical states of infection, hypoxia, hypovolemia, hypothermia, acidosis, and hyperosmolality. Vaso-occlusion is probably caused by dynamic endothelial-leukocyte-erythrocyte adhesive interactions in the postcapillary venules and precapillary obstruction by rigid, deformed erythrocytes. Episodic microvascular occlusion and ischemia can be interrupted by restoration of blood flow and reperfusion, which further promote inflammatory stress and tissue injury.

Hemolysis has recently been shown to contribute to the development of progressive vasculopathy, characterized by endothelial dysfunction and proliferative changes in the intima and smooth muscle of blood vessels. The degree of hemolysis is associated with the development of pulmonary hypertension in sickle cell disease. An important role is ascribed to free hemoglobin, which inactivates nitric oxide and generates reactive oxygen species. Both these factors may further contribute to the hypercoagulability and vasculopathy.

Clinical Manifestations

The clinical manifestations of sickle cell disease are individualized and age dependent (Fig. 51-3). A chronic low-grade hemolytic anemia always occurs and predisposes to gallstones. The most prevalent clinical problem is periodic crises of bone pain. During the first years of life, bone pain presents as the hand-foot syndrome, and over the years it can result in avascular necrosis of the heads of the femur and humerus. Other disabling complications include cerebrovascular accident (stroke) resulting from occlusion of major cerebral

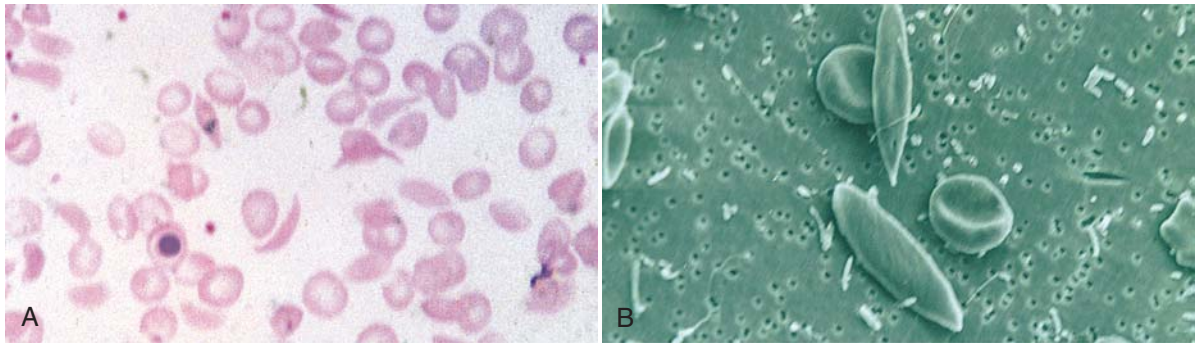

Figure 51-1 Sickle cells. A, Characteristic sickle cell erythrocytes in peripheral blood film of a patient with homozygous sickle cell anemia. **B,** Electron micrograph showing two normal and two sickle-shaped erythrocytes. *(Courtesy Professor Sally C. Davies.)*

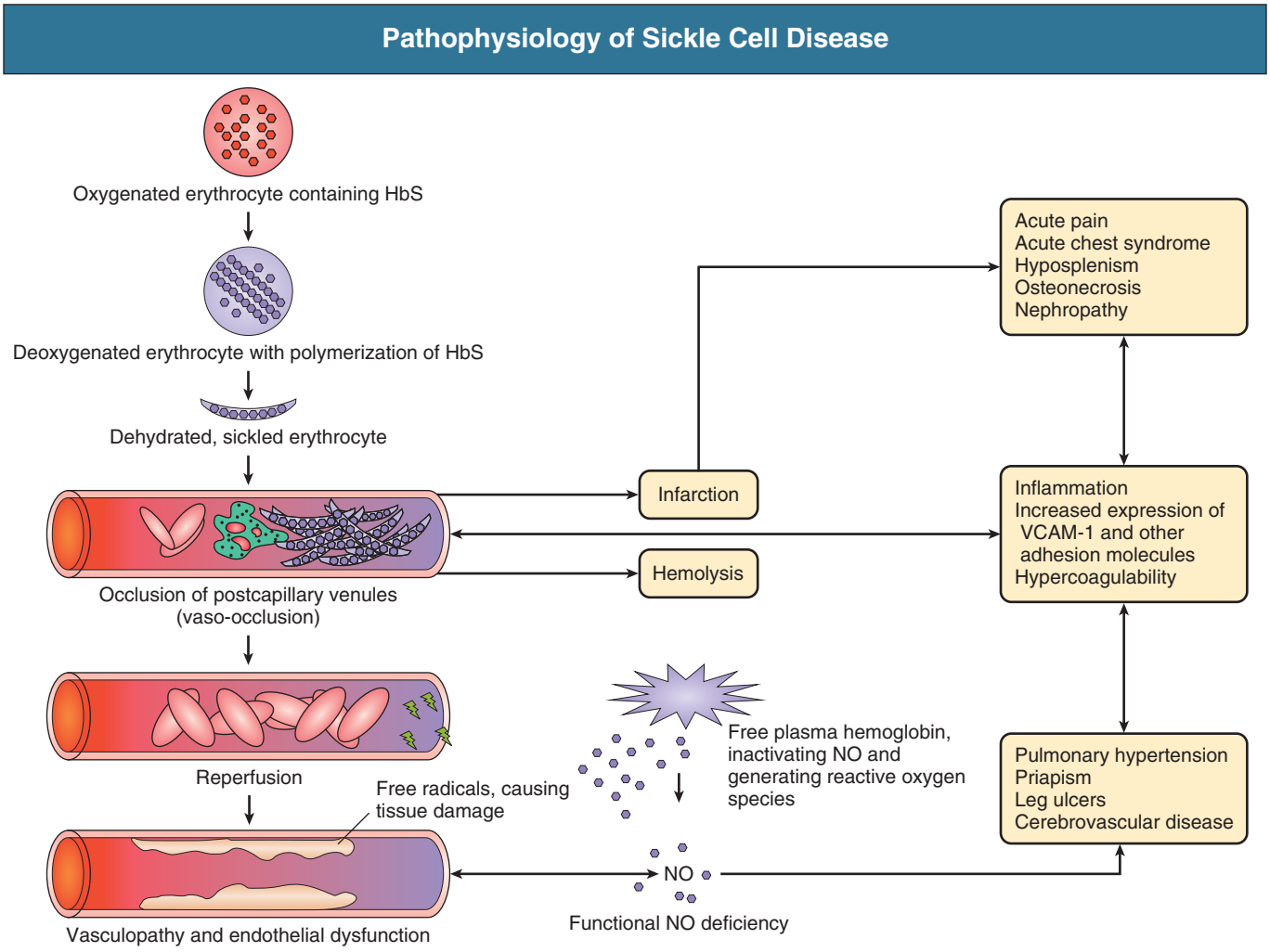

Figure 51-2 Pathophysiology of sickle cell disease. *HbS,* Hemoglobin S [sickle Hb]; *NO,* nitric oxide; *VCAM-1,* vascular cell adhesion molecule 1. *(Modified from reference 5.)*

vessels, the acute chest syndrome, priapism, chronic leg ulceration, chronic pulmonary disease with pulmonary hypertension, and chronic kidney disease.[6,7]

Patients with sickle cell disease are prone to infections because of functional asplenia early in life as a result of splenic sequestration, recurrent splenic infarction, and consequent autosplenectomy. Common bacterial infections, especially with encapsulated organisms, can be fatal in these patients. Bacterial isolates during invasive bacterial infections show *Streptococcus pneumoniae* (38%), *Salmonella* spp. (33%), *Haemophilus influenzae* (14%), *Escherichia coli* (11%), and *Klebsiella* spp. (4%).[8] *S. pneumoniae* and *H. influenzae* occur predominantly before 5 years of age, *Salmonella* increases almost linearly with age, and *Klebsiella* and *E. coli* predominate in patients older than 10 years. Pneumococcal infections carry high morbidity and mortality rates in the early years of life, necessitating vaccination or prophylaxis.[2]

Fever is common in patients with sickle cell disease. Common complications accompanying fever are painful crisis and acute chest syndrome. Bacteremia is not always confirmed, and in some cases, the fever may be viral in origin or related to infections from atypical organisms. Nevertheless, early antibiotic treatment is recommended pending microbiologic information.

There are remarkable differences in clinical severity and outcome of disease. Sickle cell trait is a rather benign condition. Patients with HbSS tend to have more severe disease than those with HbSC. Likewise, patients with HbS–β^+-thal do better than those with HbS–β^0-thal. The Bantu haplotype is associated with the highest frequency of organ damage. However, the severity of disease may also differ among patients with an identical genotype. In part, these differences can be explained by the amount of HbF present because it protects against clinical severity. In addition, endothelial factors probably play an important role. Degree of adherence between sickle erythrocytes and endothelial cells has been shown to correlate with the clinical severity of disease. Also, an association has been found between circulating activated endothelial cells of microvascular origin and the onset of painful sickle cell crises.[9]

Natural History

Life expectancy is reduced in sickle cell disease, especially in patients with symptomatic disease. An increased risk for early death is associated with low levels of HbF, renal failure, the acute chest syndrome, and seizures.[7,10] Childhood survival to age 20 years has improved during the past decades. In the course of life, irreversible organ damage caused by arterial and capillary microcirculation obstructive vasculopathy gradually becomes more prevalent. The diagnosis of a clinically evident form of organ damage, such as leg ulcer, osteonecrosis, or retinopathy, predicts the development of a more lethal form of organ damage, such as chronic lung disease, renal failure, or stroke.[11] Overall, the primary causes of death in patients with sickle cell anemia are chronic lung disease in 20%, renal failure in 14%, and stroke in 10%. In younger patients, the primary cause of death is infection; in older patients, the primary cause of death is irreversible organ damage (Fig. 51-4).

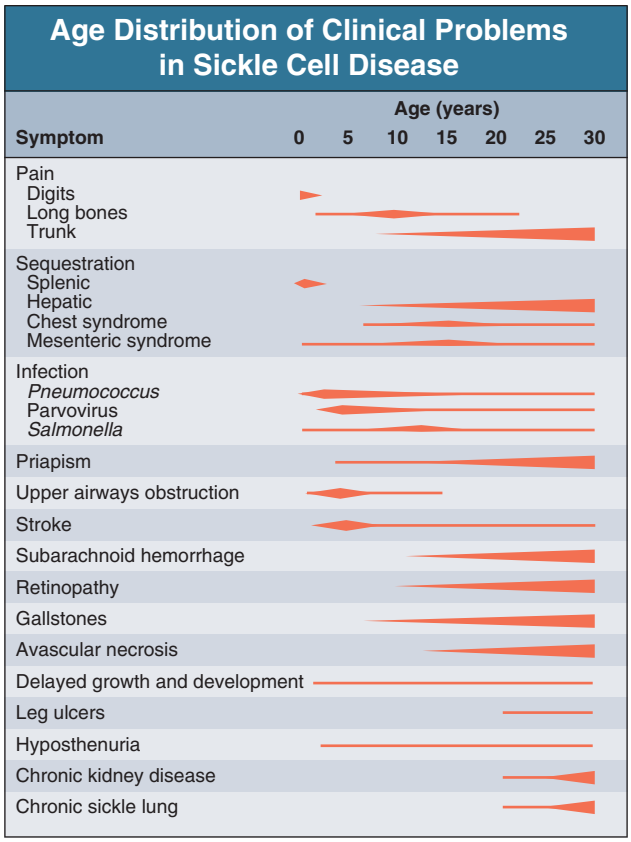

Figure 51-3 Age distribution of clinical problems in sickle cell disease. *(Modified from reference 2.)*

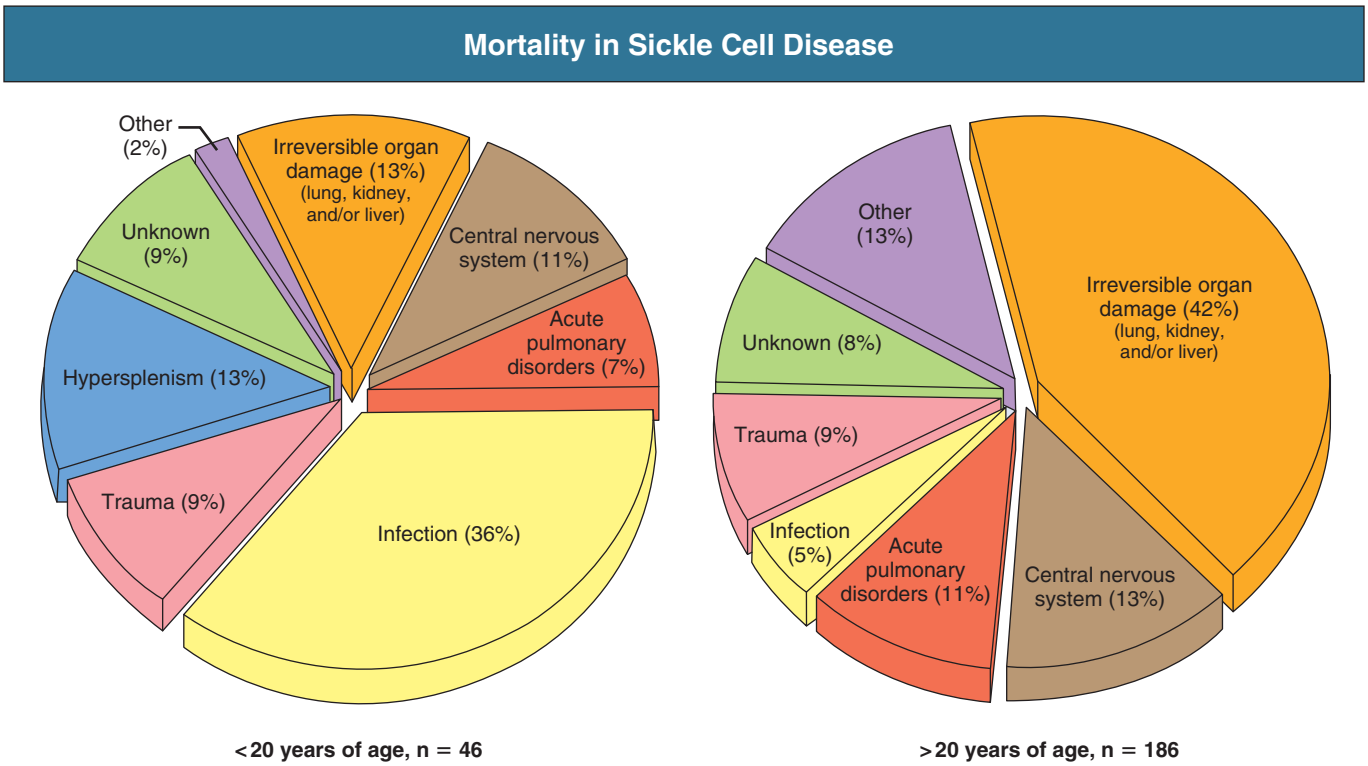

Figure 51-4 Mortality in sickle cell disease. Causes of death among 232 HbSS patients, comparing patients younger than 20 years (46 died) with patients older than 20 years (186 died). The infection category includes both bacterial and viral diseases. *(Modified from reference 11.)*

Treatment

Management of sickle cell disease is primarily directed at the relief of symptoms and prevention of complications, whereas newer treatments are being devised that target the pathophysiologic changes of the disease.[12] Daily oral penicillin for children 2 to 5 years of age is effective in reducing both the infection rate and the mortality related to pneumococcal infection.[13] Immunization against pneumococcus is recommended for children at 2 years of age, with booster doses at 5 years, although protection from current vaccines is imperfect. Immunization against influenza in children is also important.

Empiric broad-spectrum antibiotics effective against gram-positive and gram-negative organisms should be used in adults with fever pending microbiologic confirmation. A common antibiotic is amoxicillin.

Sickle cell crises are managed with oxygen therapy, rehydration with intravenous fluids, RBC transfusions, and analgesia. In severe cases, exchange RBC transfusions may be effective. Hydroxyurea treatment in patients with sickle cell anemia and recurrent vaso-occlusive events decreases the incidence of painful crises and acute chest syndrome and overall mortality. Butyrate compounds, deoxyazacytidine, and various combinations with erythropoietin are still being tried.[12,14] Hematopoietic stem cell transplantation is potentially curative in sickle cell patients, associated with 80% to 85% disease-free survival in several series.[15] Young and presymptomatic patients with high-risk features of severe disease benefit the most from hematopoietic stem cell transplantation.

PATHOGENESIS OF SICKLE CELL NEPHROPATHY

The hallmark of sickle cell nephropathy is the combination of impaired renal concentrating capacity and a normal diluting capacity.[16,17]

Concentrating Capacity

The defect in concentrating capacity results from loss of the countercurrent exchange mechanism in the inner renal medulla through loss of the vasa recta and long loops of Henle of the juxtamedullary nephrons (Fig. 51-5). The vasa recta of the juxtamedullary nephrons present an ideal setting for sickling. The renal medulla is relatively hypoxic and hyperosmotic, with increased blood viscosity in the medullary circulation and slow medullary blood flow. Studies in transgenic sickle cell mice have demonstrated distention and

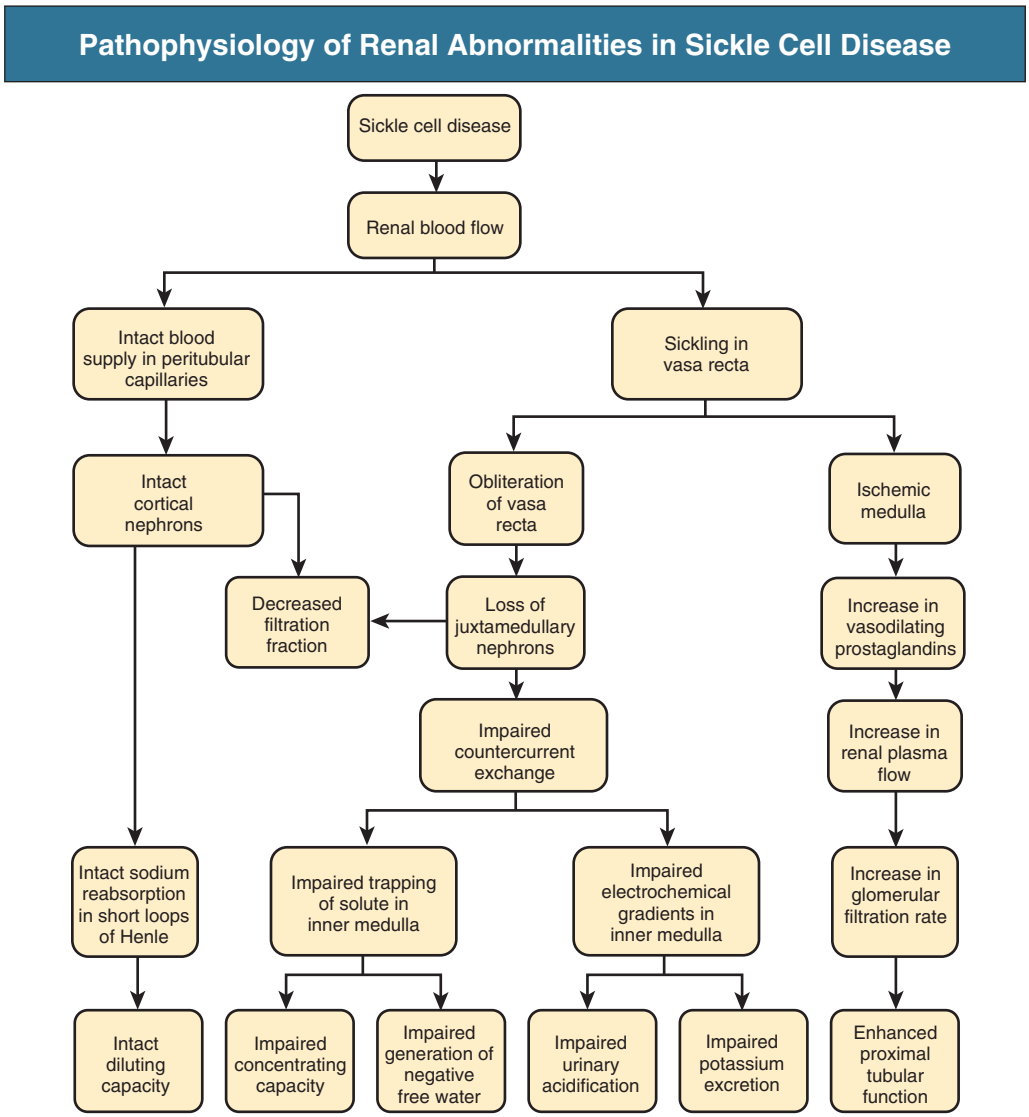

Figure 51-5 Pathophysiology of renal abnormalities in sickle cell disease.

Figure 51-6 Microradioangiography showing loss of vasa recta in sickle cell nephropathy. **A,** Kidney from control, with normal vasa recta. **B,** Patient with sickle cell anemia, with the absence of the vasa recta. *(From reference 18.)*

congestion of the vasa recta under hypoxic conditions. This environment facilitates the sickling of erythrocytes, formation of intravascular microthrombi, and obstruction of blood flow through the vasa recta. The loss of vasa recta has been confirmed by microradioangiographic studies[18] (Fig. 51-6).

Histologic examination of the medulla shows edema, focal scarring, and interstitial fibrosis resulting in tubular atrophy. Ischemic infarction in the vasa recta sometimes causes papillary necrosis. The concentration defect is found to be reversible in young children when sickling is prevented after multiple transfusions of normal blood, but it becomes irreversible thereafter. Adults with sickle cell anemia cannot concentrate the urine above 450 mOsm/kg H_2O. This relates to the interstitial osmolality at the transition of the outer and inner medulla, at the tips of the short loops of Henle of the cortical nephrons. Patients with sickle cell trait or hybrid sickling disorders show intermediate concentrating defects. Maximal osmolality varies from 400 to 900 mOsm/kg H_2O in sickle cell trait and from 400 to 700 mOsm/kg H_2O in HbSC and declines further with aging.

Diluting Capacity

The diluting capacity is normal as a result of the intact reabsorptive function of the superficial loops of Henle of the cortical nephrons. These are supplied by peritubular capillaries, which present a less ideal setting for sickling than the vasa recta. In contrast to the diluting capacity, the free water reabsorption, or capacity to generate negative free water balance, is impaired by defective trapping of solute in the inner medulla.

Urine volumes are typically higher than normal, a consequence of impaired concentrating ability. Response to a water deprivation test in sickle cell disease is usually positive with marked elevation of endogenous antidiuretic hormone, and response to desmopressin is poor. Because isosthenuria is typical, there is a susceptibility to normonatremic dehydration.

Other Tubular Abnormalities

Defects in urinary acidification and potassium excretion are other distal nephron function abnormalities.[17] These abnormalities may become overt only when there is an increased supply of acid and potassium, as during rhabdomyolysis. The exact causes are unknown, but these defects probably reflect failure to maintain the necessary energy-requiring hydrogen ion (H^+) and electrochemical gradients along the collecting ducts from the impaired medullary blood flow and hypoxia. The impaired potassium excretion is aldosterone independent.

In contrast to the functional abnormalities of the distal nephron, proximal tubular function is enhanced. Reabsorption of phosphate and β_2-microglobulin and secretion of uric acid and creatinine in the proximal tubule are increased. Therefore, creatinine clearance overestimates glomerular filtration rate (GFR) considerably. The cause of the enhanced proximal function is not clear, but it probably represents a secondary compensatory mechanism to correct for defects in medullary function.

Renal Hemodynamics

Renal hemodynamics show remarkable changes in the course of disease (Fig. 51-7). Young patients with sickle cell disease have increases in renal plasma flow (RPF) and renal blood flow and, to a lesser extent, in GFR. The increased RPF is ascribed to increased release of vasodilator prostaglandins as a result of medullary ischemia because prostaglandin inhibition significantly reduces RPF and GFR. It has been suggested that endothelial dysfunction from hemolysis can induce vasodilation in the cortex, including hyperfiltration and glomerular hypertrophy, in contrast to the prevailing vaso-occlusion in the medulla.[19]

The decrease in filtration fraction may be caused by selective damage of juxtamedullary nephrons, which have the highest filtration fractions.

Glomerular Injury

Glomerular hypertrophy is an early manifestation of sickle cell nephropathy. Histologic examination of the kidneys of young children shows glomerular enlargement and congestion, especially in the juxtamedullary glomeruli. Both afferent and efferent arterioles of these glomeruli may be dilated. Young adult patients with sickle cell

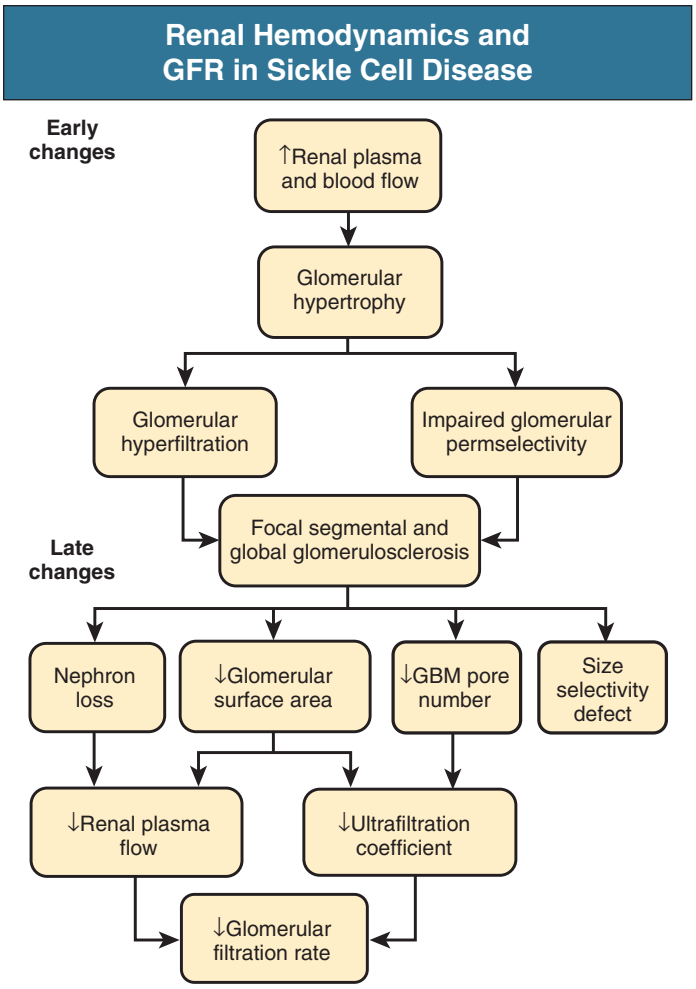

Figure 51-7 Renal hemodynamics and glomerular filtration in sickle cell nephropathy. *GBM,* Glomerular basement membrane; *GFR,* glomerular filtration rate.

anemia show a distinct pattern of glomerular dysfunction, with impaired glomerular permselectivity, increased ultrafiltration coefficient, glomerular hyperfiltration, and proteinuria.[20,21] Prolonged glomerular hyperfiltration may cause further glomerular injury. This is supported by the common histologic finding of focal segmental glomerulosclerosis (FSGS) in adult patients with sickle cell disease[22] (Fig. 51-8). Besides FSGS, other histopathologic variants are membranoproliferative glomerulonephritis, thrombotic microangiopathy, and specific sickle cell nephropathy.[23] Hypoxia did not seem to play a key role in the progression of glomerular lesions in histopathologic studies because immunohistochemistry did not reveal a specific induction of hypoxic markers at the time of renal biopsy.

In older patients, progressive ischemia and fibrosis with obliteration of glomeruli can be found. Glomerular studies show a decrease in glomerular basement membrane pore number and a size selectivity defect in patients with renal impairment.[24] Good correlation exists between tubular and glomerular dysfunction, with both contributing to nephropathy in patients with sickle cell disease.[25] Eventually, a combined decrease in ultrafiltration capacity and RPF can result in end-stage renal disease (ESRD).[20]

Hormones in Sickle Cell Nephropathy

There is relative erythropoietin (EPO) deficiency in sickle cell disease; that is, EPO levels do not increase to the expected level

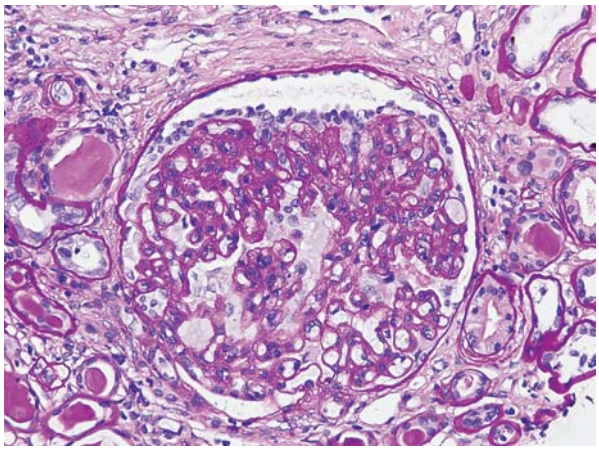

Figure 51-8 Focal segmental glomerulosclerosis in sickle cell nephropathy. There is segmental sclerosis in the upper half of the glomerulus. *(Courtesy Professor J. Weening.)*

for the degree of anemia, perhaps because of the right-shifted hemoglobin-oxygen dissociation curve. In addition, EPO levels fall with the decline in renal function, probably from renal damage caused by the sickling process.

Elevated serum renin and aldosterone levels have been reported in some studies, under standard and volume-depleted conditions, although in general normal values are found in sickle cell anemia.[16]

Hormone infusion studies have helped to localize sites of action in the kidney. Failure of low-dose infusion of atrial natriuretic peptide (ANP) to increase natriuresis in sickle cell anemia[26] suggests that ANP at this dosage exerts its natriuretic effect in the long Henle loops of the juxtamedullary nephrons, whereas insulin induces a similar sodium retention in patients with sickle cell anemia and normal individuals,[26] suggesting that its antinatriuretic effect is probably localized at a distal tubular site other than the long loops of Henle. Urinary endothelin-1 is elevated in asymptomatic sickle cell disease patients. It correlates with a urine-concentrating defect and microalbuminuria, which could be explained by a combination of functional resistance to vasopressin and fibrosis.[27]

CLINICAL MANIFESTATIONS OF SICKLE CELL NEPHROPATHY

The presentation of the clinical manifestations of sickle cell nephropathy shows an age-dependent pattern. In addition to age of the patient, duration of sickle cell disease and frequency of crises and hospitalizations are predictors of kidney disease.[28] Table 51-1 outlines the frequency and etiology of the renal abnormalities associated with sickle cell anemia, sickle cell trait, and the most common double heterozygous disorders (HbSC and HbS-thal).

Hematuria

Hematuria is a common clinical manifestation in sickle cell anemia and the hybrid sickling disorders and occurs in 3% to 4% of individuals with sickle cell trait at some time. Patients often have persistent microscopic hematuria with episodic gross hematuria. The hematuria may follow relatively minor trauma. Hematuria occurs more often in males and is usually unilateral, originating from the left kidney in 80% of patients. Urinary erythrocytes are typically isomorphic, but sickled erythrocytes are occasionally found in the urine.

Frequency and Etiology of Renal Abnormalities Associated with Sickle Cell Disease				
Type of Renal Disease	**Etiology**	**Sickle Cell Anemia**	**Sickle Cell Trait**	**HbSC and HbS-thal**
Impaired concentrating capacity	Loss of vasa recta of juxtamedullary nephrons	Irreversible defects in all adults	Intermediate defects in all adults' nephrons	Intermediate defects in all adults
Impaired urinary acidification	Incomplete form of distal renal tubular acidosis	Almost all, during acid loading	Rare	At least 30%, during acid loading
Impaired potassium excretion	Aldosterone independent	Almost all, during potassium loading	Rare	Unknown; probably at least 30%
Hematuria	Infarction, extravasation of blood in renal medulla	Common	3%-4%	Common
Proteinuria	Glomerular hyperfiltration plus impaired permselectivity	Up to 50%-60% with increasing age	Rare	20%-25%
Nephrotic syndrome	FSGS most common	About 4%	Rare	0%-4%
Chronic renal failure	See Fig. 51-7	4.2%-4.6%	Rare	About 2.4%
Renal medullary carcinoma	Possible genetic predisposition	Rare	Rare	Rare

Table 51-1 Frequency and etiology of renal abnormalities associated with sickle cell disease.

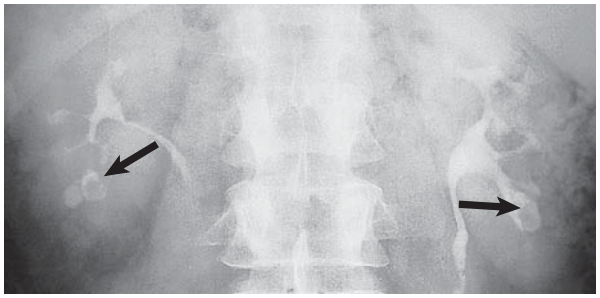

Figure 51-9 Papillary necrosis in sickle cell disease. Intravenous urography shows abnormal calyces with filling defects *(arrows)*.

Pathogenesis

Sickling The main mechanism of hematuria probably relates to sickling of erythrocytes in the vasa recta and microthrombotic infarction and extravasation of blood in the renal medulla. Histologic examination typically shows severe stasis in peritubular capillaries of the cortex and especially the medulla as well as extravasation of blood into the collecting system.

Papillary Necrosis Papillary necrosis is a frequent cause of hematuria in sickle cell anemia, hybrid sickling disorders, and sickle cell trait (Fig. 51-9). The incidence of papillary necrosis varies from 23% to 67% in studies of sickle cell disease.[17,29] This complication results from obliteration of the vasa recta, with medullary necrosis and fibrosis. Frequent analgesic use by these patients for their bone pain may also contribute to papillary necrosis. The most common presenting symptom is painless macroscopic hematuria. Other presentations are renal colic caused by the passage of blood clots or necrotic papillae, microhematuria, symptoms of urinary tract infection (UTI), and rarely acute kidney injury. Papillary necrosis may also be asymptomatic and is frequently an incidental finding during imaging.

Nutcracker Phenomenon The left-sided predominance of hematuria has been attributed to the so-called nutcracker phenomenon, with compression of the left renal vein between the aorta and the superior mesenteric artery increasing the pressure in the renal vein. This may especially contribute to the development of hematuria in sickle cell patients, because the increased renal vein pressure could worsen anoxia in the renal medulla, increasing the likelihood of sickling in the left kidney.

Clinical Manifestations

Painless macroscopic hematuria often presents after physical activity or minor renal trauma or is associated with hypoxic challenges (e.g., airplane flights). It usually is accompanied by a substantial decline in hematocrit. Bleeding typically remits spontaneously within a few days.

Diagnosis and Differential Diagnosis

Urinalysis can exclude the presence of myoglobinuria and rhabdomyolysis, which can mimic hematuria. Rhabdomyolysis can be provoked during strenuous exercise and dehydration and may also occur during severe sickle cell crises. The coexistence of hematuria with leukocyturia is not unusual and does not necessarily indicate UTI, even in combination with flank pain. Infection must be confirmed by examination of the urinary sediment and urine cultures.

Sickle cell trait has been reported in 50% of African Americans with ESRD caused by autosomal dominant polycystic kidney disease (ADPKD) but in only 7.5% of African American patients with other causes of ESRD. In addition, patients with ADPKD and sickle cell trait had an earlier onset of ESRD.[30] The prevalence of sickle cell disease in ADPKD has not been reported.

Renal medullary carcinoma has been recognized as a specific entity in sickle cell nephropathy.[17,31] It is an aggressive form of renal cell carcinoma that appears uniquely to affect patients with sickle cell hemoglobinopathies, particularly sickle cell trait or HbSC, especially in teenagers and young adults. Chronic medullary hypoxia is thought to contribute to its pathogenesis.[8] The tumors are resistant to chemotherapy and tend to be metastatic at diagnosis, with a reported postsurgical mean survival of only 15 weeks. It is not yet clear whether regular screening for renal medullary carcinoma in young patients with sickle cell disease or trait could result in an early diagnosis and a better survival.[31] Gross hematuria, flank pain, and weight loss are ominous signs of malignancy, particularly in young patients with sickle cell trait. The tumor is typically located deep in the parenchyma, unlike Wilms tumor or renal cell carcinoma. Immunohistochemical analysis for epithelial cell markers (e.g., CAM 5.5), epithelial membrane antigen, and cytokeratin may assist in diagnosis.

Von Willebrand disease has occasionally been described in patients with sickle cell trait and gross hematuria.

Further evaluation is indicated for patients with severe or prolonged hematuria who are resistant to conservative therapeutic measures. Ultrasound examination will be normal unless there is

papillary necrosis or a coincidental cause of hematuria, such as polycystic kidney disease, renal calculus, or tumor. Intravenous urography used to be the method of choice for diagnosis of papillary necrosis, but it does not distinguish reliably between papillary necrosis and other causes of filling defects in the pyelogram, including blood clots, neoplasm, calculus, and hemangioma. Ultrasound is therefore preferred, although it is suggested that contrast-enhanced computed tomography may better depict a full range of typical features.[32] The role of magnetic resonance imaging in this setting has not yet been sufficiently evaluated.

Cystoscopy is not routinely required but is indicated if the episode of hematuria is atypical, such as a first episode of macroscopic hematuria in a patient older than 40 years or an episode that persists for more than 2 weeks. Cystoscopy may also be required to lateralize the source of the bleeding if surgical intervention is considered (see later).

Renal angiography rarely identifies the bleeding source, but when identified, embolization can follow. However, the optimal approach in any institution depends on local experience with specific techniques.

Treatment

The therapeutic strategy for hematuria depends on the severity and duration of a specific bleeding episode. Bleeding will stop in most patients spontaneously or after bed rest, although it may occasionally last for weeks or months. About half of patients will have recurrent episodes.

Initial therapeutic measures include bed rest and interventions aimed at retardation of the sickling process in the anoxic renal medulla. A high urine flow rate should be induced by intravenous fluid administration and diuretics to further reduce medullary tonicity and the urine alkalinized by administration of sodium bicarbonate by mouth or by vein, with a target urine pH of 8. Blood transfusion with normal HbA is indicated if anemia becomes severe; this may also decrease the sickling process. If necessary, bladder irrigation is performed for removal of blood clots.

Hyperbaric oxygen therapy may be helpful but has not been formally evaluated. Irrigation of the pelvicalyceal system with silver nitrate has also been described. The antifibrinolytic agent ε-aminocaproic acid, although effective, may be associated with adverse renal outcomes and is not recommended.

Unilateral nephrectomy has occasionally been necessary in patients with persistent, life-threatening hematuria refractory to conservative approaches. Full evaluation for another cause of hematuria, including cystoscopy to exclude a bladder lesion and to establish which kidney is the source of bleeding, is required before proceeding with nephrectomy.

Urinary Tract Infection

Subjects with sickle cell disease have an increased susceptibility to bacterial infections; even low-grade bacteremia with a common organism may be fatal. In addition to the impaired immunity resulting from autosplenectomy, there is opsonic antibody deficiency, which predisposes to bacterial infections. The precise incidence of UTIs is not well defined. However, the incidence of asymptomatic bacteriuria during pregnancy and the puerperium appears to be twice as high in women with sickle cell disease or trait as in women without sickle cell disease and requires appropriate therapy (see Chapter 44).

Pyelonephritis and urosepsis, as with any infection, may precipitate a sickle cell crisis. The clinician should especially be aware of this possibility in young children, who often do not complain of urinary tract symptoms. Most common organisms isolated include *E. coli, Klebsiella* species, and other gram-negative *Enterobacteriaceae*. Invasive bacterial infections with *E. coli* occur especially in females after age 15 years, suggesting a greater chance of UTIs in relation to sexual activity.

Acute Kidney Injury

People with sickle cell disease sometimes present with features of acute kidney injury (AKI). Defined as a doubling of serum creatinine, AKI is reported in 10% of hospitalized patients with sickle cell anemia.[33] A potentially reversible renal dysfunction with significant reduction in GFR could occur during vaso-occlusive crises.[34]

Etiology

A pre-renal cause of AKI will be found in more than half of patients, especially volume depletion in the setting of sickle cell crisis. Patients with sickle cell disease are prone to AKI caused by volume depletion because of impaired urine-concentrating capacity; it is therefore typically nonoliguric. A less frequent pre-renal cause is congestive heart failure.

Typical intrinsic renal causes of AKI are rhabdomyolysis, sepsis, and drug nephrotoxicity. Less common are renal vein thrombosis and hepatorenal syndrome (caused by hemosiderosis-induced hepatic failure). Both exertional and nontraumatic rhabdomyolysis have been reported in patients with sickle cell disease; the latter especially occurs during a sickle cell crisis and has been ascribed to intravascular sickling and muscle ischemia. Rhabdomyolysis is a common finding in patients who develop multiorgan failure during severe sickle cell crises, in addition to the acute chest syndrome, which further contributes to AKI. The most common post-renal cause of AKI is urinary tract obstruction by necrotic papillae or blood clots.

Treatment

Treatment and recovery of renal function depend on the specific underlying pathologic process. Metabolic acidosis may be prominent and should be actively corrected with sodium bicarbonate. Patients with volume depletion have a favorable outcome after fluid replacement.[33] Renal function may recover in patients with sepsis and rhabdomyolysis, although temporary renal replacement therapy (RRT) may be necessary. AKI as a part of multiorgan failure during a severe sickle cell crisis may show a dramatic improvement with aggressive RBC transfusion therapy, although some renal function loss may persist.

Proteinuria and Nephrotic Syndrome

Microalbuminuria has been reported in 19% to 26% of children with sickle cell anemia.[35,36] The presence of microalbuminuria is directly related to age and inversely related to hemoglobin levels.[36] Proteinuria has been reported in 17% to 33% of patients with sickle cell disease by semiquantitative or dipstick measurement.[7,28] The prevalence of proteinuria is lower in patients with coinheritance of sickle cell anemia and α-thalassemia than in those with sickle cell anemia and intact α-globin genes (13% vs. 40%).[37] The "renoprotective" effect of α-globin gene microdeletions could be related to a lower mean corpuscular volume or lower erythrocyte hemoglobin concentration in sickle erythrocytes. The frequency of proteinuria increases with age (56% in patients 40 years or older), and its presence is associated with renal impairment.

The nephrotic syndrome has been estimated to occur in 4% of patients with sickle cell anemia. The eventual development of renal failure appears virtually inevitable once the patient has nephrotic syndrome.

Pathology

The most common pathologic lesion is FSGS,[22,23] which is also the major lesion in patients who develop renal failure (see Fig. 51-8). Another specific pathologic lesion is a form of membranoproliferative glomerulonephritis (MPGN) with mesangial expansion and basement membrane duplication.[3] The absence of immune complexes and electron-dense deposits discriminates this entity from idiopathic MPGN type I. It has been proposed that this form of MPGN is caused by intracapillary red cell fragmentation. Fragments of erythrocytes become lodged in isolated capillary loops and are continuously phagocytosed by mesangial cells. As a result, the mesangium expands and lays down new basement membrane material.

Patients may become hepatitis C positive from multiple blood transfusions, which may also be associated with MPGN, although it is rare with appropriate screening procedures before transfusion. In our series, hepatitis C positivity was observed in only one patient (0.26%), a reflection of the generally low seroprevalence rate in the environment.[28] On occasion, other causes have been reported, such as poststreptococcal glomerulonephritis, minimal change disease, and immune complex–mediated glomerulonephritis. Glomerulonephritis has also been described in association with aplastic crises in parvovirus infection. Renal vein thrombosis should be considered when nephrotic syndrome develops in sickle cell disease, but its incidence is not exactly known.

Treatment

Theoretically, dietary protein restriction may reduce hyperfiltration and retard the development of renal failure in those with FSGS, but this has not been evaluated specifically in sickle cell disease.

Short-term treatment with angiotensin-converting enzyme (ACE) inhibitors significantly reduces the degree of proteinuria without affecting blood pressure (BP) or renal hemodynamics. More prolonged ACE inhibition reduces proteinuria with a slight decrease in BP. Short-term angiotensin receptor blocker (ARB) use has led to regression of microalbuminuria, overt proteinuria, and improvement in GFR in sickle cell patients with nephropathy.[38] However, it remains to be established whether long-term treatment with ACE inhibitors or ARBs delays the development of progressive renal failure. Combinations of ACE inhibitor and hydroxyurea have been found to be useful in retarding progression of microalbuminuria to overt proteinuria.[35,39]

Prevention of hyperfiltration theoretically also can be obtained with nonsteroidal anti-inflammatory drugs (NSAIDs), but these drugs reduce RPF and GFR in sickle cell anemia and are thus contraindicated.

Sodium and Acid-Base Disturbances

Distal Tubular Function

Impaired potassium excretion and impaired urinary acidification are caused by an incomplete form of distal tubular acidosis. However, hyperkalemia and metabolic acidosis are not present under normal circumstances and may become manifested only during potassium or acid loading, with mild renal impairment or volume depletion, and during rhabdomyolysis.[16,17] Hyperkalemia may also develop more readily during treatment with NSAIDs, ACE inhibitors, β-blockers, potassium-sparing diuretics, or heparin.

Urine pH does not fall below 5 during acid loading tests unless maximal acidifying stimuli are used. The titratable acid and H^+ excretion is reduced, whereas the ammonium excretion is either normal or decreased. Metabolic acidosis that develops during renal impairment or intercurrent diseases in sickle cell disease requires active treatment with sodium bicarbonate because acidosis stimulates the sickling process. Plasma bicarbonate should be monitored routinely and oral sodium bicarbonate supplements given to keep it within the reference range.

Proximal Tubular Function

Proximal tubular function abnormalities modify solute handling, producing increased reabsorption of phosphate and increased secretion of uric acid. Hyperphosphatemia may develop easily when renal function declines, necessitating dietary phosphate restriction and the use of phosphate binders early in renal impairment. The increased uric acid secretion protects patients with sickle cell disease against hyperuricemia, with elevated uric acid production resulting from hemolysis. However, the incidence of hyperuricemia and risk for gout increase with age as renal function declines.

Hypertension

Epidemiology

The prevalence of hypertension in patients with sickle cell anemia is about 2% to 6%, which is significantly lower than in age- and gender-matched controls.[16,28,40] However, BP in patients with sickle cell anemia is higher than in matched patients with β-thalassemia and similar degrees of anemia. Hypertension in sickle cell anemia especially occurs in the presence of advanced renal failure.

Pathogenesis

It is not yet clear whether the relative hypotension in sickle cell patients compared with controls relates to the pathologic renal medullary condition in sickle cell disease or to other mechanisms. The kidney in sickle cell disease has a normal overall capacity for sodium conservation, despite a tendency to lose sodium and water through the medullary defect.[16,40] This sodium conservation in sickle cell disease may follow stimulation of the renin-angiotensin system, which has been described in some but not all studies. The relative hypotension may be related to general vasodilation, because skeletal vascular resistance is reduced in sickle cell patients. Increased production of vasodilatory prostaglandins or nitric oxide may be involved. Systemic vasodilation and increased flow is a compensatory mechanism for microcirculatory flow disturbances and intermittent microvascular occlusion.[41] In addition, reduced vascular reactivity has been demonstrated in sickle cell patients and may protect against BP elevation.[40]

Treatment

The antihypertensive treatment of choice is an ACE inhibitor or ARB because of the potential beneficial effects on the progression of proteinuria and renal failure and because of the reported increments in plasma renin activity. However, the risk for hyperkalemia is increased. There are no specific recommendations on target BP in sickle cell disease, and the targets for other nondiabetic nephropathies are appropriate.

An alternative therapeutic option is a calcium channel blocker, but CCBs recognized to worsen proteinuria, such as the short-acting dihydropyridines, should be avoided. Loop diuretics are less effective in patients with sickle cell disease because of the specific medullary defect.

Chronic Kidney Disease

Epidemiology

In a prospective, 25-year longitudinal study, chronic kidney disease (CKD) developed in 4.2% of 725 patients with sickle cell anemia and in 2.4% of 209 patients with HbSC.[42] The patients with sickle cell

anemia were much younger at the diagnosis of renal failure than those with HbSC (median age, 23.1 and 49.9 years, respectively). However, in another study of 368 patients with sickle cell anemia with an overall prevalence of CKD of 4.6%, the prevalence of CKD clearly increased with age.[43] The prevalence of CKD will probably increase even more in the future with further improved medical care and longer life expectancy. In our series, younger age at diagnosis and higher duration of sickle cell disease were found to strongly predict the development of nephropathy.[28]

Predictors of CKD are hypertension, proteinuria, hematuria, increasingly severe anemia, the nephrotic syndrome, and inheritance of the Bantu or Central African Republic β-globin gene cluster haplotype.[42] In addition to an apparent genetic predisposition, glomerular capillary hypertension and prolonged glomerular hyperfiltration seem to be important in the development of renal failure.

Natural History

Patients with sickle cell anemia and CKD have increased mortality compared with patients without renal failure (Fig. 51-10). Patients with renal failure are also prone to other manifestations of sickle-induced vasculopathy, such as cerebrovascular diseases, chronic restrictive lung disease, and leg ulcers, leading to frequent hospitalizations.[42] Adults with sickle cell disease and ESRD have an increased mortality risk (hazard ratio 2.80; 95% confidence interval 2.31 to 3.38) compared to those without sickle cell disease but with ESRD.[44] Patients with sickle cell disease and ESRD receiving predialysis care had lower mortality than those with sickle cell disease and ESRD who did not receive predialysis care (hazard ratio 0.67; 95% CI 0.45 to 0.99).

As nephropathy progresses in sickle cell disease, strategies aimed at retarding progression and preparations for eventual RRT should be initiated. Table 51-2 summarizes the changing profile of renal

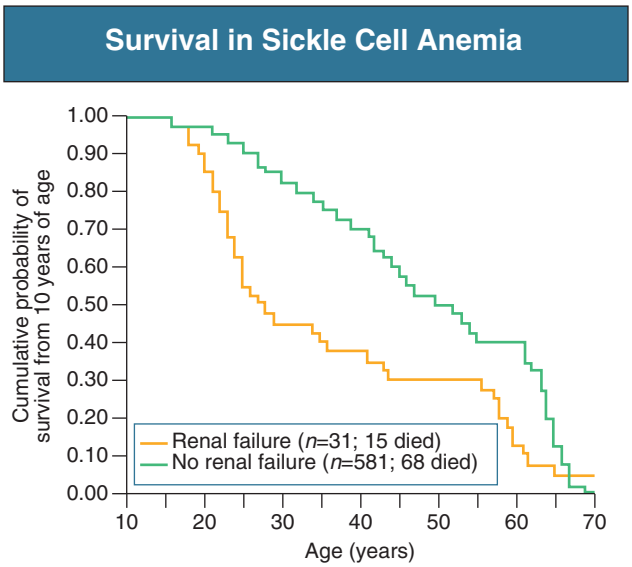

Figure 51-10 Survival in sickle cell anemia in the presence and absence of renal failure. *(Modified from reference 43.)*

Changing Profile of Renal Dysfunction in Sickle Cell Disease with Age and Available Treatment Options

Average Age (yr)	Clinical Observations	Process	Modifiers*	Treatment Options
1	Anemia, pain	Sickling	HbF level (+)	Hypertransfusion, hydroxyurea, zinc supplements
			Level of aberrant β-globin (±)	β-globin gene therapy
			Increased HbA level (+)	Bone marrow transplantation
5-10	Hematuria	Medullary congestion	Increased WBC adhesion, resultant RBC adhesion (–)	Hydration
			High blood oxygen level (+)	
	Increased GFR, decreased serum creatinine	Hyperperfusion	High prostaglandin E production (+)	ACE inhibitor Avoid NSAIDs
		Hypertrophy	Hypoxia (–)	Somatostatin analogue
		Papillary necrosis	High NO synthesis (+)	Hydration
			High caspase-3 level (+)	
			High HSP-70 level (+)	
			Increased COX-2 production (+)	
			High CRP level (–)	
			High HO-1 level (+)	
		Hyperfiltration	Increased angiotensin II production (+)	ACE inhibitor or ARB
			High prostacyclin level (+)	Prostacyclin analogue
15	Microalbuminuria	Hyperperfusion	High prostaglandin E production (+)	ACE inhibitor
20	High urinary NAG and β_2-microglobulin	Tubular damage	Unknown	No specific treatment
30	Proteinuria	Glomerular hypertension, FSGS	Increased angiotensin II production (+)	ACE inhibitor or ARB
35	Low GFR	Loss of glomerular function	Unknown	Strategies to retard CKD progression
40	Falling GFR	Further loss of glomerular function	Unknown	Strategies to retard CKD progression, preparation for RRT

Table 51-2 Changing profile of renal dysfunction in sickle cell disease with age and available treatment options. *ACE,* Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *CKD,* chronic kidney disease; *COX-2,* cyclooxygenase-2; *CRP,* C-reactive protein; *FSGS,* focal segmental glomerulosclerosis; *GFR,* glomerular filtration rate; *HbA,* hemoglobin A; *HbF,* fetal hemoglobin; *HO-1,* heme oxygenase 1; *HSP-70,* heat shock protein 70; *NAG, N*-acetylglucosamine; *NO,* nitric oxide; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *RBC,* red blood cell; *RRT,* renal replacement therapy; *WBC,* white blood cell. *(+), Ameliorating factor; (–), risk factor. *(Modified from reference 17.)*

dysfunction in sickle cell disease with age and available treatment options.[17]

Treatment

For the development of progressive renal failure to be delayed, it is important to control hypertension and to avoid the use of nephrotoxic drugs, especially NSAIDs. Although plausible, it remains to be established whether the reduction of the degree of proteinuria with ACE inhibitors or a low-protein diet retards the progression of renal failure.

The response to EPO therapy is poor, even when high doses are used during long treatment periods. EPO treatment predominantly results in the release of HbS-containing reticulocytes, with only a modest increase in the more stable HbF. A marked increase in hemoglobin levels, although unexpected, may precipitate sickle cell crisis. Routine use of EPO is therefore not recommended, but it can be tried on an individual basis with higher doses than needed in other forms of ESRD. As an alternative, supportive RBC transfusion may be necessary. Excessive iron accumulation should be prevented in patients undergoing regular transfusions, who are at risk for hemochromatosis, although organ dysfunction caused by tissue iron overload seems less predictable in sickle cell disease than in thalassemia major. Metabolic acidosis is also prominent and requires correction with sodium bicarbonate supplements.

In patients with sickle cell disease, ESRD has been treated successfully with hemodialysis, peritoneal dialysis, and transplantation. Hemodialysis has been used more frequently than peritoneal dialysis. Sickle cell crises are not common despite the potential for hypotension, hypoxemia, and cytokine release during hemodialysis. The 30-month survival of 77 patients predominantly treated with hemodialysis was 59%, comparable to survival in other patient groups with multisystem disorders receiving dialysis.

TRANSPLANTATION

Transplantation is an appropriate form of RRT in sickle cell nephropathy. Patient survival in sickle cell disease after kidney transplantation has recently improved. Survival at 6 years was lower among sickle cell disease patients in the early era (1988-1999) compared with other diagnoses (56% vs. 78%; $P < .001$).[45] In the more recent era (2000-2011), patient survival at 6 years in sickle cell disease improved (70%) and was no longer significantly lower than for other diagnoses (80%; $P = .07$).[45] Patient survival among sickle cell recipients in the recent era is comparable to survival in matched diabetic kidney transplant recipients.[45]

In sickle cell disease patients, perioperative risks such as severe crisis and massive sickling can be reduced by preoperative transfusions of normal blood, thereby reducing the proportion of HbS. After transplantation, hematocrit increases and may even be higher than in patients with sickle cell disease and normal renal function. Sickle cell crisis may occur after transplantation, but it is not yet clear whether the increase in hematocrit enhances the risk for a crisis. Standard immunosuppressive therapy does not increase the risk for sickle cell crisis. However, caution is warranted with the use of antilymphocyte antibodies because the onset of a crisis has been related to this therapy in a few patients, perhaps because of increased cytokine release. The recurrence of hyposthenuria and sickle cell nephropathy after transplantation has occasionally been described.

Hematopoietic cell transplantation is the only curative treatment for sickle cell disease. However, this therapy has been used only on a very limited scale thus far, when patients have serious complications of sickle cell disease, such as cerebrovascular disease in children who are dependent on transfusions.[5]

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CHAPTER 52

Congenital Anomalies of the Kidney and Urinary Tract

John O. Connolly and Guy H. Neild

Congenital anomalies of the kidney and urinary tract can result in renal problems and renal failure. Almost half of children who develop end-stage renal disease (ESRD) have asymmetric, irregularly shaped kidneys.[1,2] This appearance, often referred to as "bilateral renal scarring," is frequently associated with lower urinary tract anomalies that include vesicoureteral reflux (VUR). The most serious conditions involve bladder outflow obstruction, and many anomalies are now detected antenatally.

These cases were previously described as *reflux nephropathy* or *chronic pyelonephritis.* With advances in genetics and developmental biology, however, it is becoming clear that many anomalies are caused by primary renal malformations, or *renal dysplasia,* often associated with congenital malformations of the ureter, bladder, and urethra. This is a change from the view that renal scarring and damage are secondary to the outflow problem and ureteral reflux. Although still somewhat debatable, the British Association for Pediatric Nephrology has stated that the clinical distinction between reflux nephropathy and renal dysplasia is arbitrary and unnecessary.[1]

CLINICAL PRINCIPLES

Congenital renal tract abnormalities may present in one of five settings:

1. *Antenatal diagnosis by fetal ultrasound screening*
2. *Failure to thrive in an infant or young child*
3. *Investigation of urinary tract infection (UTI)*
4. *An incidental finding in a child or adult*
5. *An adult with abnormal urinalysis, stones, hypertension, or renal impairment*

The identification of these problems always poses the following questions:

- What is the cause?
- What is the natural history?
- Is surgical intervention required?

Such patients fall into two broad groups. The first group of patients appear to have normal bladders without outflow obstruction and normal-caliber ureters when not micturating, described as having either primary VUR or primary renal dysplasia. The second group has some form of bladder outflow dysfunction that causes secondary VUR and dilated upper urinary tracts, the most common cause of which is posterior urethral valves in males.

As predicted by the Brenner hypothesis,[3] small asymmetric kidneys with reduced glomerular filtration rate (GFR) develop all the features of glomerular hyperfiltration, with the onset of progressive renal failure signaled by increasing proteinuria. This can now be significantly modified by treatment with renin-angiotensin blockade.[4,5] The details of antenatal and pediatric management of these patients are beyond the scope of this chapter, which focuses on management in adolescence and adult life.

DEVELOPMENT OF THE URINARY TRACT

The urinary tract develops from the cloaca and intermediate mesoderm in parallel with the early differentiation of the metanephric blastema (future kidney)[6-8] (Fig. 52-1). At the fifth week of gestation, the mesonephric (wolffian) duct connects to the allantois and the cloaca. By the sixth week, the urorectal fold appears and divides this cavity, which separates the future urinary system (urogenital sinus) from the rectum (hind gut). Growth of the anterior abdominal wall between the allantois and the urogenital membrane is accompanied by an increase in size and capacity of this bladder precursor. The allantois remains attached to the apex of the fetal bladder and extends into the umbilical root, although it loses its patency and persists as the urachal remnant, the median umbilical ligament, which connects the bladder to the umbilicus. By the seventh week, there is a separate opening of the mesonephric duct into the bladder at what will become the vesicoureteral opening and the area known as the *trigone.* The distal part of the primitive urogenital sinus will form the definitive urogenital sinus. In females, this gives rise to the entire urethra and the vestibule of the vagina. In males, it gives rise to the posterior urethra, whereas the anterior urethra is formed from the closure of the urethral folds.

In the 6-week embryo, the mesonephric and paramesonephric (müllerian) ducts run in parallel. By 7 weeks, in the male, the müllerian duct starts to regress, and the wolffian duct will eventually develop into the epididymis and the caudal part of the vas deferens. In the female, the müllerian ducts fuse to become the uterovaginal cord, which opens into the urogenital sinus and will develop into the vagina.

As the urogenital tract develops, there is simultaneous development of the fetal kidney (Fig. 52-1). The ureteric bud arises from the distal end of the wolffian duct as an unbranched diverticulum (day 28) and invades the adjacent metanephric mesenchyme, initiating the branching collecting duct system within the primitive kidney. In the absence of the ureteral bud, the metanephric kidney does not form. Fetal urine reaches the bladder by 8 to 10 weeks and makes a significant contribution to the amniotic fluid by 16 weeks. Nephron formation is complete by 34 weeks' gestation.

Renal development is orchestrated by the expression of transcription factors, growth and survival factors, and adhesion molecules.[6,8,9] Mutations of genes encoding all classes of these molecules cause

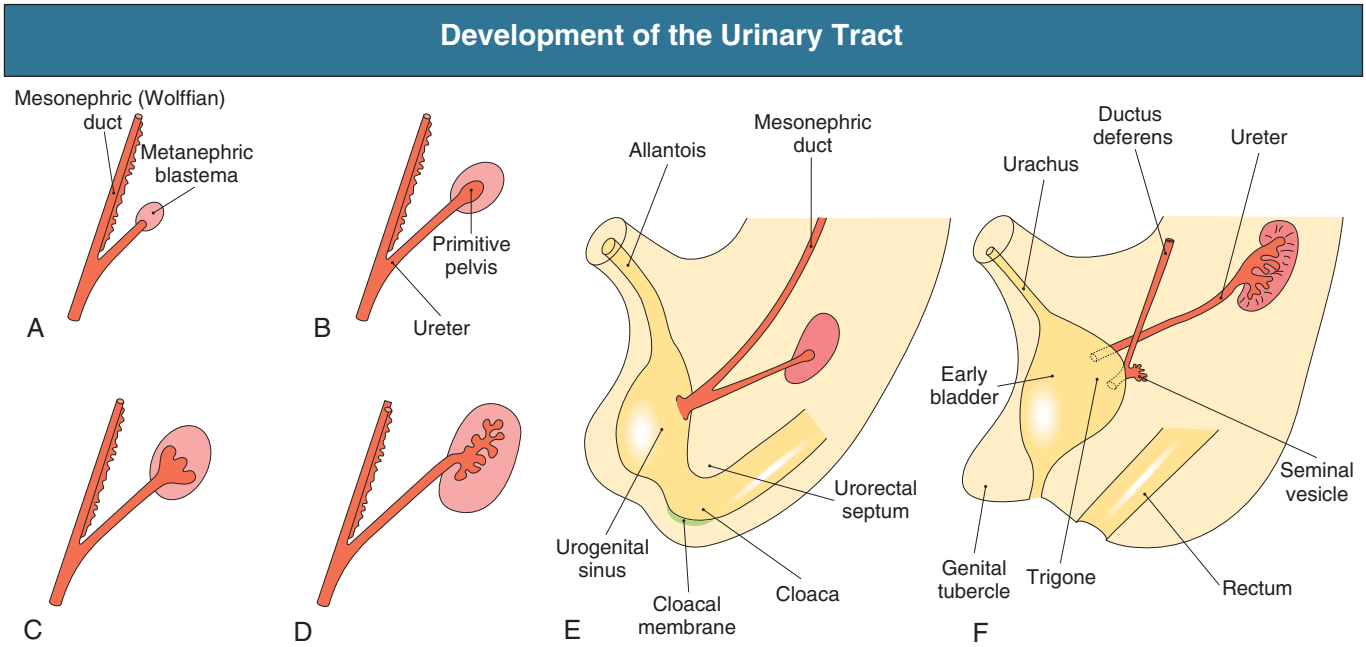

Figure 52-1 Development of the urinary tract. Growth and development of the ureter, pelvis, and calyces are shown in parts **A** to **D. A,** The metanephric kidneys first become detectable as small areas in the mesoderm close to the aorta. The primitive epithelial ureter buds off from the mesonephric duct and makes contact with the metanephric mesenchyme. **B,** Under the influence of signals from the ureter, the mesenchyme condenses and proliferates around the ureteral tip, with simultaneous elongation and branching of the ureteral tip. **C** and **D,** A primitive pelvis appears, then branches to form the divisions of the calyces. The branching process continues, with the epithelial system eventually differentiating into the nephrons of the renal parenchyma. As the fetus grows, the kidney ascends because of the continuous rostral growth. **E,** Growth and development of the cloaca during weeks 5 to 6 of gestation. **F,** Growth and development of the urogenital sinus into bladder and outflow tract during weeks 8 to 9.

urinary tract malformations in mice.[8-10] One family of transcription factor proteins contains the paired DNA-binding domain and is encoded by the *PAX* genes. Studies in mice show that these *PAX* genes regulate the development of brain, eyes, lymphoid system, musculature, neural crest, and vertebrae.[11,12] *PAX2* is expressed in the metanephros and in cell lineages that are forming nephrons and also in those that are destined to differentiate into the ureter, renal pelvis, and branching collecting duct system. The ablation of a single *PAX2* allele in knockout mice causes impaired metanephric growth and fewer nephrons than normal as well as megaureter, a finding consistent with gross VUR.[12] *WT1,* which is mutated in a proportion of Wilms tumors, is another transcription factor whose mutation is associated with abnormal urinary tract development.

Normal development appears to depend on urine flow from the fetal kidney. This requires peristalsis and no anatomic obstruction to flow. A number of diverse defects can now be unified as it becomes clear they play some key role in peristalsis. This may be caused by defects in smooth muscle development or innervations in the ureter. For example, mice lacking the transcription factor "teashirt 3" fail to develop normal smooth muscle in the ureter and have congenital hydronephrosis without anatomic obstruction.[13] Angiotensin plays a key role in initiating the peristalsis, and mice in whom the angiotensin type 1 receptor is knocked out fail to develop a renal pelvis and die of renal failure.[9]

Angiotensin type 2 receptor gene null mutant mice display congenital anomalies of the kidney and urinary tract. These include unilateral agenesis, unilateral megaureter and hydronephrosis, and pelviureteral junction (PUJ) obstruction and mimic a range of abnormalities found in humans.[9] Administration of angiotensin-converting enzyme (ACE) inhibitors throughout pregnancy in humans can cause hypotension and anuria in the baby with histologic features of renal tubular dysplasia. This phenotype is also caused by mutations in genes encoding renin, angiotensinogen, ACE, and angiotensin II receptor type 1. Little is yet known about the genetics of congenital bladder outlet obstruction.[13]

Other syndromes associated with dysplasia and agenesis in which the mutation is now known include branchio-oto-renal syndrome (*EYA1* mutation, transcription factor–like protein), Fraser syndrome (*FRAS1* mutation, putative cell adhesion molecule), Kallmann syndrome (X-linked form, *KAL1* mutation, cell adhesion molecule; autosomal form, *FGFR1* mutation, growth factor receptor), and renal cysts and diabetes syndrome (*HNF1* mutation, transcription factor).[14]

RENAL MALFORMATIONS

Congenitally abnormal kidneys may be large or small, cystic or irregular in outline, and absent or misplaced. These conditions were traditionally discussed on the basis of findings on intravenous urography (IVU), but the findings on computed tomography (CT) and magnetic resonance imaging (MRI) are now increasingly being emphasized.

Large Kidneys

Enlarged kidneys resulting from congenital problems are usually hydronephrotic or cystic. Wilms' tumor must also be considered. The differential diagnosis in adults of enlarged kidneys, both congenital and acquired, is shown in Chapter 5 (see Fig. 5-1), and the differential diagnosis of cystic kidney disease is discussed further in Chapters 46 and 47.

Definitions of Renal Dysplasia and Malformation	
Term	**Characteristics**
Renal agenesis	Absence of the kidney or an identifiable metanephric structure
Renal aplasia	Severe dysplasia with extremely small kidney, sometimes identifiable only by histologic examination
Renal dysplasia	Abnormal differentiation of renal parenchyma with development of abnormal structures, including primitive ducts surrounded by collars of connective tissue, metaplastic cartilage, variety of nonspecific malformations such as preglomeruli of fetal type, and reduced branching of collecting ducts with cystic dilations and primitive tubules
Renal hypoplasia	Significantly reduced renal mass and nephron number without evidence of maldevelopment of parenchyma
Renal multicystic dysplasia	Severe cystic dysplasia with extremely enlarged kidney full of cystic structures; occurs as an isolated renal lesion in response to ureteral atresia and urethral obstruction; 10% of patients have a family history.

Table 52-1 **Definitions of renal dysplasia and malformation.**

Irregular Kidneys

Irregularity of the renal outline may result from fetal lobulation or a "dromedary hump," neither of which has any functional implications. Much more important is the diagnosis of renal dysplasia.

Renal Dysplasia

Table 52-1 presents the range of dysplastic and other malformations of the kidney. Clearly, abnormalities of the ureter, bladder, and urethra are often associated with renal dysplasia.[15,16] All types of renal dysplasia can also occur as isolated developmental anomalies. Renal dysplasia, although typically producing small, irregular kidneys, may be cystic or multicystic renal dysplasia.

Renal Hypoplasia (Oligomeganephronia)

Renal hypoplasia is defined as a congenitally small kidney (two standard deviations below the expected mean) that lacks evidence of either parenchymal maldifferentiation (renal dysplasia) or acquired disease sufficient to explain the reduced size. The term is often used loosely, however, and most patients with a small kidney and other malformations will have *oligomeganephronia.* This is a type of renal hypoplasia resulting from a congenital reduction in the number of nephrons. It results from arrested development of the metanephric blastema at 14 to 20 weeks of gestation with subsequent hypertrophy of glomeruli and tubules in the kidney. The hypertrophy and hyperfiltration result in progressive nephron injury and sclerosis later in life. Oligomeganephronia is recognized on renal biopsy by the large size of the glomeruli and tubules and the small number of glomeruli seen in a good core of renal cortex. It is reported in congenital syndromes caused by mutations in *PAX2* and hepatocyte nuclear factor 1β *(HNF1β).*

Differential Diagnosis of Scarred Kidneys

Dysplasia Versus Reflux Progressive scarring and renal failure were once considered to be caused by chronic parenchymal infection (so-called chronic pyelonephritis) and were regarded as a consequence of VUR. The 1980s, however, saw a retreat from the paradigm of the primary role of infection, and emphasis was placed on scarring as a result of reflux and the progressive nature of the glomerular lesion associated with glomerular hypertension (or hyperfiltration), so-called reflux nephropathy.[3,17,18] The emphasis is changing again to the concept that scarring is often a consequence of renal dysplasia, and that the reflux is a secondary or incidental feature (Fig. 52-2). Thus, irregular kidneys with normal-caliber ureters are more likely to be caused by primary dysplasia, and no evidence of VUR may be seen.

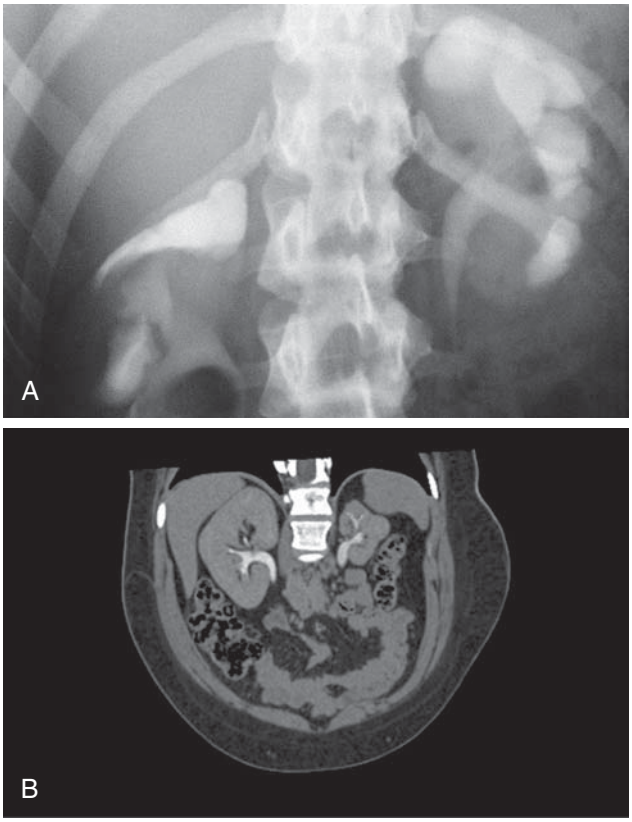

Figure 52-2 **Renal dysplasia. A,** Intravenous urogram (IVU) shows gross bilateral scarring in a 20-year-old woman who has been assessed since age 2 years. Progressive scarring has been observed in the absence of urinary tract infections and obstruction. This probably represents primary renal dysplasia. **B,** Computed tomography (CT) IVU shows gross scarring of right kidney. *(Courtesy Dr. A. Kirkham, University College Hospitals, London.)*

Renal Scarring in Adults A practical clinical problem is the differential diagnosis of scarred, asymmetric kidneys. With older patients, the differential diagnosis of scarred or "lumpy bumpy" kidneys widens. Often attributed to analgesic nephropathy in the 1970s, this appearance now is often designated "reflux nephropathy." In older patients, multiple scarring from atheromatous arterial disease and embolization of the kidney is an increasingly important cause of renal failure. The diagnosis has historically been made by the radiologic features on IVU, but in practice, patients often have advanced renal impairment and are unable to excrete enough radiocontrast to delineate the anatomy of the calyces and pelvis and their relationship to the scarring. Newer techniques that include CT and MR urography have supplanted the IVU.[19] With urologic conditions, there will be distortion and clubbing of calyces; with other conditions, the calyceal pattern should be normal, except for examples of papillary necrosis (Fig. 52-3). Scarring is best demonstrated by technetium 99m–labeled dimercaptosuccinic acid (^{99m}Tc-DMSA) scintigraphy.

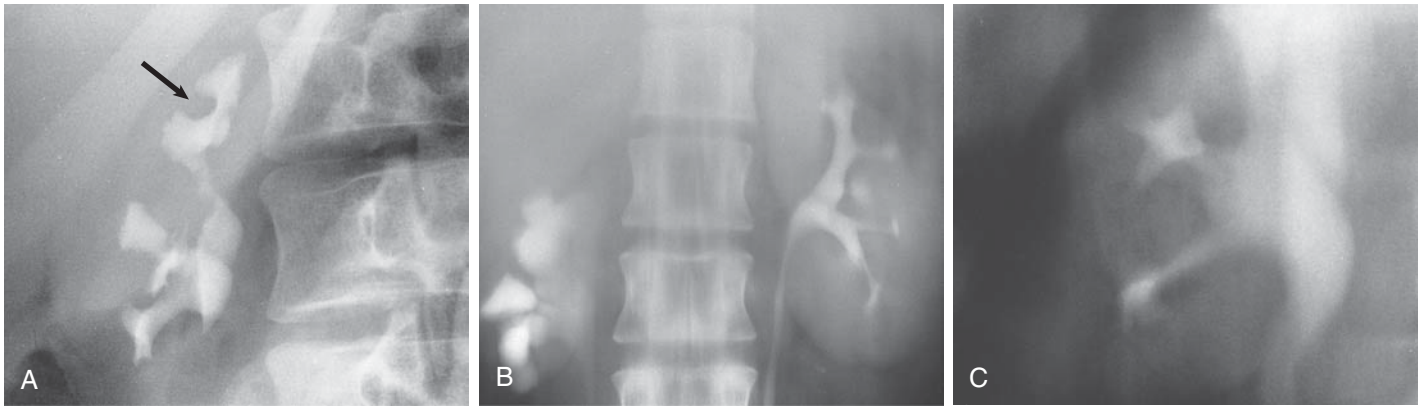

Figure 52-3 Differential diagnosis of "lumpy bumpy" kidneys from appearances on intravenous urography. A, Sickle cell disease: papillary necrosis. Missing papillae leave a round hole in the medulla *(arrow)* and give a clubbed appearance. Otherwise, the calyceal architecture is relatively well preserved. **B,** Reflux nephropathy. There is gross scarring and distortion of the calyceal pattern of the right kidney, giving rise to clubbed appearance of the dilated calyces. With reflux, there is a predilection for scarring of the upper and lower poles; with papillary necrosis or analgesic nephropathy, changes are less predictable. **C,** Analgesic nephropathy. The uniformly small shrunken kidney has relative preservation of the calyceal pattern. A plain film showed areas of calcification in both kidneys.

Absent Kidneys

Unilateral Renal Agenesis

Complete absence of one kidney occurs in 1 in 520 to 1000 births. It can be familial, and the term *hereditary renal aplasia* is used by pediatricians. It is an autosomal dominant trait with incomplete penetrance and variable expression and can be associated with bilateral renal agenesis or severe dysplasia. In some families, mutations in uroplakin-IIIa are found.[20]

Typically, there is no ureter, and the ipsilateral half of the bladder trigone is missing. The remaining kidney is usually hypertrophic, but it may be ectopic, malrotated, or hydronephrotic with a megaureter. The more severe the dysplasia of the remaining kidney, the earlier is the presentation. The ipsilateral testis and seminal tract are usually absent, and in 10% of cases, the adrenal gland is also missing. Girls can have an absent fallopian tube or ovary or malformation of the vagina or uterus. Other associations include imperforate anus and malformations of the vertebrae and cardiovascular system. Agenesis could result from failure in formation of the metanephros or the ureteral bud; however, in association with cloacal abnormalities, the ureteral bud is more likely.

Normality of the single kidney should be confirmed by ^{99m}Tc-DMSA scintigraphy, normal isotopic GFR, and absence of proteinuria. If the remaining kidney is not normal, lifelong follow-up is necessary. Ultrasound of the kidneys is recommended in first-degree relatives in all families in whom there is an individual with unilateral or bilateral renal agenesis.

Bilateral Renal Agenesis

Bilateral renal agenesis is lethal. It is associated with pulmonary hypoplasia and a characteristic facial appearance (Potter facies) caused by intrauterine compression, which is a consequence of oligohydramnios. The prevalence is about 1 in 10,000 births, with risk for occurrence in siblings of about 3%, unless there is a family history of agenesis, when risk rises to 15% to 20%.

Misplaced Kidneys

Renal Ectopia, Malrotation, and Crossed Fused Kidneys

The starting position of the fetal kidney is deep in the pelvis. Kidneys that fail to ascend properly and therefore remain lower than usual occur in 1 in 800 births (Fig. 52-4; see also Fig. 5-16). During development and ascent of the kidney, the renal pelvis comes to face more medially. The most common anomaly is for the pelvis to face forward. The more ectopic the kidney, the more severe is the rotation and more abnormal the appearance. In more than 90% of ectopia, there is fusion of both kidneys. This is now best visualized on CT or MR urography (Fig. 52-5). Symptoms and complications, if any, are caused by associated reflux or PUJ obstruction.

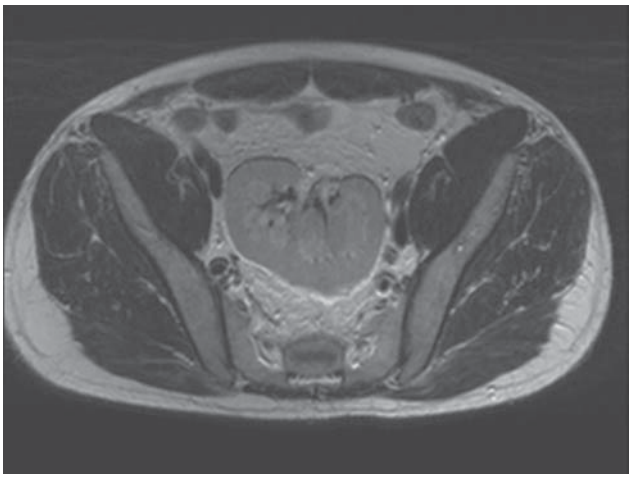

Figure 52-4 Single pelvic kidney. Magnetic resonance (MR) scan, transverse section, shows single midline pelvic kidney. *(Courtesy Dr. A. Kirkham, University College Hospitals, London.)*

Horseshoe Kidney

If both kidneys are low, they may join at the lower pole and are usually drained by two ureters (Fig. 52-6). The kidneys lie lower than normal, and further ascent is prevented by the root of the inferior mesenteric artery. Horseshoe kidney occurs in 1 in 400 to 1800 births and is more common in males (2:1). Patients present, if at all, with complications of reflux, obstruction, or stone formation.

Calyceal Abnormalities

Hydrocalyx and Hydrocalycosis

Dilated calyces are usually caused by obstruction. Focal dilation can also be caused by congenital infundibular stenosis, extrinsic compression from vessel or tumor, stones, or tuberculosis. If obstruction

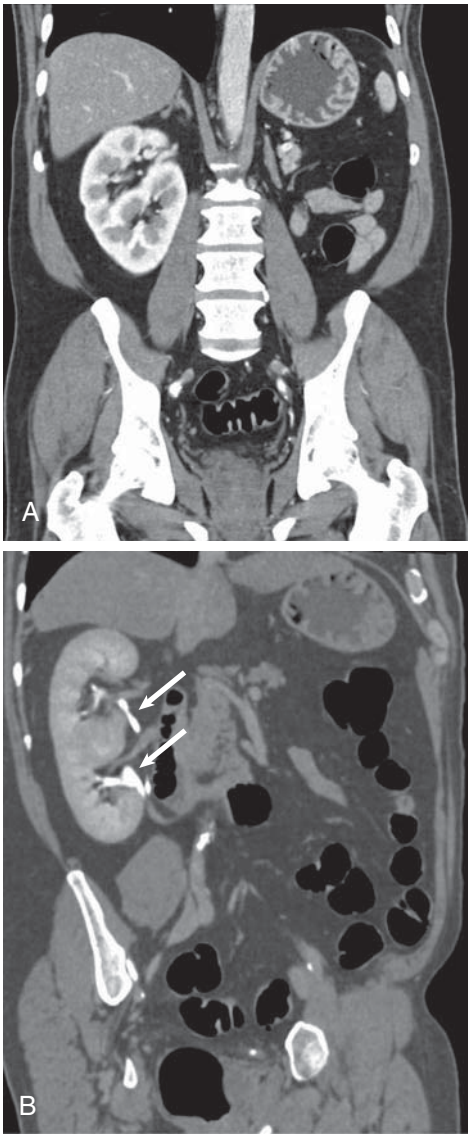

Figure 52-5 Crossed fused ectopia. A, MR scan shows fused kidneys on right. **B,** There are two ureters *(arrows). (Courtesy Dr. A. Kirkham, University College Hospitals, London.)*

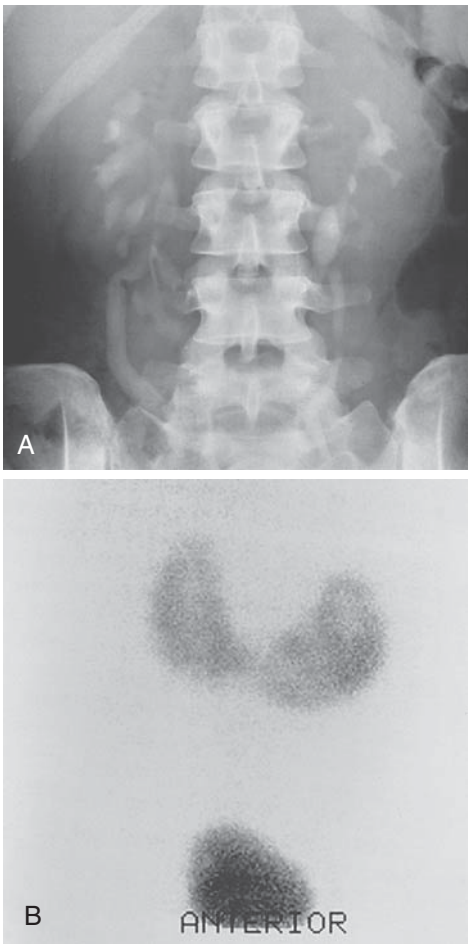

Figure 52-6 Horseshoe kidney. A, IVU soon after pregnancy in a 25-year-old woman shows not only the horseshoe kidney joining in the midline but also dilated ureters as a transient effect of pregnancy. **B,** Dimercaptosuccinate scan shows a horseshoe kidney.

is excluded, the appearance is likely to be a congenital abnormality and can be an incidental finding. Moreover, if the GFR is normal and the divided function of the kidneys is 50:50, surgery to "improve" the anatomy should not be attempted.

Megacalycosis

In megacalycosis, there is bizarre dysplasia of the calyceal system with an increase in the number of calyces. There is no obstruction, and the cause is malformation of renal papillae. Megacalycosis is congenital, usually unilateral, and an incidental finding. It is much more common in males (6:1) and occurs only in Caucasians. Bilateral disease is confined to males, and segmental, unilateral disease to females, which suggests an X-linked partially recessive gene with reduced penetrance in females. There may be an associated ipsilateral segmental megaureter, usually affecting the distal third.

Calyceal Diverticulum (Calyceal Cyst)

A calyceal diverticulum is a cavity peripheral to a minor calyx that is not a closed cyst but rather is connected to the calyx by a narrow channel. It is usually an incidental finding in 5 per 1000 IVUs and is best seen on a delayed film (Fig. 52-7). If a calyceal diverticulum is present, symptoms relate to stones or infection within the cavity.

Bardet-Biedl Syndrome

Multiple calyceal clubbing and calyceal diverticula are the characteristic features of the renal dysplasia seen in Bardet-Biedl syndrome (formerly known as Laurence-Moon-Biedl syndrome).[21] This autosomal recessive condition is characterized by retinitis pigmentosa, dysmorphic extremities (sometimes with polydactyly), obesity, and hypogonadism. Calyceal malformation is associated with parenchymal dysplasia; renal failure in early adult life is common. Since it was shown that Bardet-Biedl syndrome was caused by a defect of the basal body of ciliated cells,[22] mutations in 15 genes coding for different proteins located in the basal body and cilia of the cell have been reported, making the syndrome an archetypal ciliopathy.

Pelviureteral Junction Obstruction

In children, PUJ obstruction is one of the most frequent causes of obstructive uropathy. The condition is usually congenital but can have an acquired mechanical basis caused by stenosis or external compression from adhesions, aberrant lower pole vessels, or kinking of the most proximal ureter. Associated abnormalities are common, and up to 50% of infants have another urologic abnormality, such as

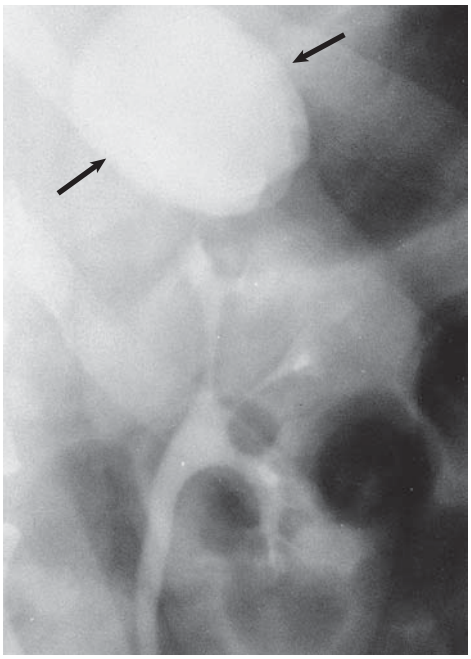

Figure 52-7 Calyceal cyst. IVU shows an upper pole calyceal cyst filled with contrast *(arrows)*. Plain abdominal radiograph showed a group of stones in the floor of the cyst.

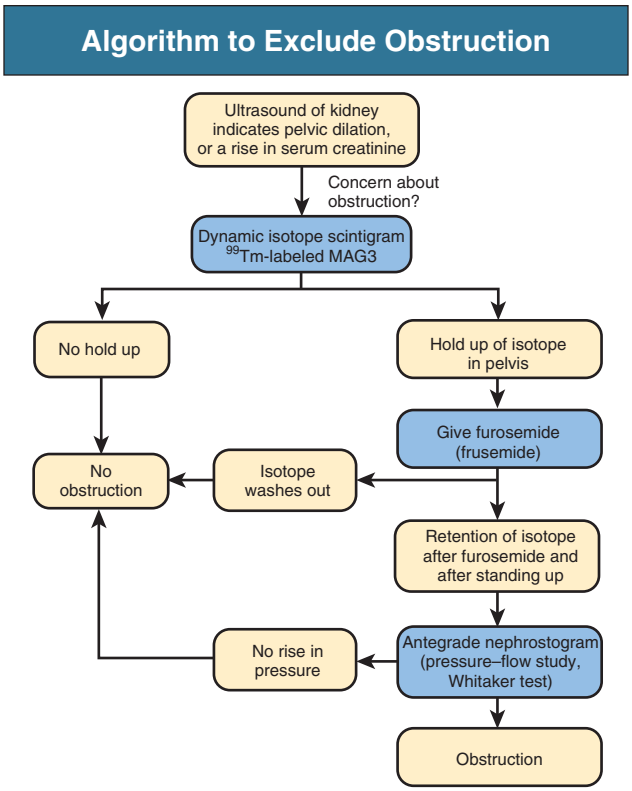

Figure 52-8 Algorithm to exclude pelviureteral junction (PUJ) obstruction. Diagnostic path used to differentiate between significant PUJ obstruction and congenital ectasia of renal pelvis.

contralateral PUJ, contralateral renal dysplastic and multicystic kidney, minor degrees of VUR, and contralateral renal agenesis.

Older children can present with an abdominal mass or with pain in the flank, hematuria secondary to mild trauma, or UTI. Hypertension is unusual but can occur temporarily after surgical correction.

Diagnostic procedures need to differentiate between significant obstruction that requires surgical correction and congenital ectasia of the renal pelvis, in which case surgery is not indicated (Fig. 52-8). Indications for surgical intervention include impairment of renal function, pyelonephritis, renal stones, and pain. Kidneys with good function can generally be left alone, and surgery is indicated only when function is clearly shown to deteriorate.[23]

Gonadal Dysgenesis

The problems of intersex, gender identity, and micropenis are beyond the scope of this chapter and rarely encountered in adult practice. Patients will be met, however, with ESRD who are phenotypically female but are genotype XY and have mutations of *WT1* (Denys-Drash and Frasier syndromes). They have gonadal dysgenesis and must have their streak ovaries removed; otherwise, gonadoblastomas will develop.

URETERAL ABNORMALITIES

The Ureter

The ureter is lined by a multilayered, watertight epithelium (urothelium) surrounded by smooth muscle that generates peristaltic waves distally from pelvis to bladder. The molecular mechanism and growth factors initiating and regulating ureteric budding and branching are increasingly understood, and some genes already implicated in ureteric dysplasia include *PAX2, HNF1β, GATA3, ROBO2,* and *UPK3A*.[24]

Duplex Ureters

Duplication of the ureter and the renal pelvis is a common anomaly, with an incidence of about 1 in 150 births; unilateral duplication is six times more frequent than bilateral. It is more common in girls. If duplication has been detected in a patient, the likelihood of another sibling with duplication rises to 1 in 8.

Pathogenesis

If the ureteral bud bifurcates after its origin from the mesonephric duct but arises at a normal site, an incomplete ureteral duplication with a Y ureter will develop.[7] Complete ureteral duplication occurs if there are two ureteral buds, one in the normal location and the other in a low position. The normal bud ends in a correct site on the trigone in the bladder and is nonrefluxing. The lower bud, representing the ureter of the lower pole of the kidney, ends in the bladder as a lateral orifice with a short submucosal tunnel. The lower pole ureter is therefore often associated with VUR, and scarring of the lower pole can result.

If there are two ureteral buds, one with a normal location and one with a high position, the upper ureter is incorporated into the developing bladder, ending more distally and medial to the normal one. Thus, the upper pole ureter ends ectopically, and because of obstruction or dysplasia, there is often severe scarring of the upper pole moiety.

Clinical Manifestations

In most adult patients, ureteral reduplication is asymptomatic and causes no long-term problems. Children with ureteral duplication often have VUR. The spontaneous disappearance of reflux is less common in duplex ureters than in patients with a single ureter.[25]

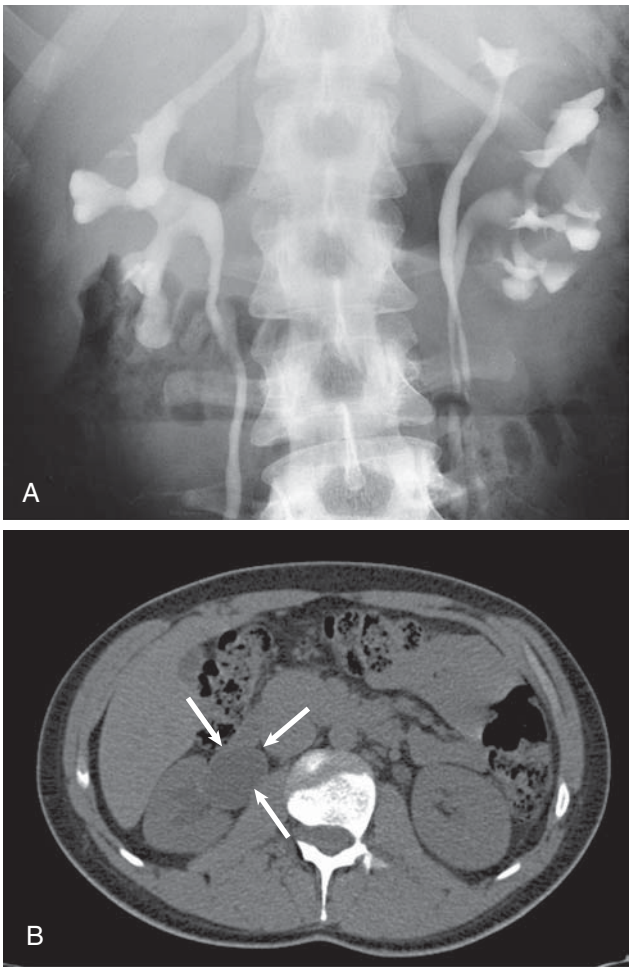

Figure 52-9 Duplex kidney. A, IVU shows a duplex left kidney. The lower pole is scarred and shows evidence of reflux damage. The two ureters entered the bladder separately, with the lower pole ureter in the abnormal location. The right kidney also shows features of reflux, with clubbing of the calyces and some scarring. **B,** CT scan shows an isolated right-sided megaureter *(arrows)*.

Duplex ureters are best diagnosed by CT urogram. PUJ obstruction of the ureter draining the lower pole of the kidney can occur.

Associated conditions, such as ectopic ureters and ureterocele (see later discussion), usually cause problems in early life and therefore have been addressed by adolescence. Upper pole scarring is associated with an ectopic ureter, and lower pole scarring with VUR (Fig. 52-9, *A*).

Ectopic Ureters

Ectopic ureters are almost always associated with ureteral reduplication, and 10% are bilateral. There is a female-male ratio of 7:1. The ectopic ureter comes from the upper pole and inserts into the bladder more distally and toward the bladder neck, or it opens into the upper urethra. In females, the ureter may end in the urethra, vagina, or vulva, and patients present with incontinence, UTIs, or a persistent vaginal discharge, particularly if the external sphincter is damaged, as during labor.

Ectopic ureters are rare in males and present as UTI. Usually, there is a single ureter associated with a dysplastic kidney, which ends in the posterior urethra, ejaculatory duct, seminal vesicle, or vas. Males are usually continent because the ureter is proximal to the external sphincter.

Ectopic ureters are best visualized by CT or MR urography. A voiding cystourethrogram shows reflux into the lower pole of the kidney in 50% of patients.

Ureterocele

Ureteroceles are cystic dilations of the terminal segments of the ureter and are caused by maldevelopment of the caudal ureter. Ureteroceles affect females more than males (4:1) and almost exclusively affect Caucasians, and 10% are bilateral. Ectopic ureters and ureters with ureteroceles frequently (80%) drain the upper pole and are often associated with dysplastic or nonfunctional renal tissue. These usually present in childhood with infection; when large, they can obstruct the bladder neck or even the contralateral ureter. In adults, ureteroceles typically present with stones in the lower ureter.

The treatment of simple ureteroceles is surgical excision with reimplantation of the ureter or simple incision if they subtend a well-functioning moiety. There are usually no medical sequelae.

Megaureter

Isolated dilation of the ureter does not necessarily imply obstruction. There are three broad groups of conditions with widely dilated ureters, as follows:

1. Obstruction of the ureter itself. This may be intrinsic (e.g., stone) or extrinsic (e.g., retroperitoneal fibrosis); it is not associated with reflux.
2. Bladder outflow obstruction, with secondary ureteral obstruction. Examples include a neuropathic bladder and posterior urethral valves; this may or may not be associated with reflux.
3. A dilated but nonobstructed ureter. This often occurs without reflux, and there can be normal renal function; this may be caused by an adynamic segment of the lower ureter (Fig. 52-9, *B*).

Pathogenesis

In the normal ureter, there is a characteristic helical orientation of muscle fibers. When the megaureter is secondary to bladder outflow obstruction, there is muscle hyperplasia and hypertrophy of the ureteral wall. In megaureters with no apparent cause, a variety of abnormalities of muscle orientation are described, or there may even be absence of muscle fibers at the proximal end of the undilated segment.

Electron microscopy shows an increase in collagen between the muscle bundles at the level of the obstructing segment. Obstruction appears to be caused by a failure of peristalsis through the distal ureteral segment.

Clinical Manifestations

Most cases of megaureter associated with obstruction present in childhood with severe infections, often complicated by septicemia. These patients have a high incidence of other congenital abnormalities. In less severe cases or with no obstruction, patients can present with abdominal pain, loin pain, hematuria, and UTI. Renal stones can form easily in the dilated systems. The exclusion of obstruction is often established only by an antegrade pressure-flow study (Whitaker test), in which a nephrostomy is placed in the renal pelvis and contrast material infused at 10 ml/min.[26]

Treatment

A definitive diagnosis must be made on whether an obstruction exists (see Fig. 52-8). The current view is that patients with asymptomatic nonobstructed disease should be managed conservatively, and most do well with this approach.

BLADDER AND OUTFLOW DISORDERS

Prune-belly Syndrome

The prune-belly syndrome occurs in males and consists of absence of the muscles of the anterior abdominal wall, bizarre malformations of the urinary tract with gross dilation of the bladder and ureters, and bilateral undescended testes.[27-29] When the disorder is diagnosed early, renal outcome is related to the degree of renal dysplasia. There are incomplete forms of prune-belly syndrome (pseudo-prune). Rarely, a similar megacystis or megaureter may be seen in a male or female patient.

Pathogenesis

No gene defect or unifying hypothesis has emerged to explain these features. The incidence of prune-belly syndrome varies from 1 : 30,000 to 1 : 52,000 births. There are a few familial cases, and the condition has been reported in twins, but there is 100% discordance reported in identical twins, which is a powerful argument against a genetic basis. There is evidence for a primary, localized arrest of mesenchymal development. This is supported by the lack of prostatic differentiation; the epithelial element in the prostate is absent or hypoplastic. Ultrastructural studies of the ureter show massive replacement of smooth muscle with fibrous and collagen tissue and the absence of nerve plexuses. An almost identical syndrome can result from fetal urethral obstruction, including urethral atresia.

Clinical Manifestations

The prognosis depends on the degree of renal dysplasia and injury. Three prune-belly groups can be distinguished. In group I (20%), complete urethral obstruction causes stillbirth or neonatal death. In group II (20%), acute, early presentation requires diversion and reconstruction. In group III (60%), good health and renal function continue despite urologic appearances.

There is complete absence or incomplete formation of the rectus abdominis and other muscles, which leads to the wrinkled abdominal wall of the prune infant (see Fig 52-11, C). This gives way to a fairly smooth "pot belly" in later life (Fig. 52-10). Reconstructive surgery is not normally required. The patients grow up physically active and strong but cannot sit up directly from a supine position. Abnormalities of the thoracic cage, such as pectus excavatum, are common.

Although true outflow obstruction may be present, the gross and irregular dilation of the urinary tract characteristic of prune-belly syndrome is primarily caused by a developmental defect with a variable degree of smooth muscle aplasia leading to aperistaltic ureters (Fig. 52-11). Urodynamic studies are often difficult to interpret because of gross VUR, but typically there is a low-pressure bladder. With late presentation, some patients have detrusor instability.

Differential Diagnosis

In severe cases of megacystis or megaureter with gross impairment of renal function (often with dysplastic kidneys), the differential diagnosis of prune-belly syndrome includes posterior urethral valves, renal dysplasia with or without multiple congenital defects, neuropathic bladder, and nephrogenic diabetes insipidus.

Natural History

Once any outflow obstruction is addressed, usually in infancy, the renal function should remain stable despite the frightening radiologic appearances. In prune-belly patients observed in our unit for up to 40 years, renal deterioration and hypertension have been rare. In the small number who have progressed, recurrent infection, hypertension, and proteinuria have been warning signs of impending trouble. Renal scarring should be assessed by isotopic DMSA scintigraphy and renal function followed by serial isotopic GFR measurements. Lifelong attention to blood pressure, UTIs, and stones is necessary.

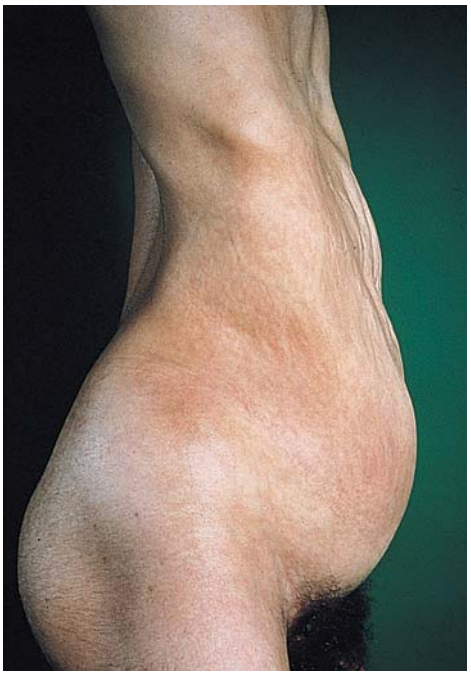

Figure 52-10 Prune-belly syndrome. Note the lax abdominal musculature leading to a pot-bellied appearance. There is also marked thoracic cage deformity. *(Courtesy Prof. C. R. J. Woodhouse, University College Hospital, London.)*

Treatment

In all children with prune-belly syndrome, even with good renal function, a careful search for obstruction should begin with the urethra and work up to the PUJ. Often, however, no obstruction is found, and no surgery is required. In many other patients, the floppy bladder is not anatomically obstructed, but bladder emptying is improved by urethrotomy ("functional obstruction"). In infancy, there is debate about the need for reconstructive surgery. Certainly, a group of patients born with severely compromised renal function do require reconstruction after stabilization by early diversion.[30]

The current view is that the testes should be brought down to the scrotum in infancy. It is hoped that earlier surgery will produce proper germ cell development and thus preserve fertility. Thus far, however, no prune-belly patient has been shown to be fertile.

Bladder Exstrophy (Ectopia Vesicae)

Classic exstrophy is the failure of the anterior abdominal wall and bladder to close. However, these defects range from epispadias of an otherwise normal penis to major cloacal abnormalities (Fig. 52-12).

Pathogenesis

Failure of growth of the lower abdominal wall between the allantois and the urogenital membrane coupled with breakdown of the urogenital membrane leaves a small, open bladder plate, a low-placed umbilical root, and diastasis of the pubic bones (Fig. 52-13, *B*). The genital tubercle is probably placed lower in these patients, and the cloacal membrane ruptures above it, leading to a penis with an open

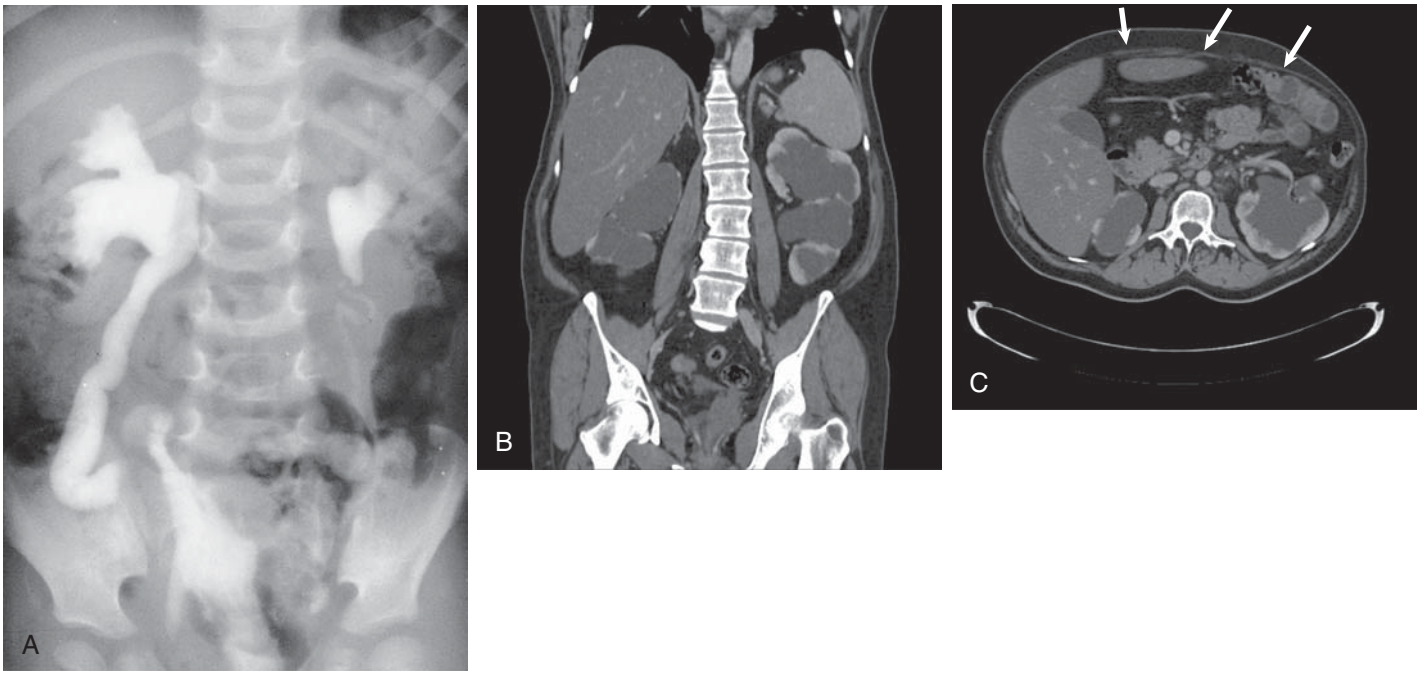

Figure 52-11 Prune-belly syndrome. A, Typical IVU appearance of a patient with prune-belly syndrome and good renal function. Often, the ureters are extremely dilated and tortuous. **B,** CT urogram showing gross bilateral hydronephrosis. **C,** Absence of anterior abdominal wall musculature *(arrows)*.

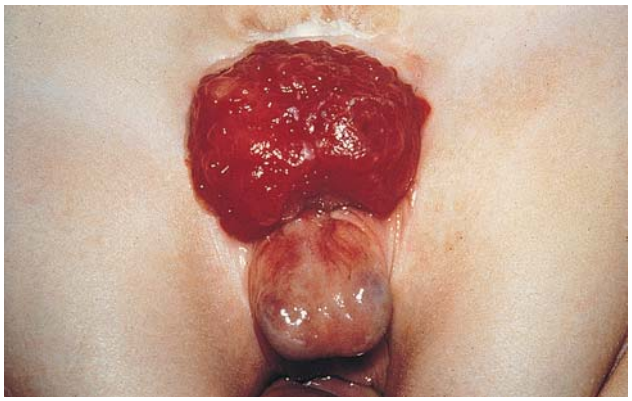

Figure 52-12 Bladder exstrophy. The entire length of the penis is also open (epispadias). *(Courtesy Prof. C. R. J. Woodhouse, University College Hospital, London.)*

dorsal surface that is continuous with the bladder plate. A midline closure defect causes a failure of fusion of the lower anterior abdominal wall, including the symphysis pubis, lower urinary tract, and external genitalia. There are rare reports of a familial incidence. The condition occurs in 1 in 10,000 to 52,000 births. The male-female ratio is 2:1.

Clinical Manifestations

In severe cases, the bladder mucosa lies exposed on the lower abdominal wall, with the bladder neck and urethra laid open. The prostate and testes are normal. Most patients have normal kidneys at birth, although many reports do not record the state of the kidneys at birth. In one series, 33% had dilated ureters at presentation, but IVU was usually normal after diversion. In another series, however, one third of patients were said to have "unilateral renal agenesis."[31] Renal function may be preserved after the diversion, although reflux is common (Fig. 52-13).

Other congenital abnormalities are only rarely present. More severe cloacal abnormalities are associated with imperforate anus and high or low rectal atresia.

Natural History

Long-term renal outcome depends on the bladder. Up to 25 years, the kidneys survive much better with a well-functioning bladder; 13% of those with a good bladder had significant renal damage compared with 82% with ileal conduits, 22% with nonrefluxing colonic conduits, and 33% with ureterosigmoidostomy.[32] Currently, the bladder is usually augmented (enterocystoplasty, ileocystoplasty, cecocystoplasty) or replaced by bowel (intestinal reservoir). In a study of 53 such patients monitored more than 10 years, renal function deteriorated (GFR decrease ≥20%) in only 10 patients (~20%).[33]

Treatment

When the infant is born, the three urologic treatment goals are to close the abdominal wall, to establish urinary continence and preserve renal function, and to reconstruct cosmetically acceptable genitalia. The aim of initial surgery is to convert the defect to a complete epispadias (Fig. 52-14). At 4 years of age, reconstruction of the bladder neck and correction of the epispadias can be performed. If the bladder is small, intestinal augmentation is required. Patients may be able to void, but many have to use catheters. Incontinence may be a long-term problem.

Neuropathic Bladder

In childhood, the most common cause of a neuropathic bladder is myelomeningocele, although with antenatal diagnosis, it is becoming less common. A neuropathic bladder may also be seen without associated neurologic or other obvious causes (Table 52-2). The principal consequences are incontinence, infection, and reflux with upper tract dilation and subsequent renal failure. Early urodynamic assessment is essential (Fig. 52-15). Three different patterns of bladder behavior are seen: contractile, intermediate, and acontractile.

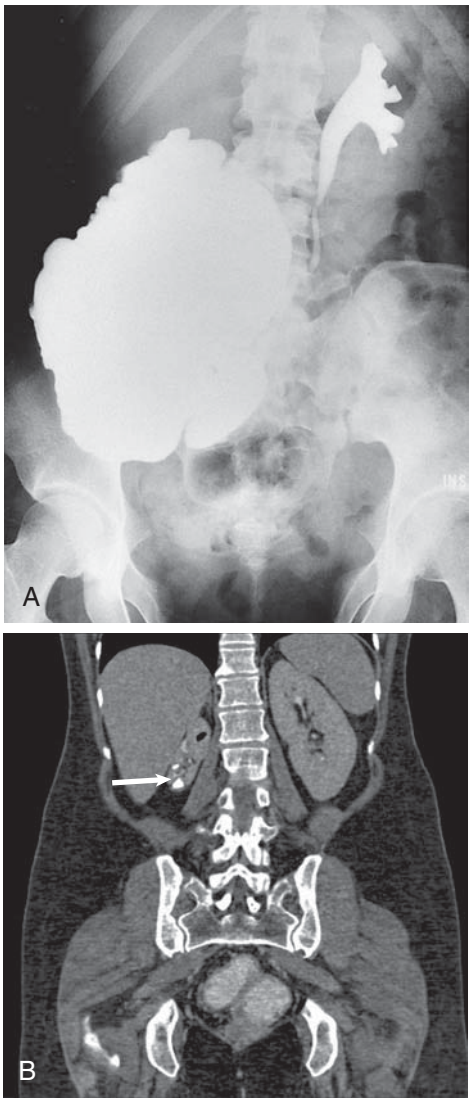

Figure 52-13 Cystography in bladder exstrophy. A, A 26-year-old woman with bladder exstrophy who has a continent Mitrofanoff system (see Fig. 52-19) with use of the colon to create a reservoir. There is reflux into the left kidney. Reflux also occurs into the right kidney, but the kidney is obscured by the full reservoir. Glomerular filtration rate is 130 ml/min. **B,** MR scan of a patient with bladder exstrophy shows scarred, small left kidney with several renal calculi *(arrow)*. Note widely splayed symphysis pubis.

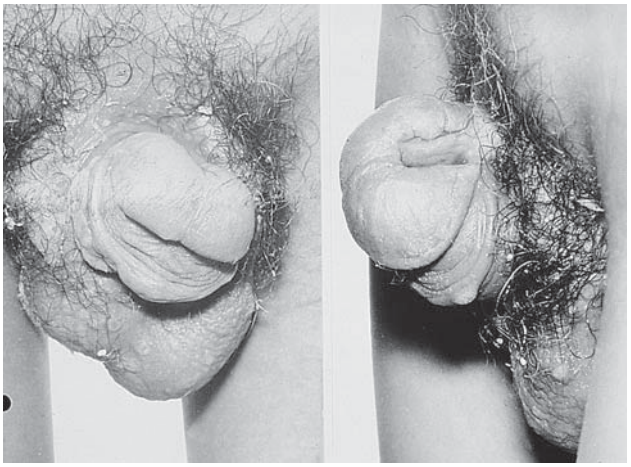

Figure 52-14 Epispadias. Result of multiple surgeries to close the epispadias and to lengthen the penis. *(Courtesy Prof. C. R. J. Woodhouse, University College Hospital, London.)*

Causes of Neuropathic Bladder	
Site of Lesion	**Causes**
Cerebral	Cerebrovascular accident/cerebral palsy, encephalopathy, trauma, Parkinson disease, dementia
Spinal	Isolated (no other neurologic features), trauma, multiple sclerosis, compression, spina bifida, spinal dysraphism, tethered cord, sacral agenesis, sacral teratoma
Peripheral nerve	Pelvic surgery, diabetes

Table 52-2 Causes of neuropathic bladder.

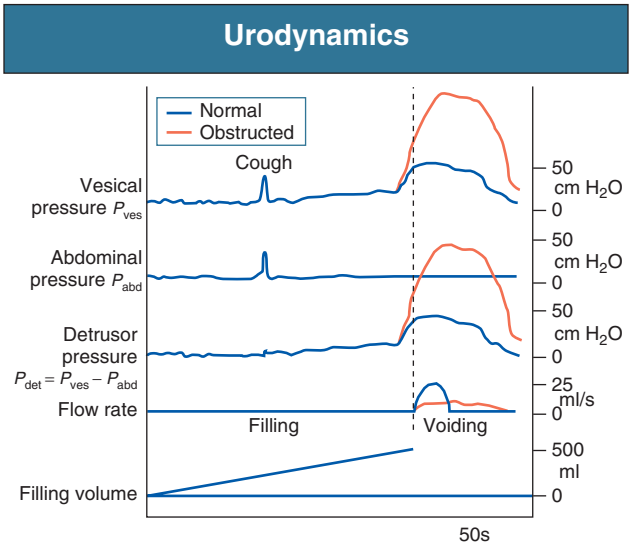

Figure 52-15 Urodynamic assessment by cystometrography. The vesical pressure is measured simultaneously with the abdominal pressure through the rectum; the detrusor pressure is the difference. A cough is used as a marker to show that the system is working. During filling, the first desire to void is normally at a detrusor pressure of less than 10 cm H_2O. This point is noted. The voiding pressure should normally be less than 40 cm H_2O (and is lower in women). Detrusor instability is an unstable (spontaneous) contraction occurring with a detrusor pressure above 15 cm H_2O. Higher pressure can cause incontinence. In combination with radiologic imaging (videocystometrography), the following are recorded: bladder neck, closed or open; bladder pressure, end filling; voiding detrusor pressure; bladder stability; compliance; flow rate, maximum; sensation, first; volume, voided and residual. *(Courtesy Prof. M. Craggs, University College London.)*

Contractile Behavior

An overactive detrusor (hyperreflexia) can produce some bladder emptying (incontinence). Unfortunately, 95% of patients have sphincter dyssynergia (inability to relax urethral sphincter), which results in no relaxation and incomplete emptying of the bladder. Patients with incomplete lesions may have some control of the distal sphincter and normal anal and sacral reflexes. Ironically, although this latter group has the least neurologic deficit, they have the worst bladder situation, generating high pressures and great risk for renal injury. The bladder becomes progressively hypertrophic, fibrotic, and poorly compliant.

Intermediate Behavior

These patients have some detrusor activity, but not sufficient to empty the bladder. These intermediate bladders are poorly compliant, and patients have no voluntary control of their sphincters. Any

rise in bladder pressure tends to cause incontinence, or the high intravesical pressures lead to renal injury.

Acontractile Behavior

About 25% of patients have no detrusor activity, and the bladder overflows when it is sufficiently full. This acontracile bladder is not usually associated with renal failure.

Myelodysplasia

Myelodysplasia refers to a group of neural tube anomalies that primarily affect the lumbar and sacral segment of the spinal cord and are the most common cause of neurogenic bladder dysfunction in children. *Spina bifida* reflects defective fusion of the posterior vertebral arches. *Meningocele* implies that the meninges extend beyond the confines of the vertebral canal with no neural elements contained inside. A *myelomeningocele* has neural tissue protruding with the meningocele. *Spinal dysraphism* (symptomatic spina bifida occulta) defines a group of structural anomalies of the caudal end of the spinal cord that do not result in an open vertebral canal but are associated with incomplete fusion of the posterior vertebral arches.

Sacral agenesis is a rare anomaly in which part or all of two or more vertebral bodies is absent. It occurs early in fetal development when there is failure of ossification of the lowest vertebral segments. The only known teratogen is insulin. Sacral agenesis occurs in 1% of children born to insulin-dependent mothers. Partial sacral agenesis can be associated with an anterior meningocele.

Pathogenesis

The neural tube normally forms as the neural folds close over and fuse, starting in the cervical region and progressing caudally. It is believed that the embryologic defect is an incomplete tubularization of the neural tube, with inadequate mesodermal invagination and subsequent arrest of vertebral arch formation.

The incidence of myelodysplasia varies from 1 to 5 in 1000 live births, but there are wide geographic variations. Monozygotic twins are often discordant for spina bifida, but siblings are at increased risk (1:10 to 1:20), and children of affected parents have a 4% chance of having a similarly affected child. Myelomeningocele accounts for more than 90% of myelodysplastic infants. Folic acid supplements taken during the last trimester reduce the incidence of myelodysplasia by 52%.

Clinical Manifestations

All causes of tethered cord can produce a variable neurologic deficit. During development, some children develop progressive neurologic disturbance with bladder dysfunction, bowel dysfunction, scoliosis, and a syndrome of pes cavus and limb growth failure.

Bladder Dysfunction Neuropathic bladder can be an isolated problem with abnormal urodynamic studies but a normal neurologic examination.[34]

Bowel Dysfunction Bowel dysfunction is often present and needs to be treated accordingly. There may be severe constipation and overflow incontinence. The antegrade continent enterostomy procedure has been developed to improve the management. The appendix is brought out to the abdominal surface, and thus the colon can be irrigated antegrade with saline.

Cognitive Impairment Patients with myelomeningocele may have some intellectual impairment, especially those who have required ventriculoperitoneal shunting for associated hydrocephalus. Manual dexterity may also be affected. These are crucial issues in long-term management.

Natural History

About 14% of patients have renal complications at birth and are at high risk in the next few years. Ultimately, about 52% will develop upper tract problems, although these can take up to 30 years to occur (Fig. 52-16). In one prospective study, renal outcome could be predicted by the urodynamic findings, with worst outcomes related to increased bladder wall thickness, degree of reflux, urethral pressures above 70 cm H_2O, and reduced bladder capacity. VUR occurs in 3%

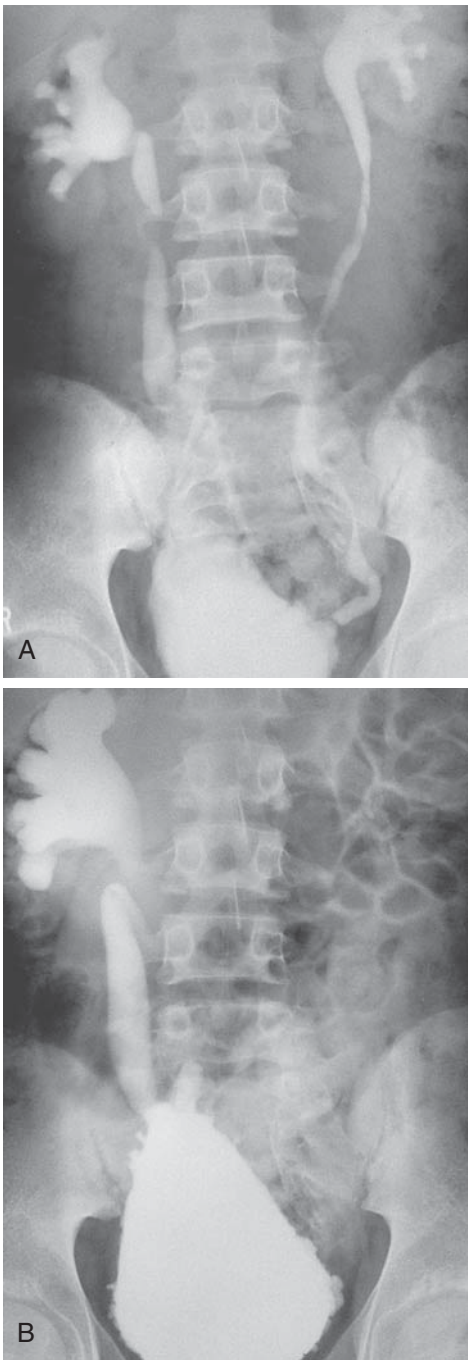

Figure 52-16 Sacral spina bifida with neuropathic bladder. A, IVU shows evidence of a previous hydronephrosis and subsequent scarring of the right kidney. The architecture of the left kidney is well preserved. **B,** Micturating cystogram. The typical tapering, hypertrophied, trabeculated bladder gives the characteristic fir (pine) cone appearance. Note the gross reflux on the right side. This is probably helping to protect the left kidney by acting as a "pop-off" mechanism. This is analogous to the protection that can occur in boys with posterior urethral valves.

to 5% of newborns with detrusor hypertonicity or dyssynergia. Without treatment, this increases to 30% to 40% by age 5 years.[35]

Treatment

The management of the bladder depends on the urodynamic findings. In the 1970s, clean intermittent self-catheterization (CISC) was introduced,[36] but before that time, urinary diversion was the usual treatment. Currently, when reflux and hydroureter are present, the management is principally with CISC and antimuscarinic drugs that increase bladder compliance. With persisting symptoms related to bladder storage or hyperreflexia, bladder wall injection with botulinum toxin type A1 is offered. In the presence of deteriorating renal function or intractable symptoms, continent bladder augmentation or sometimes ileal conduit is required.[37]

Bladder Neck Obstruction

Congenital bladder neck obstruction is rare and is usually caused by a neuropathic bladder, posterior urethral valves, or an ectopic ureterocele.

Posterior Urethral Valve

Posterior urethral valves are the most common cause of severe subvesical obstruction in the male infant (but account for only 10% of neonatal hydronephrosis). As a result, bilateral hydronephrosis and megaureter occur. Obstruction is caused by a diaphragm that extends from the floor to the roof of the urethra at the apex of the prostate. Valves appear as mucosal folds in the posterior urethra below the verumontanum. There is dilation of the proximal urethra and bladder wall hypertrophy and trabeculation. Above the valves, the prostatic urethra dilates, undermining the bladder neck. The valves obstruct flow only in one direction, and therefore a catheter can be passed without difficulty.

Pathogenesis

The urethra develops in two parts: differentiation of the urogenital sinus part (posterior urethra) and tubularization of the urethral plate (anterior urethra). Early obstruction during renal development can result in severe renal dysplasia.

Clinical Manifestations

Most cases of posterior urethral valves are now detected antenatally by ultrasound. Half of all patients present before age 1 year. Infants present with a palpably distended bladder and enlarged kidneys, abnormal urine stream, or failure to thrive due to renal failure. At diagnosis, 30% to 52% of children also have VUR. Children with less severe disease present with poor stream, hematuria, incontinence, acute UTI, or renal failure. However, late presentation is also associated with worse outcome.[38]

Three abnormal features can help protect the kidney, reducing the high pressures generated during voiding: massive unilateral reflux, usually with ipsilateral renal dysplasia (thereby protecting the other kidney); large bladder diverticulum; and urinary extravasation, often with urinary ascites. These protective mechanisms are referred to as "pop-off" mechanisms[39] (Fig. 52-16, *B*). Ultrasound can show the bladder thickening, dilated system, and dilation of the posterior urethra. A specific diagnosis should be documented by videocystometrography (see Urodynamics).

Natural History

In the 1960s, 25% of children with posterior urethral valves died within the first 12 months, and 25% died later in childhood, including "renal death" (i.e., ESRD). By the late 1990s, early mortality was less than 5%, and after 15 years of follow-up, only 15% to 20% of patients had reached ESRD.[40]

The bladder may become stretched, resulting in poor emptying, or unstable, leading to poor compliance, unsuppressed detrusor contractions, and high storage pressure. Both these situations are exaggerated by progressive polyuria. Such patients may have a daily urine volume of 5 liters. Urodynamic follow-up studies suggest that instability decreases with time; bladder capacity increases, but there are unsustained voiding contractions. The prognosis correlates with the nadir serum creatinine value once obstruction has been relieved. Despite adequate early treatment, chronic kidney disease (CKD) caused by renal dysplasia develops in many children.[38,41]

Treatment

All children have had transurethral resection of their valves in infancy. Bladder diversion should be avoided. The question of "undiversion" of ileal conduits previously created is discussed later. Bladder instability and poor bladder compliance must be treated, regardless of whether symptoms result. Boys with substantial residual volumes can be managed by CISC, but compliance is often poor because of urethral discomfort or because previous urethral surgery has made the passage of catheters difficult. Compliance is a particular problem with adolescents who are continent and for whom renal failure is too abstract a concept. Continence often improves spontaneously at puberty but can be helped by imipramine. Deterioration in renal function will require further examination of urine flow rate and exclusion of urethral stricture.

Urethral Diverticulum

Urethral diverticulum usually occurs in boys and is rare. It may present with UTI, obstruction, or stones. The two types are anterior and posterior. The anterior type can be associated with anterior urethral valves and obstruction.

Other Congenital Causes of Bladder Outflow Obstruction

Non-neurogenic neurogenic bladder, or Hinman syndrome, has been used to describe a group of patients with severe bladder dysfunction, urodynamically consistent with a neurogenic bladder, but in whom no neurology defect can be demonstrated. The genetic background to some of these disorders has been discovered.

Urofacial Syndrome

Urofacial syndrome, or Ochoa syndrome, is a rare autosomal recessive disease characterized by facial grimacing when attempting to smile and failure of the urinary bladder to void completely, despite a lack of anatomic bladder outflow obstruction or overt neurologic damage. Patients present with enuresis and UTI and all the features of a neuropathic bladder together with dilated upper tracts. They are at risk of renal failure. Some but not all families have mutations of *HPSE2* (heparanase-2), which is expressed in the fetal and adult central nervous system, and also in bladder smooth muscle, consistent with a role in renal tract morphology and function.[42]

Prune-belly–like Syndrome

A prune-belly–like syndrome, or "pseudo-prune," can result from mutation of *CHRM3* (muscarinic acetylcholine receptor M3). A similar bladder problem can be modeled in mice by knocking out this gene. In males, this syndrome can masquerade as posterior urethral valves.[43]

Management of Congenital Renal Tract Abnormalities

- Educate and explain to encourage compliance
- Review urologic status
- Find cause of urinary tract obstruction and treat
- Control blood pressure
- Monitor renal function and proteinuria
- Treat acidosis
- Prevent bone disease
- Check for stones
- Clean intermittent self-catheterization for chronic retention
- Maintain bladder storage pressure below 40 cm H_2O
- Maintain bladder volume below 400 ml

Box 52-1 General principles of management of congenital renal tract abnormalities.

GENERAL MANAGEMENT OF CONGENITAL TRACT ABNORMALITIES

The principles of management of congenital tract abnormalities are shown in Box 52-1. The most important part of the management is ensuring that the patient, family, and primary care physician know what can and must be done. First, they must understand the necessity of long-term follow-up at least annually. ESRD often occurs when a patient is lost to follow-up, often presenting later with accelerated hypertension and rapid loss of renal function.

Clinical Evaluation

By the time the adolescent requires an adult physician, it is assumed that the urinary tract is not obstructed and that further surgery is not required. Nevertheless, it is the responsibility of the nephrologists and urologists who care for these young people to review this aspect periodically.

Symptomatic UTI is common and must be treated promptly. Increase in frequency or severity of infections must lead to investigations to find the cause.[44] The blood pressure must be monitored regularly and kept normal. Finally, renal function must be monitored, proteinuria assessed, and the cause of any deterioration identified. As in any renal condition, the remnant kidney function may decline inexorably, which is associated with increasing proteinuria and hypertension. As with other renal conditions, kidney function is usually stable when proteinuria is minimal or absent. Deterioration in the absence of proteinuria must alert the physician to the likelihood of obstruction or the adverse effect of a nephrotoxic drug.

The routine investigations performed to document the current situation act as a reference point for the future (Table 52-3). If the bladder empties completely with an adequate flow rate (15 ml/s), no problems should arise. If there is any doubt about the condition of the bladder, urodynamic investigations are necessary. If the clinical situation changes, further investigations are required. An increase in UTIs might suggest a stone or increase in residual urine. With an unexpected decline in renal function, obstruction again must be excluded.

The patient should keep a 24-hour urine volume diary every 6 to 12 months, recording the time of voiding and volume passed. It is best to ask patients to do this on 2 consecutive days, to determine the maximum bladder capacity and the total 24-hour urine volume. This should be done before urodynamic investigations, because results can be misleading if bladder is not filled to capacity.

Monitoring Patients with Congenital Renal Tract Abnormalities

Baseline Measurements	Reason for Test
Radiology	
Abdominal x-ray film	Exclude stones
Ultrasound	
Ultrasound of kidneys	Baseline
Ultrasound of bladder after micturition	Assess residual volume
Urine flow rate	Ensure adequacy
Scintigraphy	
Glomerular filtration rate: ^{51}Cr-labeled EDTA	Baseline
Dynamic isotope scan: ^{99}Tc-labeled MAG3 or DTPA	Assess outflow obstruction/ holdup
Static isotope scan: ^{99}Tc-labeled DMSA	Assess scarring and divided function
Biochemistry	
Urine protein-creatinine ratio	Baseline

Table 52-3 Monitoring patients with congenital renal tract abnormalities. Routine investigations for assessment of clinical status. *^{51}Cr,* Chromium 51; *DMSA,* dimercaptosuccinic acid; *DTPA,* diethylene triamine pentaacetic acid; *EDTA,* ethylenediaminetetraacetic acid; *MAG3,* mercaptoacetyltriglycine; *^{99}Tc,* technetium 99.

Exclude Obstruction

Obstruction must always be excluded if there is a change in renal function. The possibility of obstruction may be raised by a routine ultrasound (see Fig. 52-8) and should be pursued with mercaptoacetyltriglycine (MAG3) scintigraphy to exclude obstruction (Fig. 52-17).

In patients with conduits, obstruction can be excluded by infusion of contrast material into the loop (loopogram) and demonstration of reflux up the ureter.

Rarely, in patients with large bladders or in transplant recipients, the kidney may become obstructed when the bladder reaches a certain volume. This can be investigated by filling the bladder by a catheter and performing ^{99m}Tc-labeled MAG3 scintigraphy, initially with the bladder full. If there is no excretion, the bladder volume can be reduced in 100-ml increments until there is flow down the ureter (Fig. 52-18).

Urodynamics

Any urodynamic investigation should start with a free urine flow rate. Provided the flow rate is normal and the bladder empties completely (leaving no residual volume on postmicturition ultrasound), it can be assumed that there is no significant bladder outflow obstruction.

Complete investigation of abnormalities of bladder and urethral function requires synchronous recordings of intravesical and intrarectal pressures taken during bladder filling and emptying (see Fig. 52-15). Combined with radiologic imaging, the study is known as videocystometrography (VCMG).

Surgical Correction of the Urinary Tract

A normal bladder acts as a low-pressure, good-volume urine reservoir that is continent, is sterile, and empties freely and completely. Any other form of urine reservoir aims to recreate such an

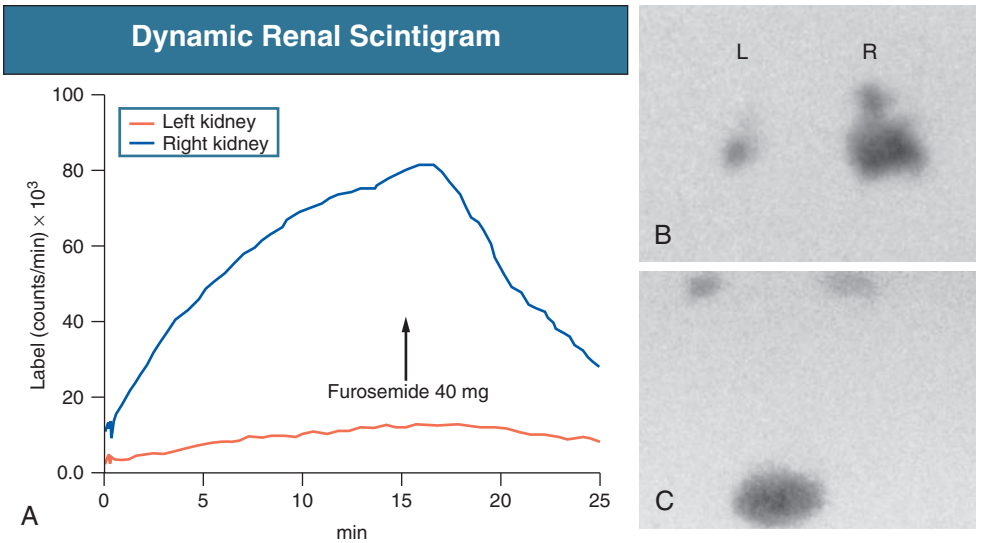

Figure 52-17 Dynamic ^{99m}Tc-labeled MAG3 renal scintigram. A, Time-activity curve showing accumulation of isotope in right kidney that washes out after furosemide, thus excluding significant obstruction. **B** and **C,** Images from the same study showing holdup of isotope in dilated right *(R)* renal pelvis (**B**) that washes out into the bladder after furosemide (**C**), excluding significant obstruction.

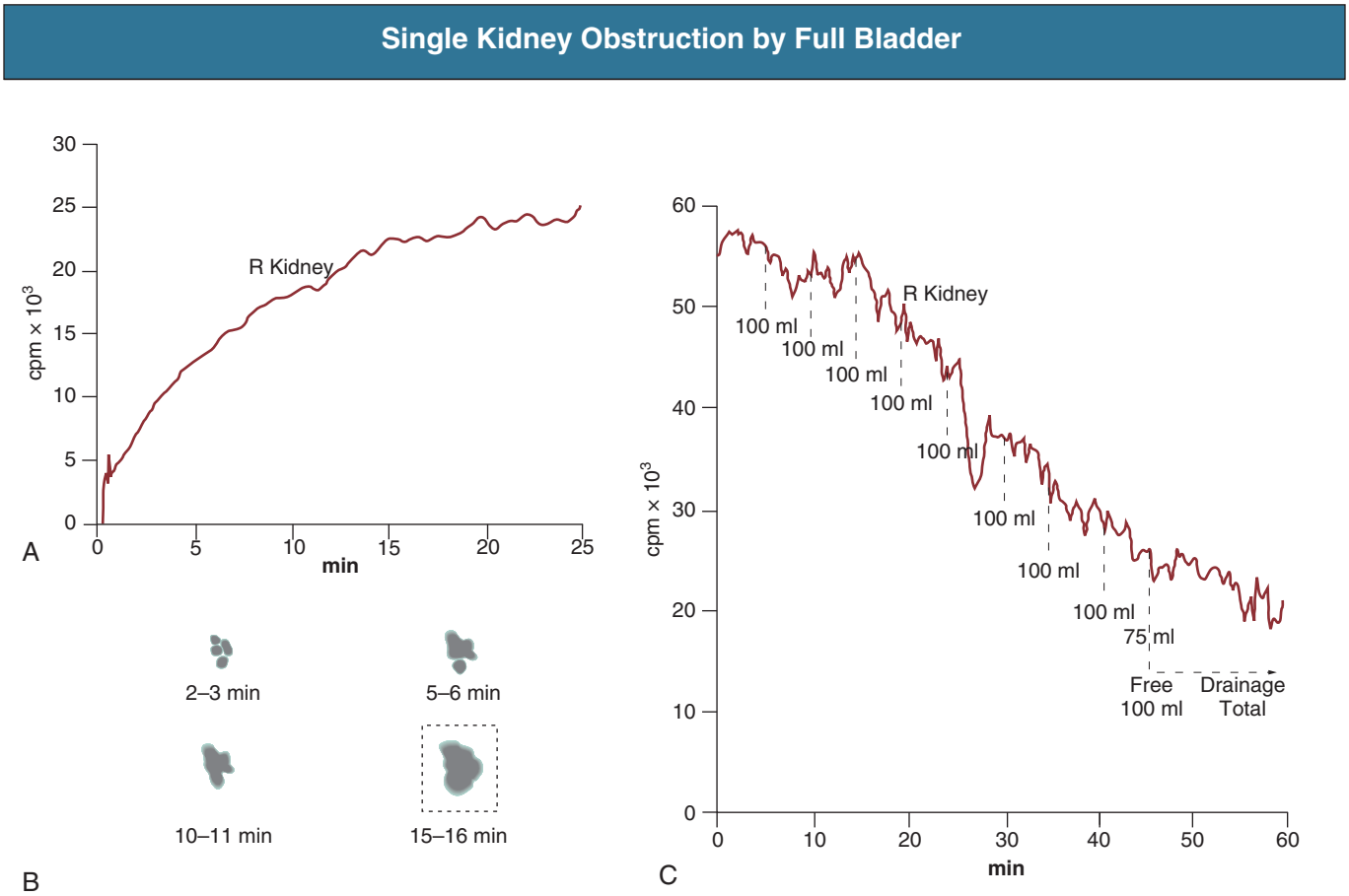

Figure 52-18 Dynamic isotope scan (MAG3) starting with bladder full in a patient with solitary right kidney. A, Rising curve of tracer accumulating in kidney and showing no excretion. *cpm,* Counts per minute. **B,** Accumulation of isotope in hydronephrotic pelvis without excretion to bladder. **C,** The 100-ml increments of fluid removed from bladder result in eventual free drainage of the kidney.

environment. When this is not achieved in either a natural or a reconstructed bladder, complications such as sepsis and renal dysfunction can occur.

A variety of conduits and continent reservoirs have been developed to replace unusable bladders. Ileal conduit diversion has been most widely used for native kidneys, although deterioration in renal function frequently results from long-term complications, including urosepsis, renal calculi, and most often stenosis, leading to obstruction or to reflux with ureteral dilation. There is an overall complication rate of 45%, but with a high index of suspicion and an aggressive diagnostic and therapeutic approach, many of these problems can be detected and treated early, with resultant good long-term function

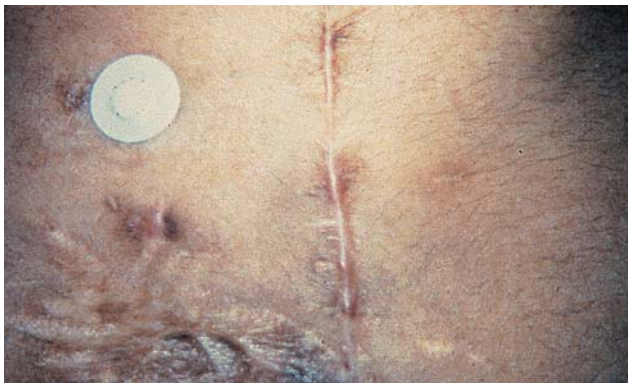

Figure 52-19 Mitrofanoff stoma. This patient was born with bladder exstrophy and has had a successful renal transplant for 22 years. Her kidney is plumbed into a colonic reservoir, and she catheterizes herself through a continent Mitrofanoff stoma, which is covered by a small piece of plaster in the photograph.

of native kidneys. Similar results may be obtained when renal transplantation is performed in these patients.[45] Other forms of urinary diversion that are continent and therefore more socially acceptable to patients are now widely used in general urologic practice and are being encountered in renal transplantation (Fig. 52-19; see also Fig. 52-13). These forms include augmented bladders draining through the urethra and augmented or intestinal bladders draining through continent stomas.

Undiversion of Conduits

The only certain improvement with undiversion is cosmetic. Initially, undiversion was undertaken because of poor results or complications from conduits. Current indications are convenience and cosmetic appearance (see Fig. 52-19). Before undiversion is considered, the following four questions must be answered:

1. Is there residual obstruction?
2. What is the function of the bladder?
3. What is the function of the sphincters?
4. What is the normal 24-hour urine volume?

In particular, the bladder storage pressure must be considered because a low-pressure reservoir must be achieved. This is a particular problem when patients are polyuric. The potential capacity of the bladder will often need to be reassessed after a period of bladder cycling, when the bladder is repeatedly filled through a suprapubic catheter and the volume, voiding capacity, and residual volume are determined. If the native bladder is not of sufficient volume and compliance, some form of augmentation will be required.

COMPLICATIONS

Urinary Tract Infections

Symptomatic UTIs are common.[44] Risk factors include stagnation of urine, stones, foreign bodies (stents, catheters), previous infections, and renal scarring. UTIs must be treated promptly after a urine culture specimen (midstream or catheter specimen) has been taken. Recurrent UTIs, particularly after a period of stability, must lead to further investigations to exclude stones or obstruction, including abdominal radiography, renal ultrasound, and postmicturition bladder ultrasound.

Asymptomatic UTIs often do not require treatment (except during pregnancy). For patients with urinary diversions, it is important to obtain a catheter specimen of urine because urine taken from a bag is invariably infected.

It is sometimes appropriate to give prophylactic antibiotics, such as trimethoprim or nitrofurantoin, to eradicate infection. Many patients believe that cranberry juice helps them; it reduces the incidence of *Escherichia coli* infection but will not treat a symptomatic infection. Tetracycline and oxytetracycline are contraindicated because they cause acute or chronic deterioration in renal function, but doxycycline can be used. Nitrofurantoin and nalidixic acid are avoided if GFR is reduced below 50 ml/min, because both are renally excreted and toxic in renal failure. Quinolones should not be used for prophylaxis, if possible, because of the risk for inducing resistance. When foreign bodies such as stones remain, attempts to sterilize the urinary tract are unlikely to be successful.

If prophylactic antibiotics are no longer effective at preventing infection, it is advisable to stop all antibiotics and to give the patient a supply of antibiotics to treat symptoms arising at home.

Hypertension and Glomerular Hyperfiltration

If renal function is declining with proteinuria and hypertension, glomerular hyperfiltration is likely, although all other causes of renal dysfunction must be excluded. Patients should be treated with renin-angiotensin blockade with ACE inhibitors and angiotensin receptor blockers (ARBs).[4]

Proteinuria and Progressive Renal Failure

Can progression to ESRD be predicted, and does treatment with ACE inhibitors delay or prevent this?[4] We investigated this in a retrospective review of patients with scarred irregular kidneys caused by primary renal dysplasia or abnormal bladder function. All patients had at least 5 years of follow-up, and when ACE inhibitors were started, estimated GFR (eGFR) was below 60 ml/min/1.73 m^2 (mean, 41 ml/min), with mean proteinuria of 1.7 g/24 h. ESRD developed in 46% of patients but in none with proteinuria less than 0.5 g/24 h and in only 2 of 18 patients with eGFR above 50 ml/min. The renal outcome of the two groups was similar whether there was primary renal dysplasia or abnormal bladder function. There was a watershed GFR of 40 to 50 ml/min above which ACE inhibitor treatment improved renal outcome.[4] The similar outcome of the two groups indicates that progressive renal failure in young men born with abnormal bladders is caused by intrinsic renal pathophysiologic processes, in contrast to the view that it is a result of poor bladder function.

Hypertension

Hypertension is common in the presence of scarred kidneys, but it is usually controlled easily with one or two drugs. Patients in whom CKD is secondary to obstruction tend to have volume contraction and therefore often have normal blood pressure or only mild hypertension. ACE inhibitors or ARBs are preferred for patients with proteinuria and progressive renal failure. Diuretics should not be used if the patient is volume-contracted.

Stones

Stones that form in the presence of infected urine are typically magnesium ammonium phosphate (struvite) or calcium phosphate (hydroxyl apatite, carbonate apatite, calcium hydrogen phosphate [brushite], tricalcium phosphate [whitlockite]). These salts are poorly soluble in alkaline urine. In 90% of patients, the infecting

organism is *Proteus* spp.,[46] but other urea-splitting organisms (including some staphylococci and *Pseudomonas* spp.) also generate ammonia.[42]

Stones, usually calcium phosphate, are common in conduits because of the alkaline environment and occur in 5% to 30% of ileal conduits. Stones must be suspected if UTIs recur or become more frequent, if renal function suddenly deteriorates, or if there is an unexplained sterile pyuria.

Tubular Dysfunction

Patients whose renal failure is secondary to obstruction have significant tubular injury. This may cause problems, in particular with urinary concentration, acidification, and sodium reabsorption.

Polyuria

Nocturia is one of the most significant symptoms in the assessment of patients in whom obstruction or tubular dysfunction is suspected. Overfilling of the bladder or reservoir is an important cause of intermittent upper tract obstruction and deteriorating function. The 24-hour urine volume diary is a simple way to assess this.

Salt Depletion

Patients with tubular damage may have a salt-losing tendency. Patients typically have a cool periphery and constricted hand veins with no peripheral edema. Increasing salt intake can relieve cramps, improve renal function, and reduce hyperuricemia, but at the cost of increasing blood pressure. With patients who are salt depleted, it is important to give sodium chloride because it is the chloride anion that is deficient and responsible for the reduction in circulating volume.

Acidosis

There is often a metabolic acidosis disproportionate to the degree of renal impairment. This is secondary both to a proximal tubular failure of bicarbonate reabsorption and to a distal tubular failure to secrete hydrogen ions. It is our practice to give sufficient sodium bicarbonate to correct the plasma bicarbonate into the normal range.

Bone Disease

In addition to the typical bone disease of progressive CKD, acidosis contributes significantly to osteomalacia. Growing children are particularly vulnerable to osteomalacia, and great care must be taken to correct acidosis and actively manage bone disease.

Urinary Diversions

Ureterosigmoidostomy

Fortunately, it is now rare to meet a patient who still has a ureterosigmoidostomy, which was widely used as a technique for urinary diversion until the 1970s. The ureters were anastomosed directly into the sigmoid colon with no disruption of bowel continuity. This technique was most often used in patients with bladder exstrophy. Although patients start with normal renal function, there is frequently deterioration in function. In one series of 25 patients, significant renal damage occurred in 50%. Stones, infection, and ureteral strictures are common, and patients remain at risk for colonic carcinoma, with a 10% incidence of carcinoma at 20-year follow-up. However, this diversion is probably best known for the hyperchloremic, hypokalemic acidosis that occurs. Once the urine is in contact with the colonic mucosa, the urinary sodium exchanges for potassium and the chloride for bicarbonate, and large quantities of ammonium ions are produced by the action of the fecal bacteria on urinary ammonia. Ammonium ions are absorbed both with chloride and in exchange for sodium. The severe acidosis is caused by ammonium ion retention and stool loss of bicarbonate. Patients are managed with large doses of oral sodium bicarbonate, which is titrated to keep the plasma bicarbonate in the normal range (>22 mmol/l).

Ileal Conduits

Unlike the sigmoidostomy, in which urine enters a reservoir, the ileal conduit is free flowing, with rapid urinary transit and no reservoir. Therefore, metabolic complications are much less common, although again the bowel can exchange sodium and chloride for potassium and bicarbonate.[47,48] A number of other complications of ileal and colonic conduits can lead to progressive loss of renal function (Box 52-2).

Enterocystoplasty and Intestinal Urinary Reservoirs

In 53 patients with bladder exstrophy monitored more than 10 years with serial isotopic GFRs, renal function deteriorated (GFR decrease ≥20%) in only 10 (~20%).[33] Loss of function was caused principally by chronic retention with or without infection in poorly compliant patients who did not catheterize regularly. Patients must also be checked regularly to ensure that anastomotic stenoses and high-pressure reservoirs do not occur. Stones are common and occur in up to 52% of patients.[49]

END-STAGE RENAL DISEASE AND TRANSPLANTATION

This group of patients presents two important problems at ESRD. First, because of multiple abdominal surgeries, continuous ambulatory peritoneal dialysis (CAPD) is often impossible, although if there is any doubt, CAPD should be attempted. Second, the bladder and urinary reservoir must be suitable for renal transplantation. If a bladder has just destroyed two good native kidneys, it is likely to do the same to a transplant kidney. Most patients will be maintained on hemodialysis, but it is frequently difficult to establish a good arteriovenous fistula because of chronic hypovolemia and venoconstriction. Patients receiving dialysis often continue to pass 1 liter or more of

Long-term Complications of Urinary Diversion

- Pyelonephritis and scarring
- Calculi
- Obstruction
- Strictures
- Bladder mucus causing obstruction
- Cancer at intestinal-ureteral anastomosis
- Hyperchloremic acidosis
- Delayed linear growth in children
- Effects of intestinal loss from gastrointestinal tract (e.g., vitamin B_{12} deficiency)
- Complications related to abnormal pelvic anatomy (e.g., in pregnancy)
- Psychological and body image problems

Box 52-2 Long-term complications of urinary diversion.

urine per 24 hours, and they also remain at risk for serious UTI and pyelonephritis.

Pretransplantation Assessment

Transplantation into the abnormal lower urinary tract requires careful evaluation and follow-up. Thorough preoperative assessment of bladder function is essential. Patients considered to have normal bladders require at least postmicturition bladder ultrasound and urinary flow rate.

All patients with abnormal bladders or reservoir must have a full videocystometrogram to ensure that the bladder reservoir is large and adequately compliant. If the bladder is small or has not been used for some time, *bladder cycling,* which involves periodically filling and distending the bladder through a suprapubic catheter, may be required. A urodynamic study before transplantation indicated that poor bladder function, as shown by small bladder volumes, is a predictor of graft loss even in patients with previously normal bladder function.[50]

Intermittent self-catheterization is safe and effective for a patient with a poor flow rate who fails to empty the bladder. This, however, is possible only with a normal urethra and a cooperative patient. When this is not practical, we attempt to establish suprapubic drainage through a continent stoma, such as a Mitrofanoff stoma (see Fig. 52-19). If a conduit is to be used, a loopogram and endoscopy must ensure that it is in good condition. We do not remove native kidneys unless they are causing recurrent UTI.

Transplant Outcome

In an 18-year experience, we transplanted 65 patients with abnormal bladders, with a total of 72 renal transplants.[51] In 52 cases, the ureters were transplanted into unaugmented bladder; in 20 cases, there was some form of augmentation or diversion. Results were compared with 59 transplants in 55 patients who had renal failure from renal dysplasia and whose bladder function was considered normal. There was no difference in actuarial graft survival in the two groups at 10 years (abnormal bladders, 66%; normal bladders, 61%), although longer follow-up showed an advantage for normal bladders, with a kidney half-life of 29 to 33 years compared with 15 years for the abnormal bladders.[52] UTIs were relatively common in all patients but produced problems only in patients with abnormal bladders.

Management

A double-J ureteral stent should be placed routinely at the time of transplant surgery. Adequacy of urinary drainage must be assessed frequently, even when graft function seems to be good. Two months after transplantation, when the ureteral stent has been removed, we perform as a baseline the following tests:

- Chromium 51–labeled ethylenediaminetetraacetic acid (^{51}Cr-EDTA) GFR
- Postmicturition ultrasound of kidney and bladder
- Dynamic ^{99m}Tc-MAG3 scintigraphy
- Static ^{99m}Tc-DMSA scintigraphy (baseline for renal scarring)

The GFR is repeated at 6 months and then annually. Ultrasound and ^{99m}Tc-MAG3 scintigraphy are repeated at 1 year and then when indicated. The protein-creatinine ratio is measured on a random urine sample at every outpatient visit. If there is renal dysfunction, imaging tests are repeated, and if there is a change from baseline, renal biopsy is performed to exclude an immunologic cause of graft dysfunction. If there is a documented deterioration in renal function in the absence of rejection or calcineurin inhibitor toxicity, the DMSA scan is repeated (to see whether there has been new scarring) and the bladder reassessed urodynamically.[52]

Complications

Urinary tract infections must be detected and treated early, and recurrent UTIs may require long courses of antibiotics or even removal of the native tracts. Symptomatic UTIs are common in the first 3 months after transplantation (63%); fever and systemic symptoms occur in 39% of patients with normal bladders and 59% with abnormal bladders. UTI directly contributes to graft loss in patients with abnormal bladders but causes no consequences in those with normal bladders.[44] Prophylactic administration of antibiotics for the first 6 months reduces significantly the subsequent incidence of UTI. When UTIs recur, a cause must be sought with ultrasound of kidney and bladder. A plain abdominal radiograph is essential to look for stones in native or transplant kidneys and the bladder or urinary diversion. If there is a residual volume after double micturition, the patient must be instructed to perform CISC. With these measures, good results are obtained.

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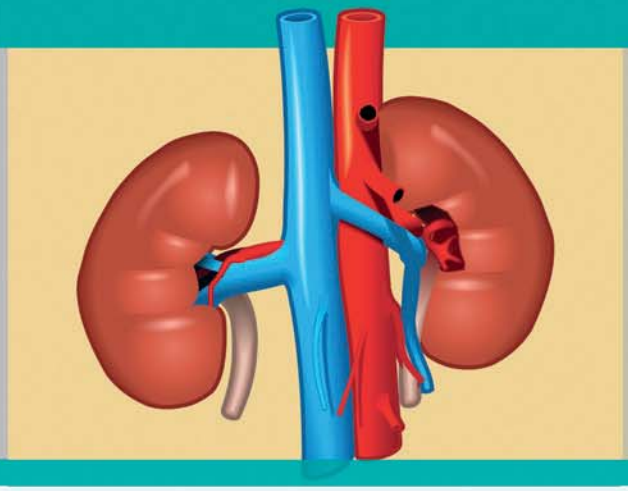

SECTION IX

Infectious Diseases and the Kidney

CHAPTER 53

Bacterial Urinary Tract Infections

Thomas Hooton

DEFINITION

Urinary tract infection (UTI) in adults can be categorized into six groups: young women with acute uncomplicated cystitis, young women with recurrent cystitis, young women with acute uncomplicated pyelonephritis, adults with acute cystitis and conditions that suggest occult renal or prostatic involvement, complicated UTI, and asymptomatic bacteriuria (Box 53-1).[1] Chapter 44 discusses UTI in pregnancy, and Chapter 63 describes vesicoureteral reflux (VUR) in children.

Complicated urinary tract infection is defined as UTI that increases the risk for serious complications or treatment failure. Patients with various conditions, such as those presented in Box 53-1, are at increased risk for complicated UTI. Complicated UTIs may require different pretreatment and post-treatment evaluation and type and duration of antimicrobial treatment than for uncomplicated UTI. On occasion, complicated UTIs are diagnosed only after a patient has a poor response to treatment.

EPIDEMIOLOGY

Acute uncomplicated UTIs are extremely common, with several million episodes of acute cystitis and at least 250,000 episodes of acute pyelonephritis occurring annually in the United States. The incidence of cystitis in sexually active young women is about 0.5 per 1 person-year.[2] Acute uncomplicated cystitis may recur in 27% to 44% of healthy women, even though they have a normal urinary tract.[3] The incidence of pyelonephritis in young women is about 3 per 1000 person-years.[4] The self-reported incidence of symptomatic UTI in postmenopausal women is about 10% per year.[5] The incidence of symptomatic UTI in adult men younger than 50 years is much lower than in women, ranging from 5 to 8 per 10,000 men annually.

Complicated UTIs encompass an extraordinarily broad range of infectious entities (see Box 53-1). Nosocomial UTIs are a common type of complicated UTI and occur in 5% of admissions in the university tertiary care hospital setting; catheter-associated infections account for most of the infections. Catheter-associated bacteriuria is the most common source of gram-negative bacteremia in hospitalized patients.[6]

Asymptomatic bacteriuria is defined as two separate consecutive clean-voided urine specimens, both with 10^5 or more colony-forming units per milliliter (cfu/ml) of the same uropathogen in the absence of symptoms referable to the urinary tract.[7] Asymptomatic bacteriuria is found in about 5% of young adult women,[8] but rarely in men younger than 50. The prevalence increases up to 16% of ambulatory women and 19% of ambulatory men older than 70 and up to 50% of elderly women and 40% of elderly men who are institutionalized.[7] Asymptomatic bacteriuria may be persistent or transient and recurrent, and many patients have had previous symptomatic infection or develop symptomatic UTI soon after having asymptomatic bacteriuria. Asymptomatic bacteriuria is generally benign, although it may lead to serious complications in some clinical settings.

PATHOGENESIS

Uncomplicated Infection

Most uncomplicated UTIs in healthy women result when uropathogens (typically *Escherichia coli*) present in the rectal flora enter the bladder through the urethra after an interim phase of periurethral and distal urethral colonization. Colonizing uropathogens may also come from a sex partner's vagina, rectum, or penis. Hematogenous seeding of the urinary tract by potential uropathogens such as *Staphylococcus aureus* is the source of some UTIs, but this is more likely to occur in the setting of persistent bloodstream infection or urinary tract obstruction.

Many host behavioral, genetic, and biologic factors predispose healthy young women to uncomplicated UTI (Table 53-1). Risk factors include sexual intercourse, use of spermicide products, and a history of previous recurrent UTI.[2,9] Nonsecretors of ABO blood group antigens are at increased risk for recurrent cystitis, the P_1 blood group phenotype is a risk factor for recurrent pyelonephritis in women, and mutations in the gene for CXCR1, the interleukin-8 receptor, are more frequent and expression of CXCR1 is lower in children prone to pyelonephritis compared with controls.[10] Factors protecting individuals from UTI include the host's immune response; maintenance of normal vaginal flora, which protects against colonization with uropathogens; and removal of bladder bacteriuria by micturition.[11] Uropathogenic *E. coli*, the predominant pathogens in uncomplicated UTI, are a specific subset of extraintestinal pathogenic *E. coli* that have the potential for enhanced virulence[12] (Table 53-1). P-fimbriated strains of *E. coli* are associated with acute uncomplicated pyelonephritis, and their adherence properties may stimulate epithelial and other cells to produce proinflammatory factors that stimulate the inflammatory response. Other virulence determinants include adherence factors (type 1, S, and Dr fimbriae), toxins (hemolysin), aerobactin, and serum resistance. Bacterial virulence determinants associated with cystitis and asymptomatic bacteriuria have been less well characterized. Triggers for development of urinary symptoms are not entirely clear.

Factors affecting the large difference in UTI prevalence between men and women include the greater distance between the usual source of uropathogens (anus and urethral meatus), the drier environment surrounding the male urethra, and the greater length of the male urethra. Risk factors associated with UTIs in healthy men include intercourse with an infected female partner, anal intercourse, and lack of circumcision, although these factors are often not present in men with UTI. Most uropathogenic strains infecting young men are highly virulent, suggesting that the urinary tract in healthy men is relatively resistant to infection.

Categories of Urinary Tract Infection in Adults

- Acute uncomplicated cystitis in young women
- Recurrent acute uncomplicated cystitis in young women
- Acute uncomplicated pyelonephritis in young women
- Acute uncomplicated cystitis in adults with a following condition suggesting possible occult renal or prostatic involvement but without other known complicating factors:
  - Male sex
  - Elderly
  - Pregnancy
  - Diabetes mellitus
  - Recent urinary tract instrumentation
  - Childhood urinary tract infection
  - Symptoms for more than 7 days at presentation
- Complicated urinary tract infection*
  - Obstruction or other structural factor: urolithiasis, malignancies, ureteral and urethral strictures, bladder diverticula, renal cysts, fistulas, ileal conduits, other urinary diversions
  - Functional abnormality: neurogenic bladder, vesicoureteral reflux
  - Foreign bodies: indwelling catheter, ureteral stent, nephrostomy tube
  - Other conditions: renal failure, renal transplantation, immunosuppression, multidrug-resistant uropathogens, health care–associated (includes hospital-acquired/nosocomial place) infection, prostatitis-related infection, upper tract infection in an adult other than a healthy young woman, other functional or anatomic abnormality of urinary tract)
- Asymptomatic bacteriuria

Box 53-1 Categories of urinary tract infection in adults. *This is a selected list of complicating factors. Some factors complicate urinary tract infections through several mechanisms. *(Data for complicating factors from reference 1.)*

Complicated Infection

The initial steps leading to uncomplicated UTI discussed earlier probably also occur in most individuals who develop a complicated UTI. Factors that predispose individuals to complicated UTI generally do so by causing obstruction or stasis of urine flow, facilitating entry of uropathogens into the urinary tract by bypassing normal host defense mechanisms, providing a nidus for infection that is not readily treatable with antimicrobials, or compromising the host immune system (see Box 53-1).[1] UTIs are more likely to become complicated in the setting of impaired host defense, as occurs with indwelling catheter use, VUR, obstruction, neutropenia, and immune deficiencies. Diabetes mellitus is associated with several syndromes of complicated UTI, including renal and perirenal abscess, emphysematous pyelonephritis and cystitis, papillary necrosis, and xanthogranulomatous pyelonephritis.[13] Uropathogen virulence determinants are less important in the pathogenesis of complicated UTIs compared with uncomplicated UTIs. However, infection with multidrug-resistant uropathogens is more likely with complicated UTI.

ETIOLOGIC AGENTS

Uncomplicated upper and lower UTI are most often caused by *E. coli*, present in 70% to 95%, and *Staphylococcus saprophyticus*, present in 5% to more than 20% (Table 53-2).[1] *S. saprophyticus* only rarely causes acute pyelonephritis.[14] Less common causes of uncomplicated UTI include other *Enterobacteriaceae* (e.g., *Proteus mirabilis, Klebsiella* spp.) and rarely *Pseudomonas aeruginosa*, *Citrobacter* species (spp.), or other uropathogens. Among otherwise healthy nonpregnant women, the isolation of organisms such as lactobacilli, enterococci, group B streptococci, and coagulase-negative staphylococci other than *S. saprophyticus* most often represents contamination of the urine specimen.[15] However, such organisms should be considered a likely causative agent in symptomatic women when found in voided midstream urine in high counts and pure growth.

A broader range of bacteria can cause complicated UTI, and many are resistant to broad-spectrum antimicrobial agents. Although

Factors Modulating Risk for Acute Uncomplicated Urinary Tract Infections in Women

Host Determinants	Uropathogen Determinants
Behavioral: sexual intercourse, use of spermicidal products, recent antimicrobial use, suboptimal voiding habits	*Escherichia coli* virulence determinants: P, S, Dr, and type 1 fimbriae; hemolysin; aerobactin; serum resistance
Genetic: innate and adaptive immune response, enhanced epithelial cell adherence, antibacterial factors in urine and bladder mucosa, nonsecretor of ABO blood group antigens, P1 blood group phenotype, reduced CXCR1 expression, previous history of recurrent cystitis	
Biologic: estrogen deficiency in postmenopausal women, glycosuria (including from SGLT-1 inhibitors)	

Table 53-1 Factors modulating risk for acute uncomplicated urinary tract infections in women.

Bacterial Etiology of Urinary Tract Infections

Organisms	Urinary Tract Infection (%)	
	Uncomplicated	*Complicated*
Gram-Negative Organisms		
Escherichia coli	70-95	21-54
Proteus mirabilis	1-2	1-10
Klebsiella spp.	1-2	2-17
Citrobacter spp.	<1	5
Enterobacter spp.	<1	2-10
Pseudomonas aeruginosa	<1	2-19
Other	<1	6-20
Gram-Positive Organisms		
Coagulase-negative staphylococci (*Staphylococcus saprophyticus*)	5-20 or more	1-4
Enterococci	1-2	1-23
Group B streptococci	<1	1-4
Staphylococcus aureus	<1	1-2
Other	<1	2

Table 53-2 Bacterial etiology of urinary tract infections. *(Data for complicated infections from reference 1.)*

E. coli is the most common, *Citrobacter* spp., *Enterobacter* spp., *P. aeruginosa*, enterococci, and *S. aureus* account for a relatively higher proportion of cases compared with uncomplicated UTIs (Table 53-2).[1] The proportion of infections caused by fungi, especially *Candida* species, is increasing (see Chapter 55). Patients with chronic conditions, such as spinal cord injury and neurogenic bladder, are more likely to have polymicrobial (multiorganism) and multidrug-resistant infections.

CLINICAL SYNDROMES

Acute Uncomplicated Cystitis in Young Women

Women with acute uncomplicated cystitis generally present with acute onset of dysuria, frequency, urgency, or suprapubic pain. Acute dysuria in a sexually active young woman is usually caused by acute cystitis; acute urethritis from *Chlamydia trachomatis, Neisseria gonorrhoeae*, or herpes simplex virus infections; or vaginitis caused by *Candida* spp. or *Trichomonas vaginalis*.[6] These three entities can usually be distinguished by the history, physical examination, and simple laboratory tests. Pyuria is present in almost all women with acute cystitis as well as in most women with urethritis caused by *N. gonorrhoeae* or *C. trachomatis,* and its absence strongly suggests an alternative diagnosis. Hematuria (microscopic or gross) is common in women with UTI but not in women with urethritis or vaginitis.

Definitive diagnosis of UTI requires the presence of significant bacteriuria, the traditional standard for which is 10^5 or more uropathogens per milliliter of voided midstream urine. Studies have shown, however, that up to half of women with cystitis have lower colony counts, which are missed with use of the traditional definition. The Infectious Diseases Society of America (IDSA) consensus definition of cystitis is 10^3 cfu/ml or more.[16] Urine cultures are generally not indicated in women with uncomplicated cystitis, because the patient's history has been shown to be highly reliable in establishing the diagnosis,[17] the causative organisms are predictable, and the culture results usually become available only after therapeutic decisions have been made.

E. coli in uncomplicated UTI is often resistant to sulfonamides and amoxicillin, and increasing resistance is also being observed for trimethoprim and trimethoprim-sulfamethoxazole (TMP-SMX, cotrimoxazole) in outpatient urinary strains in the United States and Europe.[18,19] In the United States, cotrimoxazole resistance rates among *E. coli* strains causing uncomplicated UTI range from 15% to 42% in different regions,[18] with a similar range among European countries and Brazil.[19] Many drug-resistant *E. coli* organisms are clonal and have been hypothesized to enter new environments by contaminated products ingested by community residents.[20] The prevalence of *E. coli* resistance to nitrofurantoin is generally less than 5%, although nitrofurantoin is inactive against *Proteus* spp. and some *Enterobacter* and *Klebsiella* spp. Fluoroquinolones remain active against most *E. coli* strains causing uncomplicated cystitis, although resistance is increasing in certain areas of the world.[18,19] In a recent antimicrobial susceptibility study of more than 12 million *E. coli* isolates from U.S. outpatients, fluoroquinolone resistance increased from 3% to 17% over 10 years.[21] In addition, infections caused by extended-spectrum β-lactamase (ESBL)–producing strains are increasing in number, even in the setting of uncomplicated UTI.

Recommended management of acute uncomplicated cystitis is summarized in Figure 53-1 and Table 53-3. Updated IDSA guidelines emphasize the importance of considering ecological adverse effects of antimicrobial agents (i.e., selection for colonization or infection with multidrug-resistant organisms—so-called "collateral damage") when selecting a treatment regimen.[22] Short-course regimens are recommended as first-line treatment for acute uncomplicated cystitis because of comparable efficacy, better compliance, lower cost, and fewer adverse effects than with longer regimens.[23] Given the benign nature of uncomplicated cystitis along with its high frequency, the IDSA guidelines give equal weight to the risk of ecological adverse effects and drug effectiveness in the recommendations.

Nitrofurantoin is well tolerated and has good efficacy when given twice daily for 5 days, and it has a low propensity for ecological adverse effects.[24] Despite concern about the high prevalence of resistance to TMP-SMX, this combination remains very effective and is inexpensive and well tolerated. Fosfomycin is also considered a first-line regimen because of its low propensity for ecological adverse

Oral Regimens for Acute Uncomplicated Cystitis

Drug	Dose (mg)	Interval*	Comment
Trimethoprim-sulfamethoxazole (TMP-SMX)	160/800	q12h	If used in pregnancy (not approved use), avoid in first trimester.
Trimethoprim	100	q12h	If used in pregnancy (not approved use), avoid in first trimester.
Nitrofurantoin			Less active against *Proteus* spp.
Monohydrate/macrocrystals	100	q12h	
Macrocrystals	50	q6h	
Cefpodoxime proxetil	100	q12h	Comparable to TMP-SMX, inferior to ciprofloxacin in 3-day regimen[28]
Fosfomycin	3000	Single dose	Less effective than fluoroquinolone or TMP-SMX
Amoxicillin-clavulanate	500/125	q12h	Inferior to ciprofloxacin in 3-day regimen[27]
Amoxicillin	500	q12h	Used only when causative pathogen is known to be susceptible or for empiric treatment of mild cystitis in pregnancy
Fluoroquinolones			
Ciprofloxacin	100-250	q12h	Avoid fluoroquinolones if possible in pregnancy, nursing mothers, or persons <18 years old. Although highly effective, should be considered second-line treatment to preserve their usefulness for other infections.
Ciprofloxacin extended release	500	q24h	
Levofloxacin	250	q24h	
Ofloxacin	200	q12h	

Table 53-3 Oral antimicrobial agents for acute uncomplicated cystitis or cystitis in patients with possible occult renal or prostatic involvement. *Duration of therapy depends on the clinical setting (see text and Fig. 53-1); *q6h, q12h, q24h,* every 6, 12, or 24 hours.

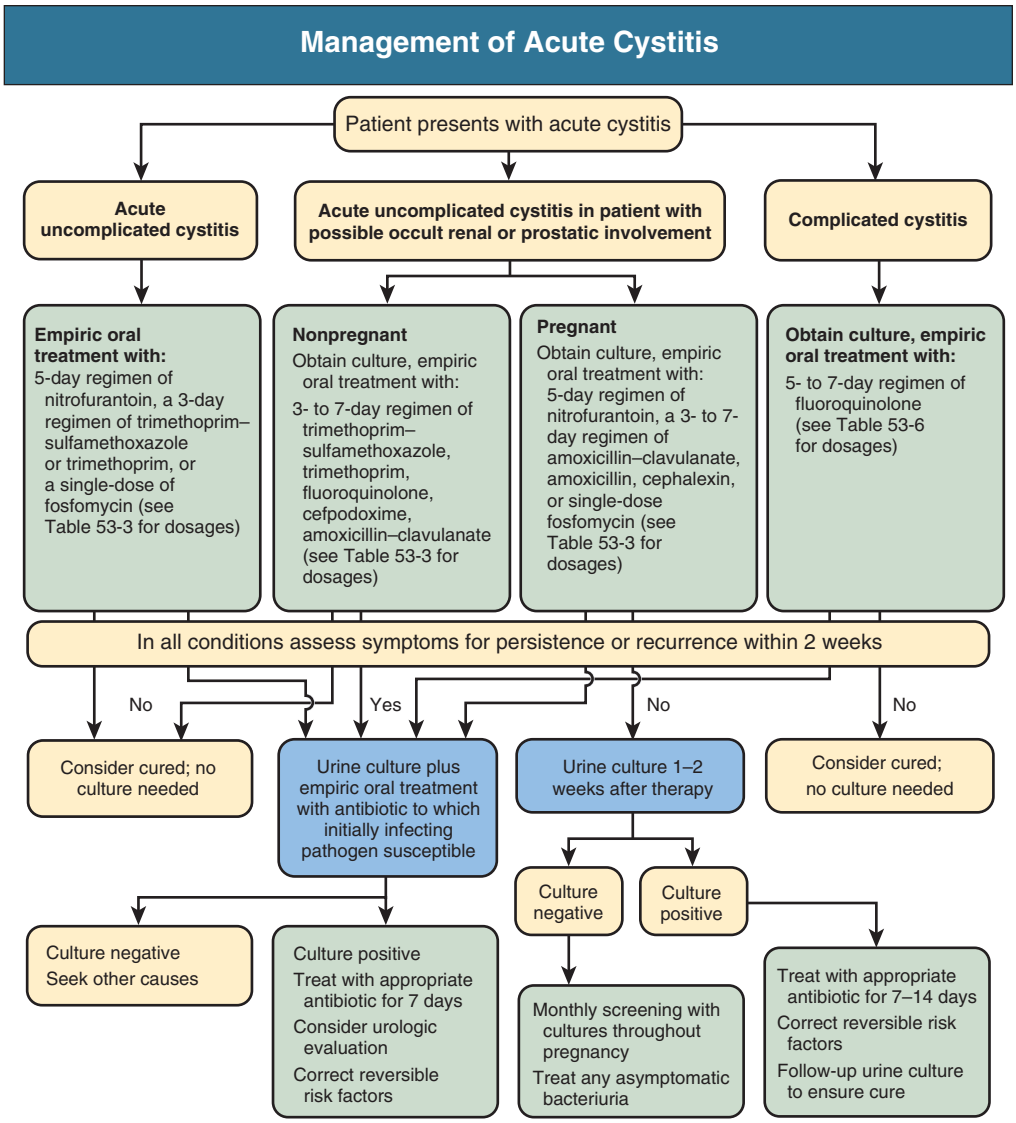

Figure 53-1 Algorithm for management of acute cystitis.

effects, even though it appears to be clinically inferior to TMP-SMX and fluoroquinolones.[22] Moreover, fosfomycin appears to have a role as a therapeutic agent effective against ESBL *E. coli* UTIs.[25]

The choice of an antimicrobial agent should be individualized based on the patient's allergy and compliance history, local practice patterns, prevalence of resistance in the local community (if known), availability, cost, and patient and provider threshold for failure.[22] If a first-line antimicrobial is not a good choice because of one or more of these factors, fluoroquinolones or β-lactams are reasonable alternatives, although it is preferable to minimize their use because of concerns about ecological adverse effects.[22] Thus, although fluoroquinolones (3-day duration) are highly effective in the treatment of cystitis, many experts recommend that they be considered as second-line therapy for uncomplicated cystitis, to help preserve their usefulness in the treatment of other infections.[22] In general, β-lactam antibiotics have been inferior to TMP-SMX or fluoroquinolones in regimens of the same duration.[26]

Although broad-spectrum oral β-lactams (e.g., cefixime, cefpodoxime, cefprozil, cefaclor, amoxicillin-clavulanate) demonstrate *in vitro* activity against most uropathogens causing uncomplicated cystitis, clinical data are sparse. Recent trials demonstrated that cure rates with 3-day regimens of amoxicillin-clavulanate[27] or cefpodoxime proxetil[28] were lower than a 3-day regimen of ciprofloxacin. Moreover, there are concerns about the possibility of ecological adverse effects with oral broad-spectrum cephalosporins, as has been observed with parenteral cephalosporins, although again few data exist. Given increasing antimicrobial resistance and the benign nature of cystitis, antimicrobial-sparing management strategies, such as the use of anti-inflammatory drugs (ibuprofen) or delayed treatment, neither of which is in common clinical use, are of increasing interest.[15]

Routine post-treatment cultures in women are not indicated unless the patient is symptomatic. If the patient remains symptomatic and has documented persistent infection, a longer course of therapy based on sensitivities, usually with a fluoroquinolone, should be used. The benefit of detecting and treating asymptomatic bacteriuria in healthy women has been demonstrated only in pregnancy and before urologic instrumentation or surgery.[7,29]

Recurrent Acute Uncomplicated Cystitis in Women

Most recurrent cystitis in healthy women is caused by repeated infection, which in many cases is caused by persistence of the initially

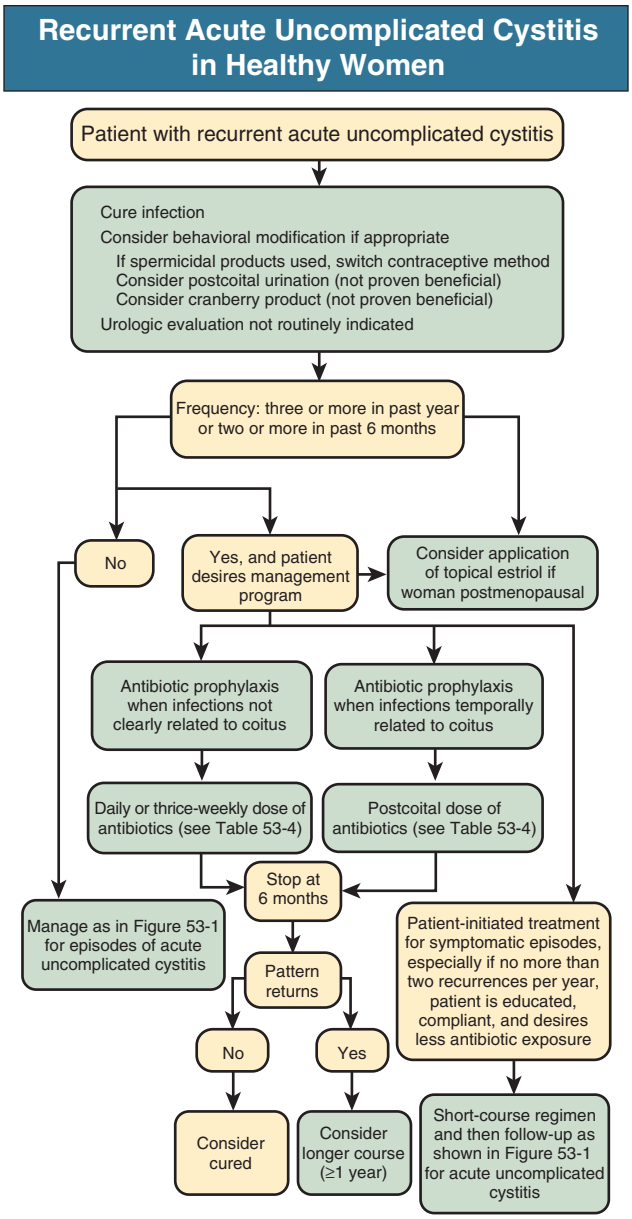

Figure 53-2 Management strategies for recurrent acute uncomplicated cystitis.

Prophylaxis for Recurrent Acute Uncomplicated Cystitis

Drug	Dose (mg)	Frequency
Continuous Prophylaxis		
TMP-SMX	40/200	Daily
TMP-SMX	40/200	Thrice weekly
Trimethoprim	100	Daily
Nitrofurantoin	50 or 100	Daily
Cefaclor	250	Daily
Cefalexin (cephalexin)	125 or 250	Daily
Norfloxacin*	200	Other fluoroquinolones are likely to be as effective.*
Postcoital Prophylaxis		
TMP-SMX	40/200	Single dose
TMP-SMX	80/400	Single dose
Nitrofurantoin	50 or 100	Single dose
Cefalexin	250	Single dose
Ciprofloxacin*	125	Single dose
Norfloxacin*	200	Single dose
Ofloxacin*	100	Single dose

Table 53-4 Antimicrobial prophylaxis regimens for women with recurrent acute uncomplicated cystitis. See text and Figure 53-2 for management strategy. *Women should be cautioned about pregnancy when fluoroquinolones are being used. Fluoroquinolones are highly effective but not recommended. *TMP-SMX,* Trimethoprim-sulfamethoxazole.

infecting strain in the fecal flora.[30] Experimental studies in mice also suggest that some same-strain recurrent UTIs may be caused by a latent reservoir of uropathogens in the bladder epithelium that persist after the initial UTI,[31] and indirect evidence indicates that this pathogenesis pathway may occur in humans.[32] If the recurrence is within 1 or 2 weeks of treatment, an antimicrobial-resistant uropathogen should be considered, and a urine culture should be performed followed by treatment with an alternative regimen. It is reasonable to treat later recurrences the same as the original infection, although if TMP-SMX has been used in the previous 6 months, an alternative drug should be considered.[15]

The goal of long-term management of recurrent cystitis should be to improve the quality of life while minimizing antimicrobial exposure.[15] Women with recurrent cystitis may benefit from behavioral modification (Fig. 53-2), such as avoiding spermicides, increasing fluid intake, and ensuring postcoital micturition, although the benefit of these practices has not been proved. Although ingestion of cranberry products has been thought to have preventive properties based on small clinical studies and *in vitro* inhibition of uropathogen adherence to uroepithelial cells, a recent randomized, placebo-controlled trial (RCT) showed no benefit from cranberry juice.[33] Women who do not want to try or who obtain no benefit from the preceding approaches should be offered antimicrobial prophylaxis.

Antimicrobial prophylaxis has been shown to reduce the risk of recurrent cystitis by approximately 95% (Table 53-4; see also Fig. 53-2).[34] Prophylaxis should be considered for women who experience three or more infections during a 12-month period, or whenever the woman thinks that her life is being adversely affected by frequent recurrences. Several approaches have been used, including continuous prophylaxis, postcoital prophylaxis, and intermittent self-treatment (which is really an early treatment method).[15] In postmenopausal women with recurrent UTI, intravaginal estriol is effective, presumably by normalizing the vaginal flora, which reduces the risk for coliform colonization of the vagina.[30] This approach offers an alternative to antimicrobial strategies (see Fig. 53-2).

Acute Uncomplicated Pyelonephritis in Women

Acute pyelonephritis is suggested by fever (temperature ≥38°C), chills, flank pain, nausea and vomiting, and costovertebral angle tenderness. Cystitis symptoms are variably present. Symptoms may vary from a mild illness to a sepsis syndrome with or without shock and renal failure. Pyuria is almost always present, but leukocyte casts, specific for UTI, are infrequently seen. Gram stain of the urine sediment may aid in differentiating gram-positive and gram-negative infections, which can influence empiric therapy. A urine culture,

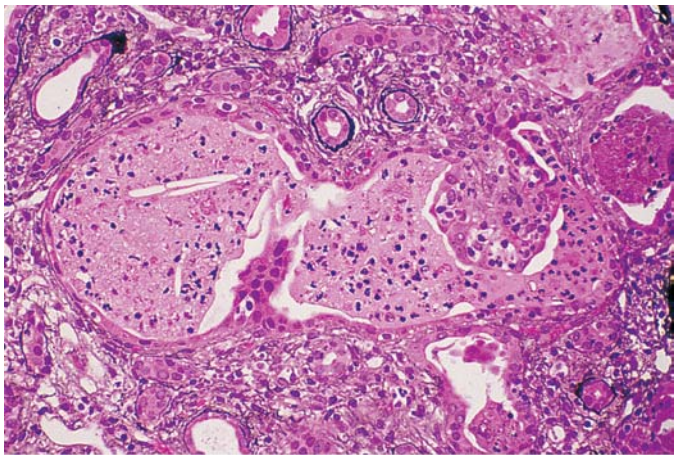

Figure 53-3 Acute pyelonephritis. Renal tissue shows a dilated tubule with neutrophils enmeshed in proteinaceous debris ("pus casts") with adjacent interstitial inflammation. *(Courtesy C. Alpers, University of Washington, Seattle.)*

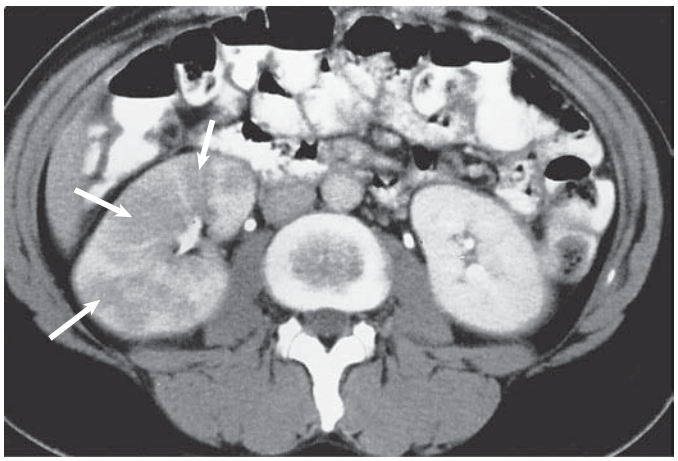

Figure 53-4 Acute pyelonephritis. Contrast-enhanced CT scan shows areas of lower density caused by infection and edema *(arrows)*. *(Courtesy W. Bush, University of Washington, Seattle.)*

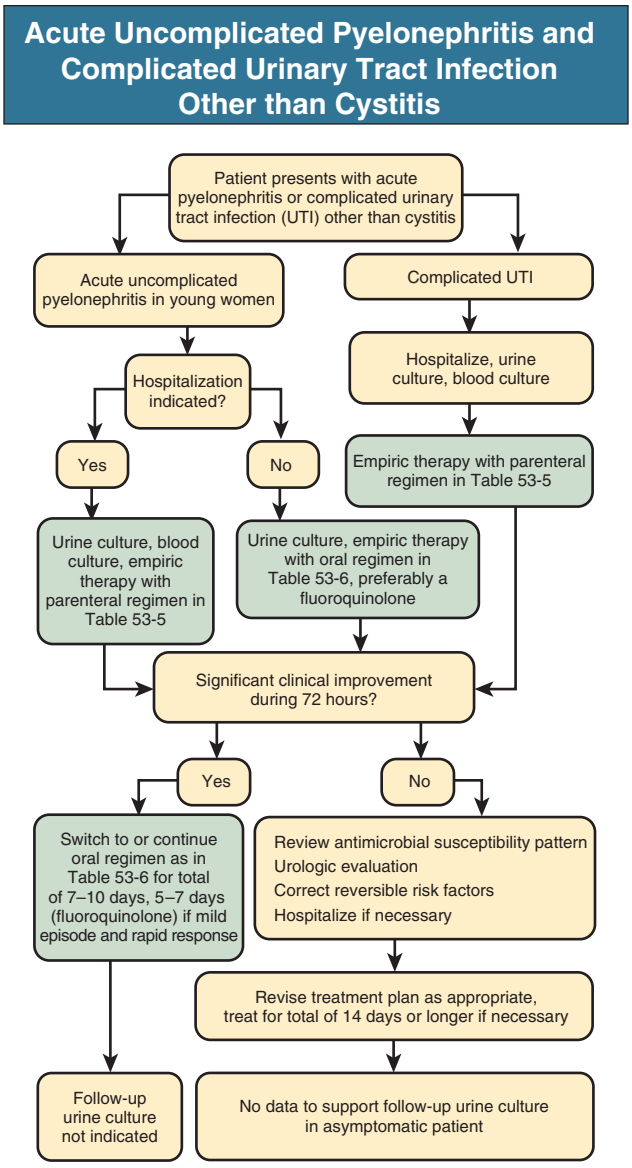

Figure 53-5 Management algorithm for acute uncomplicated pyelonephritis and complicated urinary tract infection other than cystitis.

which should be performed in all women with acute pyelonephritis, will have 10^4 cfu/ml or more of uropathogens in up to 95% of patients.[16]

On pathologic examination, the kidney shows a focal inflammatory reaction with neutrophil and monocyte infiltrates, tubular damage, and interstitial edema (Fig. 53-3). Although imaging studies are generally not performed, the infected kidney is often enlarged, and contrast-enhanced computed tomography (CT) shows decreased opacification of the affected parenchyma, typically in patchy, wedge-shaped, or linear patterns (Fig. 53-4).

The availability of effective oral antimicrobials, especially the fluoroquinolones, allows initial oral therapy in appropriate patients or, in those requiring parenteral therapy, the timely conversion from intravenous to oral therapy and reduced need for hospitalization. Indications for admission to the hospital include inability to maintain oral hydration or to take medications; uncertain social situation or concern about compliance; uncertainty about the diagnosis; and severe illness with high fevers, severe pain, and marked debility. Outpatient therapy is safe and effective for select patients who can be stabilized with parenteral fluids and antibiotics in an urgent care facility and sent home with oral antibiotics under close supervision. In one population-based study of acute pyelonephritis in adult women, only 7% were hospitalized.[4]

The management strategy for acute uncomplicated pyelonephritis is shown in Figure 53-5. Many effective parenteral (Table 53-5) and oral (Table 53-6) regimens are available for patients with acute uncomplicated pyelonephritis. In the outpatient setting, an oral fluoroquinolone should be used for initial empiric treatment of infection caused by gram-negative bacilli.[26] TMP-SMX or other agents can be used if the infecting strain is known to be susceptible. If enterococci are suspected from the Gram stain, amoxicillin should be added to the treatment regimen until the causative organism is identified. Second- and third-generation cephalosporins also appear effective, although published data are sparse. Neither nitrofurantoin nor fosfomycin is approved or recommended for the treatment of pyelonephritis. When antimicrobial resistance or tolerance of oral medications is a concern, one or more doses of a broad-spectrum parenteral antimicrobial is recommended until *in vitro* activity can be ensured.[22]

For hospitalized patients, ceftriaxone is an effective and inexpensive agent if the Gram stain is not suggestive of gram-positive bacterial infection. If enterococci are suspected on the basis of a stain showing gram-positive bacteria, ampicillin plus gentamicin, ampicillin-sulbactam, and piperacillin-tazobactam are reasonable broad-spectrum empiric choices. TMP-SMX should not be used alone for empiric therapy for pyelonephritis in areas with a high prevalence of resistance to this combination. Patients with acute uncomplicated pyelonephritis can often be switched to oral therapy after 24 to 48 hours, although longer intervals of parenteral therapy are occasionally indicated in patients whose symptoms and signs do not improve rapidly, such as those with continued high fever, severe flank pain, or persistent nausea and vomiting.

Treatment of acute uncomplicated pyelonephritis can be limited to 7 days for mildly to moderately ill patients who have a rapid response with resolution of fever and symptoms soon after initiation of treatment. However, β-lactam regimens shorter than 14 days have been associated with unacceptably high failure rates in some studies.[26] One study demonstrated superiority of a 7-day ciprofloxacin regimen over a 14-day TMP-SMX regimen, with the difference accounted for entirely by the higher rate of resistance of the uropathogens to TMP-SMX.[14]

Routine post-treatment urine cultures in asymptomatic patients are not cost-effective, but cultures should be performed if symptoms persist or recur. Recurrent infections are treated with a 7- to 14-day course of an antibiotic to which the organism is susceptible. Symptomatic patients who have persistent infection with the same strain as the initial infecting strain warrant 10 to 14 days of therapy, or even longer in some cases, and complicating factors should be looked for and corrected if found.

Parenteral Regimens for Acute Uncomplicated Pyelonephritis and Complicated Urinary Tract Infection*

Drug	Dose (mg)	Interval
Ceftriaxone	1000-2000	q24h
Cefepime	1000-2000	q12h
Fluoroquinolones†		
Ciprofloxacin	200-400	q12h
Levofloxacin	250-750	q24h
Gentamicin† (± ampicillin)	3-5 mg/kg body weight 1 mg/kg body weight	q24h q8h
Ampicillin (+ gentamicin†)	1000	q6h
Trimethoprim-sulfamethoxazole†	160/800	q12h
Aztreonam	1000	q8-12h
Piperacillin-tazobactam	3375	q6-8h
Imipenem-cilastatin†	250-500	q6-8h
Meropenem	500	q8h
Ertapenem	1000	q24h
Vancomycin§	1000	q12h

Table 53-5 Parenteral regimens for acute uncomplicated pyelonephritis and complicated urinary tract infection. *Duration depends on clinical setting (see text and Fig. 53-5). †Avoid, if possible, in pregnancy. §Recommended if methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected or known.

Acute Cystitis in Healthy Adults with Possible Occult Renal or Prostatic Involvement

Acute cystitis in healthy individuals other than young women is more likely to involve occult renal or prostatic infection (see Box 53-1) and may respond poorly to short-course therapy. Clinicians lack noninvasive tools to localize infections to the kidney or prostate, so clinical estimation of risk in a given patient is imprecise. Some patients, such as those who are diabetic or pregnant, warrant special attention because of the serious complications that can occur if treatment is inadequate. Symptoms, signs, and laboratory findings in this group are the same as those in uncomplicated cystitis in women. Urethritis must be excluded in dysuric sexually active men by a urethral Gram stain or a first-voided urine specimen wet-mount evaluation for urethral leukocytosis.

A urine culture specimen should be obtained routinely in patients before treatment (see Fig. 53-1). Empiric treatment is similar to that used for uncomplicated cystitis in women, although it is reasonable to treat men, who may have prostatic involvement, for longer. Nitrofurantoin and fosfomycin should be avoided except for cystitis in pregnancy, in which duration of treatment is 5 days or single-dose, respectively. A recent large retrospective study of male veterans with UTI found no difference in recurrence rates with 7 days of treatment versus longer, with a trend toward more *Clostridium difficile* infections in those treated longer.[35]

Routine post-treatment cultures are not indicated unless the patient is symptomatic, except in pregnant women (see Fig. 53-1). In men, early recurrence of UTI with the same species suggests a

Oral Regimens for Acute Uncomplicated Pyelonephritis and Complicated Urinary Tract Infection

Drug	Dose (mg)	Interval	Comment
Fluoroquinolones			Preferred for empiric treatment; avoid if possible in pregnancy, nursing mothers, or persons <18 years old
Ciprofloxacin	500	q12h	
Ciprofloxacin extended release	1000	q24h	
Levofloxacin	250 to 750	q24h	
Trimethoprim-sulfamethoxazole	160/800	q12h	Use only when the causative pathogen is known to be susceptible. If used in pregnancy (not approved use), avoid in first trimester.
Cefpodoxime proxetil	200	q12h	Data are sparse; use only when the causative pathogen is known to be susceptible.
Amoxicillin-clavulanate	500/125 to 875/125	q8h	Use only when the causative pathogen is known to be susceptible, or in addition to a broad-spectrum agent when empiric coverage against enterococci is desirable.

Table 53-6 Oral regimens for acute uncomplicated pyelonephritis and complicated urinary tract infection. Duration depends on clinical setting (see text and Fig. 53-5).

prostatic source of infection and warrants a 4- to 6-week regimen of either a fluoroquinolone (preferable) or TMP-SMX, depending on the antimicrobial susceptibility of the infecting strain.

Complicated Infections

Patients with complicated UTI may present with classic signs of cystitis and pyelonephritis but may also have vague or nonspecific symptoms, such as fatigue, irritability, nausea, headache, and abdominal or back pain. Signs and symptoms may exist for weeks to months before diagnosis. Complicated UTI, as with uncomplicated infection, is generally associated with pyuria and bacteriuria, although these may be absent if the infection does not communicate with the collecting system.

Urine culture should always be performed in patients with suspected complicated UTI. The IDSA consensus definition of complicated UTI is 10^5 cfu/ml or more in women and 10^4 cfu/ml or more in men,[16] but lower counts in symptomatic persons, as demonstrated in patients with uncomplicated UTI, may well represent significant bacteriuria. This is especially true when the specimen is collected from a urinary catheter. Thus, it is reasonable to use a colony count threshold of 10^3 cfu/ml or more to diagnose complicated UTI.

The wide variety of underlying conditions (see Box 53-1), diverse bacterial agents (see Table 53-2), and paucity of RCTs make generalizations about antimicrobial therapy difficult. Figure 53-1 outlines the management strategy for complicated cystitis, and Figure 53-5 provides a management algorithm for complicated infections other than cystitis.

Correction of any underlying anatomic, functional, or metabolic defect must be attempted, because antibiotics alone may not be successful.[1] For empiric therapy in patients with mild to moderate illness who can be treated with oral medication, the fluoroquinolones provide the broadest spectrum of antimicrobial activity, cover most expected pathogens, and achieve high levels in the urine and urinary tract tissue. An exception is moxifloxacin, which in contrast to other fluoroquinolones such as ciprofloxacin and levofloxacin, may not achieve sufficient concentrations in urine to be effective for complicated UTI. If the infecting pathogen is known to be susceptible, TMP-SMX or other agents are reasonable therapeutic choices.

For initial treatment in more seriously ill, hospitalized patients, several parenteral antimicrobial agents are available (see Table 53-5). The broader-spectrum agents shown in Table 53-5 are preferable for health care–associated infections. In contrast to uncomplicated UTI, *S. aureus* is more common in complicated UTIs, and if suspected, the therapeutic regimen should have activity against *S. aureus*. Studies show that a high proportion of *S. aureus* isolates, even in the community, are methicillin resistant (MRSA), so vancomycin should be included in the empiric treatment regimen if *S. aureus* is suspected. Potential concerns that must be considered in the management of complicated UTI include the increasing prevalence of resistance to fluoroquinolones in institutional settings and the frequency of enterococcal infections.

The antimicrobial regimen can be modified when the infecting strain has been identified and antimicrobial susceptibilities are known. Patients receiving parenteral therapy can be switched to oral treatment after clinical improvement. Few studies have been performed that evaluate duration of treatment in populations with complicated UTIs. However, it is desirable to limit the duration of treatment, especially for milder infections, to reduce the selection pressure for drug-resistant flora. In one study, clinical and microbiologic success rates after treatment were almost identical in patients with acute pyelonephritis or complicated UTI treated with a 5-day course of levofloxacin or a 10-day course of ciprofloxacin.[36] These data suggest that a 7- to 10-day regimen is reasonable for most patients with complicated UTI, depending on their severity of illness and clinical response; shorter regimens, such as a 5-day regimen of a urinary fluoroquinolone, are likely to be sufficient in those patients who are less severely ill, are infected with uropathogens susceptible to the antibiotic used, and have a rapid response to treatment. At least 10 to 14 days of therapy is recommended in patients who have a delayed response.

Chronic Kidney Disease

Because of the wide variety of underlying diseases and comorbidities, prior instrumentation of the urinary tract, and differences in age and gender, the incidence of UTI in patients with chronic kidney disease (CKD) is not known.[37] Moreover, there are few data on urine concentrations of antimicrobials used for the treatment of UTI in patients with CKD.[38] Studies in animals suggest that (1) urine drug concentrations are necessary to sterilize urine, (2) effective tissue concentrations are necessary to treat pyelonephritis, and (3) serum concentrations of antimicrobials are correlated with the drug concentrations in renal tissue. Thus, for patients with CKD who have a therapeutic serum drug level and adequate perfusion of the renal parenchyma, the delivery of therapeutic concentrations of both the parenchyma and the urine should be adequate, but some oral agents for cystitis may not deliver adequate concentrations to the urine.[38] For patients with low glomerular filtration rate (GFR) and pyelonephritis or cystitis, the agents listed in Tables 53-5 and 53-6 for pyelonephritis and complicated cystitis should be adequate to treat these infections in patients with chronic renal impairment if the organism is susceptible.[38]

As noted previously, however, β-lactams are not as effective as fluoroquinolones, even in patients with normal renal function.[26] For oral treatment, renally adjusted doses of ciprofloxacin or levofloxacin, but not moxifloxacin, are recommended. Nitrofurantoin and sulfamethoxazole are not recommended in patients with reduced creatinine clearance, although trimethoprim concentrations appear to be adequate.[37] Likewise, according to the package insert, renal impairment significantly decreases the excretion of fosfomycin, which thus also should not be used in such patients.

Catheter-Associated Infections

Approximately 15% to 25% of patients in general hospitals have a urethral catheter inserted at some time during their stay, and approximately 5% to 10% of long-term care facility residents are managed with urethral catheterization, in some cases for years. The incidence of bacteriuria associated with indwelling catheters is 3% to 10% per day of catheterization, and the duration of catheterization is the most important risk factor for the development of catheter-associated bacteriuria.

Catheter-associated bacteriuria is the most common source of gram-negative bacteremia in hospitalized patients. Complications of long-term catheterization (≥30 days) include almost universal bacteriuria, often with multiple antibiotic-resistant flora, and (in addition to cystitis, pyelonephritis, and bacteremia, as seen with short-term catheterization) frequent febrile episodes, catheter obstruction, stone formation associated with urease-producing uropathogens, and local genitourinary infections. Other rare complications include fistula formation and bladder cancer. An increase in mortality risk has been reported with catheter-associated bacteriuria, but it is difficult to distinguish the role of the catheter because most deaths occur in patients who have severe underlying disease.

Most episodes of catheter-associated bacteriuria are asymptomatic and do not require routine screening or treatment because

treatment does not reduce the complications of bacteriuria and can lead to antimicrobial resistance.[7] Moreover, the presence or absence of pyuria does not differentiate symptomatic from asymptomatic urinary infection.[7] Symptomatic UTIs, often caused by many multidrug-resistant uropathogens, warrant broad-spectrum therapy, as described previously. In a symptomatic catheterized patient, a urine culture specimen should be obtained from a freshly placed catheter if the catheter has been in place for a few days, because the catheter biofilm may result in spurious culture results. Moreover, clinical outcomes are improved if the catheter is replaced at the time of antimicrobial therapy.[39] Seven days is the recommended duration of antimicrobial treatment for patients who have prompt resolution of symptoms, and 10 to 14 days if response is delayed.[40]

Preventive measures are indicated to reduce the morbidity, mortality, and costs of catheter-associated infection. Effective strategies include avoidance of a catheter when possible and, when the catheter is necessary, sterile insertion, prompt removal, and strict adherence to a closed collecting system.[6,40] Bundling of preventive steps may be useful.[41] Meta-analyses have shown that rates of catheter-associated bacteriuria, at least in patients catheterized for less than 2 weeks, are higher in patients with an indwelling urethral catheter than in those with intermittent or suprapubic catheterization.[42] Likewise, condom catheterization is preferable to indwelling urethral catheterization in appropriately selected men.[43] Although highly effective in reducing catheter-associated UTI rates, prophylactic systemic antimicrobial agents are generally not recommended for routine use because of concerns about selection for antimicrobial resistance. Antimicrobial-coated catheters appear to be effective in reducing catheter-associated bacteriuria in patients catheterized for less than 2 weeks, but these have not been shown to be effective in reducing symptomatic infection.

Spinal Cord Injury

Spinal cord injury alters the dynamics of voiding and often requires the use of bladder drainage with catheters. The diagnosis of UTI in patients with spinal cord injuries is often problematic and is based on the combination of symptoms and signs (which are often nonspecific), pyuria, and significant bacteriuria. Uropathogens are usually present in quantities of 10^5 cfu/ml or more. Fluoroquinolones are the empiric oral agents of choice in patients with mild to moderate infection, although many uropathogens, even in the outpatient setting, are resistant to this class of antibiotic, and parenteral antibiotics may be needed.

Treatment of asymptomatic bacteriuria in patients with spinal cord injuries is not of proven benefit and increases the risk for infection with antimicrobial-resistant uropathogens.[7,44] Likewise, antibiotic prophylaxis is generally not recommended, although it may be considered for select outpatients with frequent symptomatic UTIs for whom there are no correctible risk factors. Recent studies have shown that use of a hydrophilic-coated catheter for intermittent catheterization is associated with a reduction in the incidence of symptomatic UTI in patients with spinal cord injury.[45]

Prostatitis

Prostatitis occurs in up to 25% of men during their lifetime, but it is caused by acute or chronic bacterial infection in a minority.[46] The most common organisms causing bacterial prostatitis are gram-negative bacilli, including *E. coli*, *Proteus* spp., *Klebsiella* spp., *P. aeruginosa,* and less frequently, enterococci and *S. aureus*. The pathogenesis of prostatitis is believed to be related to reflux of infected urine from the urethra into the prostatic ducts. Prostatic calculi, commonly found in adult men, may provide a nidus for bacteria and protection from antibacterial agents.

Acute bacterial prostatitis is rare. Patients present with dysuria, frequency, urgency, obstructive voiding symptoms, fever, chills, and myalgias. The prostate is tender and swollen. Prostatic massage, as a diagnostic test, is contraindicated in men in whom the diagnosis of acute prostatitis is being considered because of the risk for precipitating bacteremia. The patient will usually have pyuria and a positive urine culture. Patients who are severely ill require hospitalization and parenteral antibiotics, but many patients can be treated in the outpatient setting with oral fluoroquinolones. The recommended duration of treatment is 14 to 30 days.[46] Rarely, abscess formation may occur.

Chronic bacterial prostatitis is characterized by recurrent UTIs with the same uropathogen with intervening asymptomatic periods. The prostate typically is normal to palpation during asymptomatic periods. Chronic bacterial prostatitis is characterized microscopically by the presence of 10 or more leukocytes per high-power field in expressed prostatic secretions or postmassage voided urine in the absence of significant pyuria in first-voided and midstream urine specimens, as well as a uropathogen colony count at least 10-fold higher in the expressed prostatic secretions or postmassage voided urine compared with the first-voided midstream urine. In addition, macrophage-laden fat droplets (oval fat bodies) are usually prominent in the prostatic secretions. These tests, however, are infrequently performed by urologists. Cure rates, which historically have been low, are 60% to 80% with the fluoroquinolones, which are the antibiotics of choice. The optimal duration of treatment is unknown, but 4 to 6 weeks is recommended by some authorities,[46] whereas others recommend up to 3 months. Some patients require long-term, low-dose suppressive therapy to prevent symptomatic UTIs. Surgical intervention is only rarely considered and is associated with high morbidity.

Renal Abscess

Renal cortical and corticomedullary abscesses and perirenal abscesses occur in 1 to 10 per 10,000 hospital admissions.[47] Patients usually present with fever, chills, back or abdominal pain, and costovertebral angle tenderness, but they may have no urinary symptoms or findings if the abscess does not communicate with the collecting system, as often occurs with a cortical abscess. Bacteremia may be primary (cortical abscess) or secondary (corticomedullary or perirenal). The clinical presentation may be insidious and nonspecific, especially with perirenal abscess, and the diagnosis may not be made until admission to a hospital or at autopsy. CT is recommended to establish the diagnosis and location of a renal or perirenal abscess (Fig. 53-6). Empiric antibiotic therapy should be broad and cover *S. aureus* and other uropathogens causing complicated UTI (see Fig. 53-5 and Table 53-5) and modified once urine culture results are known.

A *renal cortical abscess* (renal carbuncle) is usually caused by *S. aureus*, which reaches the kidney by hematogenous spread. Treatment with antibiotics is usually effective, and drainage is not required unless the patient is slow to respond. A *renal corticomedullary abscess,* in contrast, usually results from ascending UTI in association with an underlying urinary tract abnormality, such as obstructive uropathy or VUR, and is usually caused by common uropathogenic species such as *E. coli* and other gram-negative bacilli. Such abscesses may extend deep into the renal parenchyma, perforate the renal capsule, and form a perirenal abscess. Treatment with antimicrobial agents without drainage may be effective if the abscess is small and if the underlying urinary tract abnormality can be corrected. Aspiration of the abscess may be necessary in some patients, and nephrectomy may occasionally be required in patients with diffuse renal involvement or with severe sepsis. Perirenal abscesses

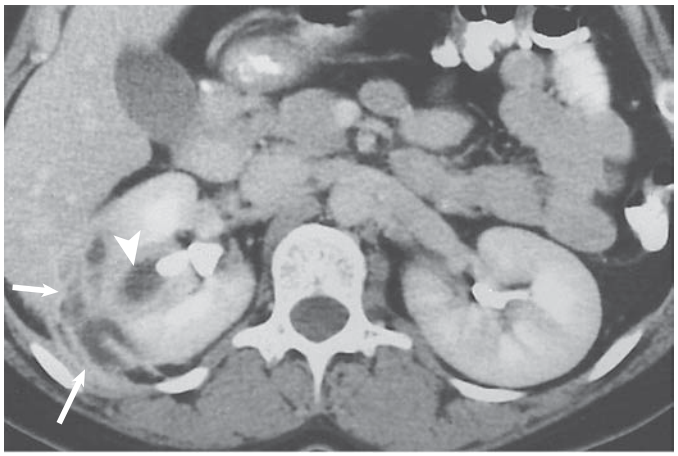

Figure 53-6 Renal abscess. Contrast-enhanced CT scan shows an abscess in the medulla of the kidney *(arrowhead)* with penetration and extension into the perinephric space *(arrows)*. *(Courtesy L. Towner.)*

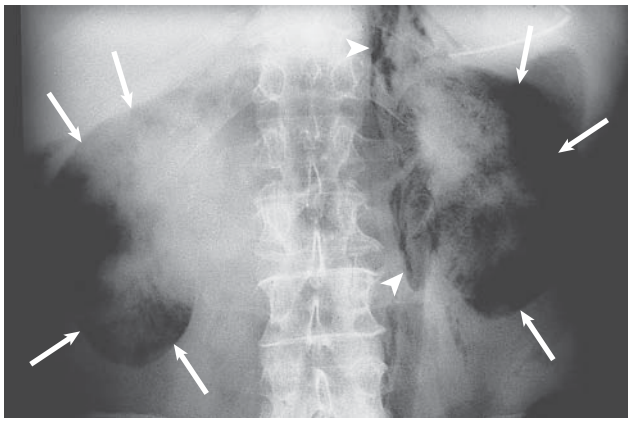

Figure 53-7 Emphysematous pyelonephritis. A plain radiograph in this febrile diabetic patient revealed diffuse gas formation throughout both kidneys *(outlined by arrows)* and gas dissecting in the left retroperitoneal space *(arrowheads)*. *(Courtesy W. Bush, University of Washington, Seattle.)*

usually occur in the setting of obstruction or other complicating factors (see Box 53-1) and result from ruptured intrarenal abscesses, hematogenous spread, or spread from a contiguous infection. Causative uropathogens are those usually found in complicated UTIs (see Table 53-2), including *S. aureus* and enterococci; polymicrobial infections are common. Anaerobes or *Mycobacterium tuberculosis* may be causative (see Chapter 54). A previously high mortality rate has been lowered with earlier diagnosis and therapy. In contrast to the other types of renal abscesses, drainage of pus is the cornerstone of therapy, and nephrectomy may be indicated.

Papillary Necrosis

More than half of patients who develop papillary necrosis have diabetes, almost always in conjunction with a UTI, but the condition also complicates sickle cell disease, analgesic abuse, and obstruction. Renal papillae are vulnerable to ischemia because of the sluggish blood flow in the vasa recta, and relatively modest ischemic insults may cause papillary necrosis. The clinical features are those typical of pyelonephritis. In addition, passage of sloughed papillae into the ureter may cause renal colic, renal impairment or failure, or obstruction with severe urosepsis. Papillary necrosis in the setting of pyelonephritis is associated with pyuria and a positive urine culture. Causative uropathogens are those typical of complicated UTI. CT is the preferred diagnostic procedure. Radiologic findings include an irregular papillary tip; dilated calyceal fornix; extension of contrast material into the parenchyma; and a separated crescent-shaped papilla surrounded by contrast, called the *ring sign*. Broad-spectrum antibiotics are indicated. Papillae obstructing the ureter may require removal with a cystoscopic ureteral basket or relief of obstruction by insertion of a ureteral stent.

Emphysematous Pyelonephritis

Emphysematous pyelonephritis is a fulminant, necrotizing, life-threatening variant of acute pyelonephritis caused by gas-forming organisms, including *E. coli*, *Klebsiella pneumoniae*, *P. aeruginosa*, and *P. mirabilis*.[48] Up to 90% of cases occur in diabetic patients, and obstruction may be present. Symptoms are suggestive of pyelonephritis, and there may be a flank mass. Dehydration and ketoacidosis are common. Pyuria and a positive urine culture are usually present. Gas is usually detected by a plain abdominal radiograph or ultrasound (Fig. 53-7). CT is the diagnostic modality of choice, however, because it can localize the gas better than ultrasound. Accurate localization of gas is important because gas may also form in an infected obstructed collecting system or renal abscess; although serious, these conditions do not carry the same poor prognosis and are managed differently. Parenteral broad-spectrum antibiotics and percutaneous catheter drainage with relief of obstruction may be adequate for less severely ill patients, but nephrectomy is warranted for those who are more severely ill and those less severely ill who do not respond to the preceding steps. Medical treatment is associated with mortality of 60% to 80%, which is lowered to 20% or less with surgical intervention (e.g., nephrectomy, percutaneous drainage).

Renal Malacoplakia

Malacoplakia is a chronic granulomatous disorder of unknown etiology involving the genitourinary, gastrointestinal, skin, and pulmonary systems.[49] It is characterized by an unusual inflammatory reaction to a variety of infections and is manifested by the accumulation of macrophages containing calcified bacterial debris called Michaelis-Gutmann bodies (Fig. 53-8). The underlying disorder appears to be a monocyte-macrophage bactericidal defect. The diagnosis is made by histologic examination of involved tissue. Genitourinary malacoplakia, most often involving the bladder, is usually associated with gram-negative UTI. Patients with renal malacoplakia generally have fever, flank pain, pyuria and hematuria, bacteriuria, and if both kidneys are involved, impaired renal function. CT usually shows enlarged kidneys with areas of poor enhancement, and the condition may be indistinguishable from other infectious or neoplastic lesions. On occasion, the malacoplakia may extend through the renal capsule into the perinephric space, simulating a renal carcinoma (Fig. 53-8). Treatment consists of therapy with a broad-spectrum antimicrobial, attempted correction of any underlying complicating conditions, and improvement of renal function. Nephrectomy is recommended for advanced unilateral disease. When the disease is bilateral or occurs in a transplanted kidney, the prognosis is very poor.

Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis is a poorly understood, uncommon but severe chronic destructive granulomatous inflammation of renal parenchyma associated with obstruction and infection of the urinary tract.[50] The renal parenchyma is replaced with a diffuse or segmental cellular infiltrate of foam cells, which are lipid-laden macrophages. The process may also extend beyond the renal capsule to the retroperitoneum. Its pathogenesis appears to be multifactorial,

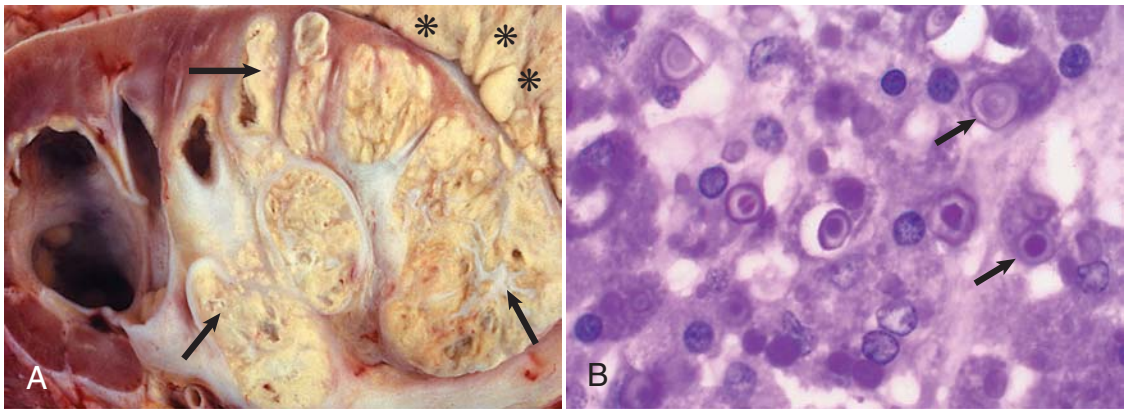

Figure 53-8 Renal malacoplakia. A, Malacoplakia involving most of the kidney *(arrows)* with extension through the capsule *(asterisks)*. A small portion of normal kidney is present that is associated with hydronephrosis secondary to obstruction by the malacoplakia. **B,** The kidney tissue shows many macrophages containing intracytoplasmic inclusions (*arrows* identify two particularly well-demarcated macrophages with Michaelis-Gutmann bodies). *(Courtesy L. Truong, Baylor College of Medicine, Houston, and N. Sheerin, Guy's Hospital, London.)*

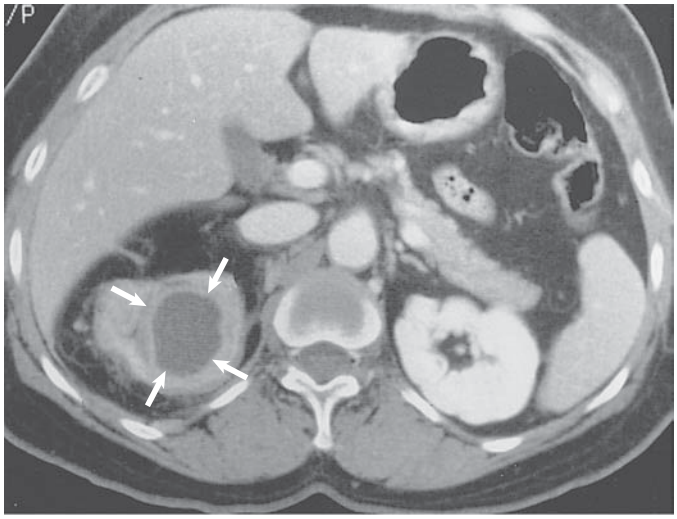

Figure 53-9 Xanthogranulomatous pyelonephritis. Contrast-enhanced CT scan with the inflammatory mass outlined by *arrows*. Pathologic diagnosis confirmed xanthogranulomatous pyelonephritis. *(Courtesy W. Bush, University of Washington, Seattle.)*

with infection complicating obstruction and leading to ischemia, tissue destruction, and accumulation of lipid deposits. Patients with xanthogranulomatous pyelonephritis are characteristically middle-aged women and have chronic symptoms such as flank pain, fever, chills, and malaise. Flank tenderness, a palpable mass, and irritative voiding symptoms are common. The urine culture is usually positive with *E. coli,* other gram-negative bacilli, or *S. aureus*. CT generally shows an enlarged nonfunctioning kidney, often the presence of calculi and low-density masses (xanthomatous tissue), and in some cases, involvement of adjacent structures (Fig. 53-9). It may be difficult to distinguish from neoplastic disease. Broad-spectrum antimicrobials are indicated, but total or partial nephrectomy is usually necessary for cure.

Asymptomatic Bacteriuria

Asymptomatic bacteriuria, as noted previously, is a common and generally benign infection.[7,29] Pyuria is often present, especially in elderly people, and is a predictor for subsequent symptomatic UTI in some groups. Causative uropathogens are the same as those causing UTIs in the same population. Screening for and treatment of asymptomatic bacteriuria is generally not warranted.[7] However, patients at high risk for serious complications warrant a more aggressive approach to diagnosis and treatment, including pregnant women and patients undergoing urologic surgery. Current management strategies in patients with a renal transplant, including long-term antimicrobial prophylaxis, help prevent both asymptomatic bacteriuria and symptomatic UTI. It is not clear, however, whether screening for or treatment of asymptomatic bacteriuria in such patients is worthwhile.[7] Some authorities advise treatment of asymptomatic bacteriuria found in patients with anatomic or functional abnormalities of the urinary tract, diabetic patients, and patients with urea-splitting bacteria (e.g., *P. mirabilis, Klebsiella* spp.).[29] Evidence-based guidelines for screening and treatment of asymptomatic bacteriuria in these populations are needed.

Asymptomatic bacteriuria in catheterized patients in hospitals and long-term care facilities, although thought to be generally benign, represents a large reservoir of antimicrobial-resistant urinary pathogens that increases the risk of cross-infection among catheterized patients and results in frequent inappropriate antimicrobial use.[40]

IMAGING OF THE URINARY TRACT

Urologic consultation and evaluation of the urinary tract should be considered in patients who present with symptoms or signs of obstruction, urolithiasis, flank mass, or urosepsis. Similarly, such an evaluation should be considered for those patients with presumptive uncomplicated or complicated UTI who have *not* had a satisfactory clinical response after 72 hours of treatment, to exclude complicating factors. A renal ultrasound can detect the size and contour of the kidneys and bladder, the presence of a renal mass or abscess, certain renal and ureteral calculi, hydronephrosis suggestive of obstructive uropathy, and elevated postvoid residual urine.[51] A plain abdominal radiograph (kidneys-ureters-bladder, KUB) can identify radiopaque calculi along the genitourinary tract, especially proximal and distal ureteral stones that can be missed on ultrasound. However, renal ultrasound and KUB are less sensitive than CT for detection of many conditions in patients with complicated UTI. Thus, any finding suggesting mass or complex fluid collection should prompt follow-up imaging with CT. CT offers fine anatomic detail and is thus the superior study for evaluation of focal inflammation, renal or perirenal abscess and masses, and both radiopaque and radiolucent stones. However, CT also carries the greatest risk profile, exposing the

patient to both intravenous contrast and ionizing radiation.[51] Non–contrast-enhanced spiral CT is a rapid, safe, and sensitive method for evaluating patients with suspected renal stones. Radionuclide imaging procedures have no role in the evaluation of adults with UTI, although they are very useful in children with pyelonephritis (see Chapter 63).

Excretory urography and cystoscopy in women with recurrent cystitis rarely demonstrate abnormalities or alter management,[3] and therefore are not recommended. Likewise, imaging studies in young women with acute pyelonephritis are also generally not cost-effective and have a low diagnostic yield, although it is reasonable to obtain such studies after two episodes of pyelonephritis, or if any complicating factor is present (see Box 53-1). Imaging studies and cystoscopy are probably unnecessary in a man who has had a single UTI with no obvious complicating factors and whose infection responds promptly to treatment.

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CHAPTER 54

Tuberculosis of the Urinary Tract

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DEFINITION

Tuberculosis (TB), caused mostly by *Mycobacterium tuberculosis,* is a major global health problem. According to a recent report by the World Health Organization (WHO), there were almost 9 million new cases in 2011 and 1.4 million deaths attributed to TB.[1] From 1999 to 2020, there will be an estimated 1 billion new cases of TB if control measures are not improved. In developed countries, TB usually affects older individuals and immigrants from countries with high prevalence. The incidence of TB is 100 times greater in patients with human immunodeficiency virus (HIV), and TB is the most common opportunistic infection in HIV-infected patients.[2] TB also is more common in patients with chronic kidney disease (CKD), especially when associated with anatomic abnormalities or immunosuppression. In some endemic areas, TB has been reported to occur in up to 9% of patients receiving hemodialysis, 9% of renal allograft recipients, and 12% of children with nephrotic syndrome.[3]

Genitourinary TB occurs in about 5% of active TB cases in the non–HIV-infected population.[4] It is almost always secondary to a symptomatic or asymptomatic primary lesion in the lung. Renal involvement may also occur as a complication of miliary (septicemic) TB.

In recent years, the incidence of multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB has increased. According to WHO estimates, there were 630,000 cases of MDR TB in 2001.[1] This scenario has compromised programs to eradicate TB.

ETIOLOGY

The tubercle bacillus is a nonmotile, nonsporing, strictly aerobic straight or slightly curved rod-like bacillus that is weakly gram positive and acid and alcohol fast. Mycobacteria have a lipid shell ("lipid barrier") containing mycolic acid that resists proteolysis and uptake into phagolysosomes; muramyl dipeptide, which stimulates a T cell response that elicits the characteristic granuloma; and cell wall glycolipids that inhibit macrophage function. This surrounding coat of inert lipids and surface proteins allows mycobacteria to survive inside phagocytes, where they may remain dormant for years.[5]

Whereas most TB including genitourinary TB is caused by *M. tuberculosis,*[5] other mycobacteria may rarely cause clinical disease, especially in immunocompromised hosts. These include *M. avium-intracellulare*, *M. kansasii, M. bovis, M. fortuitum,* and *M. szulgai*.

PATHOGENESIS

The clinical and pathologic manifestations of TB depend on the virulence of the organism and the effectiveness of the host response. The host response may lead to complete containment of infection or result in an illness of varying severity. Strain differences may also determine whether an infected person develops primary TB, reactivation TB, or a chronic asymptomatic infection. A low serum level of 25-hydroxyvitamin D may also compromise cell-mediated immunity and increase the risk for activation of latent TB.

When an infected droplet with the size of 1 to 5 μm is deposited in the respiratory tract, tonsillar fossa, or gastrointestinal tract, a primary focus develops with the formation of a nonspecific, asymptomatic granuloma. The organisms from the primary focus drain to the regional lymph gland, causing its enlargement, resulting in the *primary complex*. This is often asymptomatic and self-limited.

Bacilli from the regional lymph node may also enter through the thoracic duct into the blood, resulting in silent dissemination to various sites, including the cortex of the kidneys (Fig. 54-1). Here the bacilli elicit an inflammatory response, resulting in granuloma formation that may heal and form a scar, remain dormant for many years, or rupture into the proximal tubule of the nephron. The bacilli in the nephron are trapped at the level of the loop of Henle, where they multiply. The relatively poor blood flow, hypertonicity, and high ammonia concentration in the renal medulla impair the immune responses and favor the formation of medullary granulomas. These granulomas (tuberculomas), which contain macrophages, may undergo coagulative necrosis, forming cheese-like caseous material (Fig. 54-2), and occasionally rupture into the calyx.[6]

The renal medulla is the most common site of involvement of clinical renal TB and is usually unilateral.[7] When this caseous focus ruptures into the collecting system, cavities and ulcers are formed, and involvement of renal papillae may lead to sloughing and papillary necrosis. Healing in the kidney occurs by fibrosis and scarring, resulting in strictures and obstruction. Calcification commences intracellularly by the accumulation of phosphate ions from the disintegration of nucleoproteins and calcium ions from cell membrane damage. These lesions may harbor live mycobacteria, and such dystrophic lesions should be considered active disease and not a sign of healing. Dystrophic calcification of damaged structures may result in a nonfunctioning kidney called "putty" or "cement" kidney. Spread of TB to contiguous structures may occur; ureteritis is common and may result in strictures and obstructive uropathy (Fig. 54-3).

The bladder may develop hyperemia near the ureteral orifice, followed by superficial ulcers and granulomatous changes involving all layers (pancystitis). Healing by fibrosis at the ureteral orifice results in a refluxing "golf-hole" ureter. Extensive fibrosis of the bladder wall results in a thick, small-capacity bladder called "thimble" bladder (Fig. 54-4). Bladder infection may also rarely result from instillation of bacille Calmette-Guérin (BCG) in the bladder as part of treatment of superficial bladder carcinomas.

Involvement of the genital tract is also common. As many as 70% to 80% of men with TB of the urinary tract have epididymitis, prostatitis, seminal vesiculitis, orchitis, or cold abscesses. In women, genital tract involvement is less common; but if present, it usually presents as salpingitis, often diagnosed during investigation for infertility.

Transplanted kidneys may transmit TB to their recipients.[8]

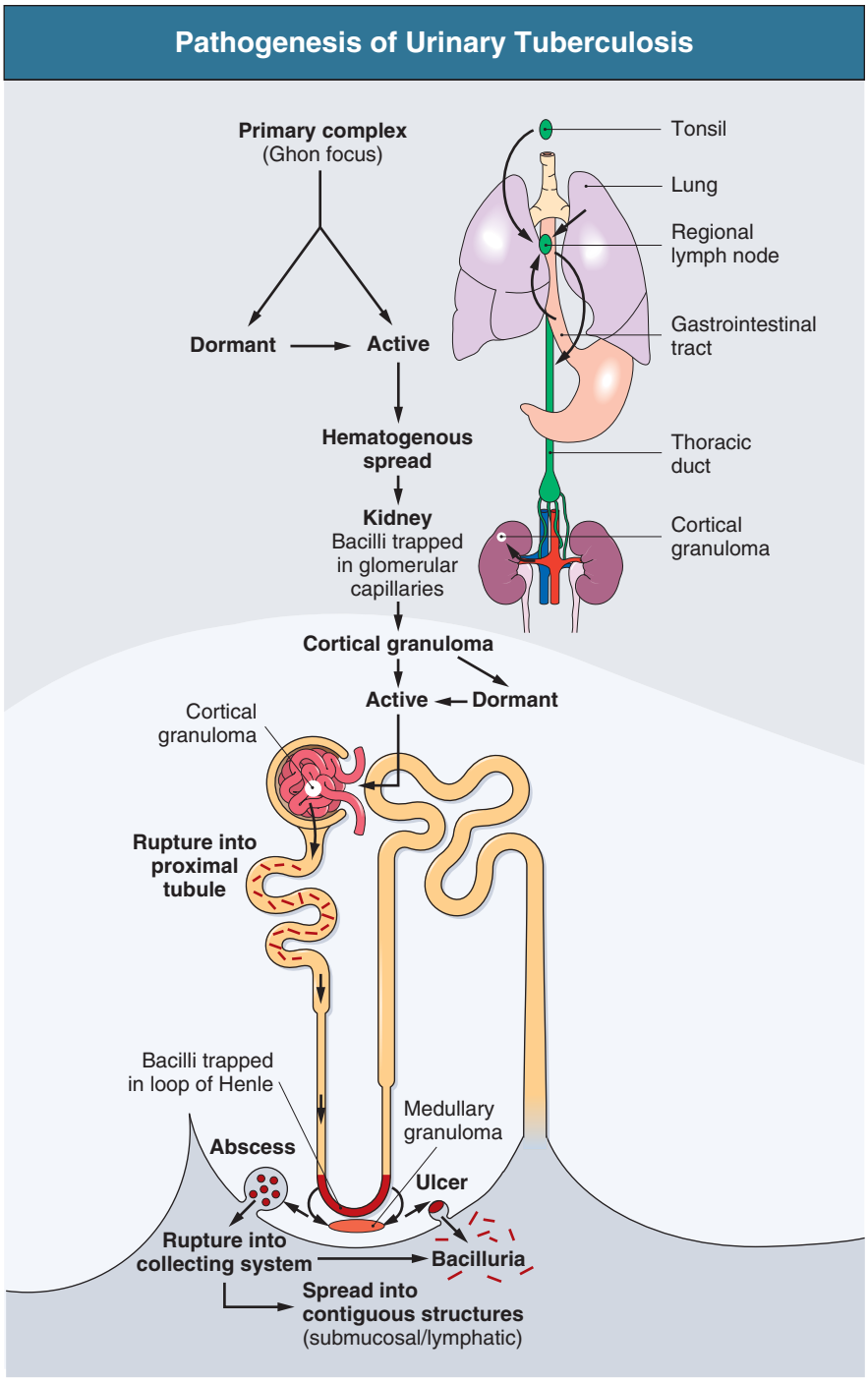

Figure 54-1 **Pathogenesis of urinary tuberculosis.**

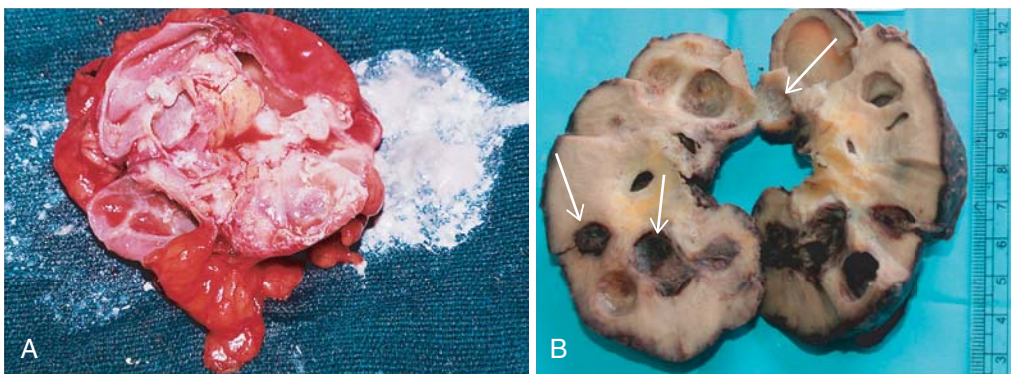

Figure 54-2 **Renal tuberculosis. A,** Cut section of kidney shows areas of cavitation and caseation necrosis (white chalky material). **B,** Cavitating lesions *(arrows)* are caused by tuberculosis in cut section of kidney (autopsy). *(**B** courtesy Department of Pathology, Amrita Institute of Medical Sciences, Kochi, Kerala, India.)*

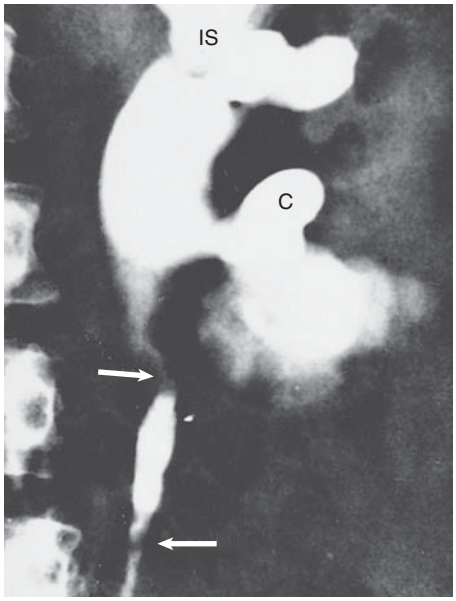

Figure 54-3 Multiple ureteral strictures. Strictures *(arrows)* associated with dilated ureter, infundibular stenosis *(IS),* and caliectasis *(C)* are seen in this intravenous urogram. *(Courtesy Professor K. Sasidharan, Kasturba Medical College, Manipal, India.)*

Clinical Features of Urinary Tuberculosis

Features	Frequency (%)	Symptoms
Asymptomatic	25	Detected during autopsy, surgery, or investigations for other diseases
Asymptomatic urinary abnormalities	25	Persistent pyuria, microscopic abnormalities, hematuria
Lower urinary tract symptoms (most common)	40	Frequency, urgency, dysuria, incontinence, nocturia, suprapubic pain, perineal pain
Male genital tract involvement	75	Epididymitis, hemospermia, infertility, reduced semen volume
Female genital tract involvement	<5	Amenorrhea, infertility, vaginal bleeding, pelvic pain
Constitutional symptoms	<20	Fever, reduced appetite, anorexia, weight loss, night sweats
Miscellaneous	—	Urolithiasis, hypertension, acute kidney injury, chronic kidney disease, abdominal colic, abdominal mass

Table 54-1 Clinical features of urinary tuberculosis.

Figure 54-4 Thimble bladder. Cystogram shows small-capacity bladder.

CLINICAL MANIFESTATIONS

Urinary tract TB may be asymptomatic or may mimic other disorders. Patients may present with constitutional symptoms or symptoms related to the lower urinary tract, abdomen, or genitalia (Table 54-1). A high index of suspicion enables early diagnosis. Most patients are 20 to 40 years of age, with a male-female ratio of 2:1. Because active genitourinary TB presents 5 to 15 years after primary infection, it is relatively rare in children. Risk factors for TB include close contact with sputum smear–positive individuals, vagrancy, social deprivation, neglect, immunosuppression, HIV infection or acquired immunodeficiency syndrome (AIDS), diabetes mellitus, CKD, vitamin D deficiency, and other debilitating illness.

Almost 25% of patients have no clinical or laboratory evidence of abnormality, and the diagnosis of urinary TB is made on investigation for other diseases, during surgery, or at autopsy. Another 25% have asymptomatic urinary abnormalities, usually persistent asymptomatic pyuria or hematuria. In patients with persistent pyuria, conventional urine cultures do not yield growth, and the urine is usually acidic; thus the term *acid-sterile pyuria*. Of the patients who are symptomatic, lower urinary tract symptoms, such as frequency, urgency, dysuria, nocturia, frank pyuria, or hematuria, occur in more than 75% of TB patients. Increased urinary frequency is an early symptom and results from inflammation of the bladder. The defect in the urinary concentrating mechanism explains the nocturia.

Recurrent bouts of painless macroscopic (gross) hematuria should alert the clinician to the possible diagnosis of urinary TB, although glomerular diseases such as IgA nephropathy should also be considered. Macroscopic hematuria in urinary TB is a result of bleeding from the ulcerating lesions, inflammation of the urothelium, or rupture of a blood vessel in the vicinity of a cavity. Colicky pain may occur as a presenting manifestation of urinary TB when it is associated with stone, clot, sloughed papilla, or other causes of acute obstruction.

In advanced disease, frequency and urgency related to reduced bladder capacity (thimble bladder) occur. Incomplete emptying, increased susceptibility to infection, and secondary vesicoureteral reflux (VUR) may also occur. In chronic ureteral obstruction, an enlarged kidney, infection, or perinephric collection leads to a dull-aching loin pain. Severe suprapubic pain with backache and dysuria suggests acute tuberculous cystitis. Patients with TB cystitis may show worsening of frequency and urgency after antituberculous treatment because of fibrosis and bladder wall contraction and is a

part of healing process. This should not be mistaken for a nonresponse to therapy. Episodes of pyuria, which may suggest secondary bacterial infection or drainage of a caseous focus into the collecting system, may also be a manifestation of renal TB. Persistence of pyuria after appropriate therapy should lead to an evaluation for urinary TB.

Longstanding renal TB may result in mild tubular proteinuria (<1 g/24 h) in up to 50% of patients. About 15% have proteinuria of more than 1 g/24 h, and nephrotic syndrome caused by amyloidosis may develop in some patients. Rare cases of mesangial proliferative glomerulonephritis have also been reported.

Anemia is seen in less than 20% of patients with nonmiliary disease, but the frequency is higher in those with CKD.[9] A few patients have nephrogenic diabetes insipidus. Renal tubular acidosis may occur. Hyporeninemic hypoaldosteronism may result from the tubulointerstitial injury secondary to obstructive uropathy.[10] Renal function is usually normal, but CKD may develop if both kidneys are extensively damaged.

Some patients with urinary TB present with reduced glomerular filtration rate (GFR), pyuria, microscopic hematuria, and proteinuria, but the urine cultures for mycobacteria are repeatedly negative. These patients respond favorably to antituberculous chemotherapy combined with corticosteroids. The kidneys are of normal size and show diffuse interstitial nephritis, with caseating granulomas containing the bacilli in 75% of the biopsy samples.[11] Hypertension is unusual in renal TB, but intimal proliferation of vessels near inflamed areas may lead to segmental ischemia and renin release.[12] In patients with a nonfunctioning kidney, nephrectomy may help improve the hypertension. Relief of any obstruction may also help lower the blood pressure. Nephrolithiasis may occur in 7% to 18% of patients. Secondary infection with *Escherichia coli* may be seen in 20% to 50% of patients.

Genital involvement is common in men with urinary TB. Epididymitis may present with scrotal discomfort, mass, or a cold abscess that may rupture, leading to a nonhealing posterior scrotal sinus. Thickening of the vas deferens may result in the "beaded" vas. TB of the prostate may present with lower urinary symptoms and perineal pain. The prostate may be hard or boggy. Penile and urethral TB may present with strictures, fistulas, ulcers, or papulonecrotic skin lesions. Hemospermia, reduction of semen volume, and infertility are other manifestations of genital involvement. Direct spread of *M. tuberculosis* to the sexual partner is possible.

Only 5% of women with renal TB also have genital TB. The major manifestation of genital involvement in women is infertility resulting from adherent salpingitis. Secondary amenorrhea, vaginal bleeding, and pelvic pain caused by inflammation may occur.

Constitutional symptoms, such as fever, weight loss, night sweats, fatigue, and anorexia, occur in less than 20% of patients and indicate active infection in other organs or secondary bacterial infection of the urinary tract. A careful examination to identify pulmonary, lymph node, or skeletal TB must be undertaken in all patients who present with constitutional symptoms. The chest radiograph may show evidence of active or healed tuberculous lesions in more than half of cases. Rarely, hypercalcemia may be present as a result of increased synthesis of calcitriol by the granulomas.

PATHOLOGY

Urinary TB may present as a miliary or ulcerocavernous pathologic process. The *miliary* form of TB is rare and is seen particularly in immunosuppressed individuals. The gross appearance of the kidney is characteristic; the cortex is studded with yellowish white, hard, pinhead-sized nodules that on microscopy show several coalescent granulomas with central caseation.

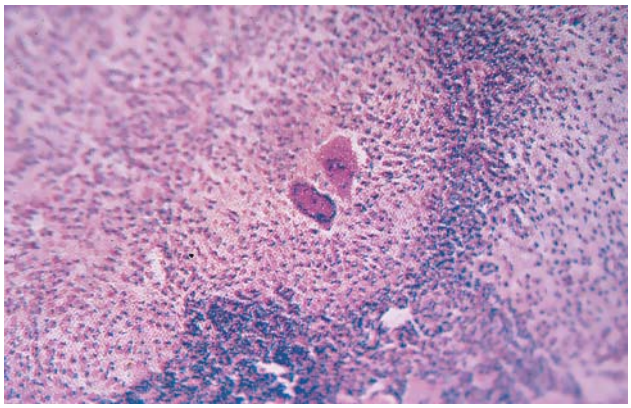

Figure 54-5 Tuberculous granuloma. The granuloma is undergoing caseating necrosis in the center surrounded by granuloma epithelioid cells and lymphocytes, and Langhans giant cell. *(Courtesy Department of Pathology, Amrita Institute of Medical Sciences, Kochi, Kerala, India.)*

In the more common *ulcerocavernous* form, the kidneys will initially appear normal or show yellow nodules on the outer surface. On cut section, granulomas and ulcers in the renal pyramid or medullary cavities may be seen. Larger cavities filled with caseous material communicating with the collecting system may also occur (see Fig. 54-2). Other gross findings include multiple ulcers in the infundibular region of the calyces, calyceal stenosis with caliectasis, ulcers or strictures of the ureter with hydronephrosis, pyonephrosis, subcapsular collections, and perinephric abscesses. The bladder may show ulcers or be grossly fibrotic and contracted.

On microscopy, in early disease, neutrophilic infiltration with phagocytosis of the bacilli may be present. Subsequent histologic features depend on the virulence of the organism and the cell-mediated immunity. In TB patients with an effective cell-mediated response, granulomas are seen, characterized by the presence of macrophages with engulfed bacilli surrounded by epithelioid cells and Langhans giant cells (Fig. 54-5). There is often a cuff of lymphocytes and plasma cells surrounding the lesion. Healing occurs by fibrosis and scarring. In those with a less effective immune response, caseating necrosis is characterized by amorphous, cheese-like eosinophilic material replacing the normal tissue architecture. The presence of caseous necrosis generally implies that the lesion is active. Later, this may calcify. Dystrophic calcification suggests activity rather than healing.

Kidneys may also be enlarged from amyloidosis or diffuse proliferative glomerulonephritis. In tuberculous interstitial nephritis, interstitial granuloma formation associated with normal-sized kidneys and negative urine cultures is seen.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A high index of suspicion is necessary to diagnose genitourinary TB. Elderly patients, those recently exposed to infection, immunocompromised individuals, and patients with TB elsewhere are at high risk. Suspicion may also occur if there is sterile pyuria, which is present in 50% of patients. The tuberculin test (Mantoux test) is useful for proving infection (or prior immunization with BCG), but not necessarily disease. A positive test response only suggests prior exposure to the antigen and does not indicate active infection. A negative test response in the absence of an immunosuppressed

state helps to rule out tuberculous infection in countries with high tuberculosis burden. Patients with stage 4 or 5 CKD, particularly in the setting of malnutrition, may display anergy and have a false-negative result.[13] *M. tuberculosis*–specific enzyme-linked immunospot (ELISPOT) assay is useful for rapid confirmation of diagnosis and is gradually replacing the Mantoux test in most countries.

Isolation of *M. tuberculosis* by urine culture is the definitive diagnostic test. Fully voided early-morning urine samples for 3 to 5 consecutive days are cultured on two standard solid mycobacterial culture media: egg-based Lowenstein-Jensen and agar-based Middlebrook 7H10. These transparent media enable earlier visualization of microcolonies, which grow by 6 to 12 weeks. Sensitivity tests are performed to choose the optimum chemotherapeutic agents. However, this may take an additional 6 to 12 weeks. Any tissue specimen submitted for mycobacterial culture should be macerated with sterile sand by a mortar and pestle before inoculation. Direct demonstration of acid-fast bacilli in urine by Ziehl-Neelsen stain is not reliable for diagnosis because *M. smegmatis,* a saprophyte, may be easily mistaken for *M. tuberculosis*.

Rapid methods for diagnosis of TB are increasingly available. With use of the radiometric broth method for acid-fast bacilli isolation, a positive growth can be obtained in about 9 days. Serologic tests with the soluble antigen fluorescent antibody test and the polymerase chain reaction (PCR) can be used for early diagnosis of TB.[14] ELISPOT assays are used as *in vitro* diagnostic tests and measure T cell–specific *M. tuberculosis* antigens. The test results are unaffected by prior tuberculin testing or low CD4 counts.[15] Another reliable and simple test using whole blood is based on quantifying the interferon-γ released from the white blood cells that have been exposed to some of the mycobacterial antigens. The availability of the result in 24 hours is the main advantage.[16] Detection of lipoarabinomannan (LAM) in urine using lateral flow assay is a simple and rapid test for the detection of TB in patients with advanced HIV infection with a CD count less than 200 cells/μL. The results are available in 30 minutes. A cartridge-based, rapid and reliable automated test endorsed by WHO to identify targeted nucleic acid sequences in the *M. tuberculosis* genome (Xpert MTB/RIF) is now available.[17] This test detects the DNA sequences specific for *M. tuberculosis* (MTB) and rifampin (RIF) resistance by PCR, and results can be generated in 2 hours.[17] Ultrasound-guided fine-needle aspiration cytology is useful as a diagnostic tool in defining the granulomatous nature of the lesion in patients with positive urine culture. Histologic diagnosis is made by identifying the pathologic triad of caseating necrosis, loose aggregates of epithelioid histiocytes, and Langhans giant cells.

Imaging studies are essential to assess the extent and severity of involvement once a diagnosis of genitourinary TB is made. Extensive dystrophic calcification in advanced renal TB is described as "cumulus cloud" calcification (Fig. 54-6). Plain radiographs of chest and spine show active or healed tuberculous lesions in 60% to 70% of patients. Abnormalities in the excretory urogram may be seen in 70% to 90%. Minimal erosion of the tip of the calyx with spasticity, incomplete filling, distortion, infundibular stenosis, hydrocalicosis, multiple ureteral strictures, hydronephrosis, hydroureter, or nonvisualization of the kidney may be present. The renal pelvis, which may be dilated initially, may eventually be obliterated, leading to a distorted appearance called "hiked-up pelvis" (Kerr kink sign). Irregularities or multiple strictures lead to a beaded or corkscrew appearance of the ureter or hydronephrosis. Later, thickening and straightening of the whole ureter may occur ("pipe-stem" ureter). The bladder may appear irregular and fibrosed, and VUR may occur. Antegrade or retrograde pyelography can identify the number, length, or site of ureteral strictures and assist in placement of a ureteric stent across the stenotic segment.

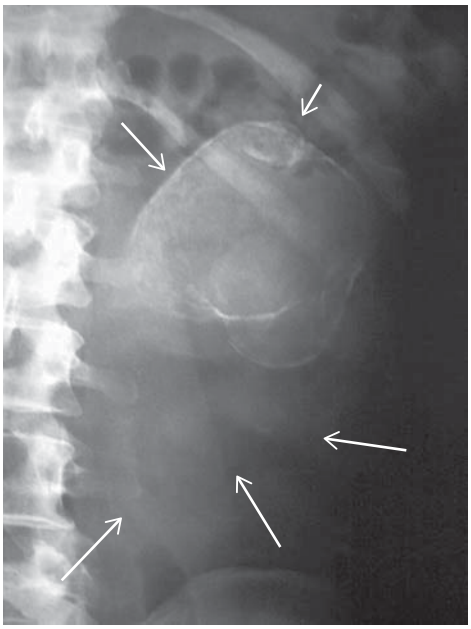

Figure 54-6 Renal calcification. Plain radiograph shows calcification in the upper half of the left kidney. Arrows outline the kidney.

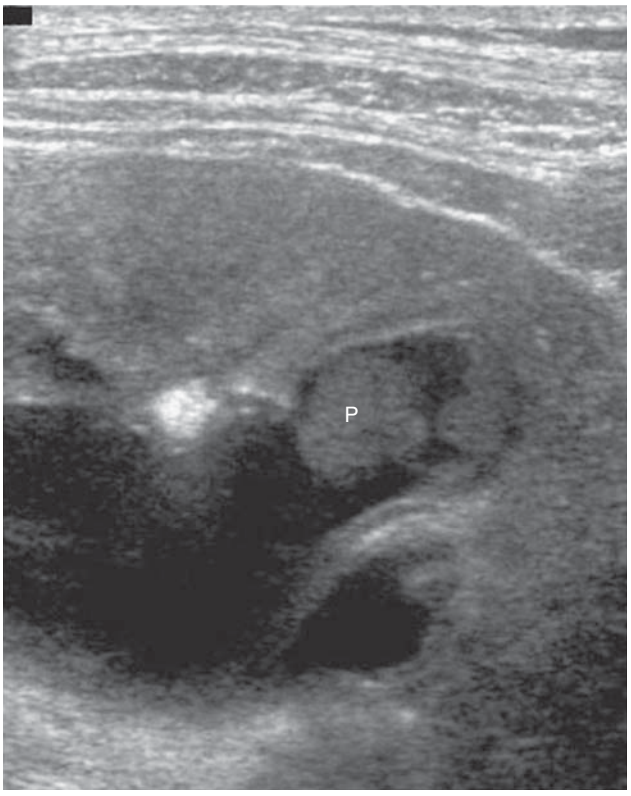

Figure 54-7 Necrosed papilla. High-resolution ultrasound scan of the kidney shows a sloughed, necrosed papilla *(P)* in the calyx. *(From reference 19, with permission of the American Institute of Ultrasound in Medicine.)*

High-resolution ultrasound is useful to rule out obstruction and to study the parenchyma closely to identify granulomas, small abscesses, bladder mucosal thickening, or calcification[18] (Figs. 54-7 and 54-8). The earliest finding is mucosal thickening and calyceal irregularity.

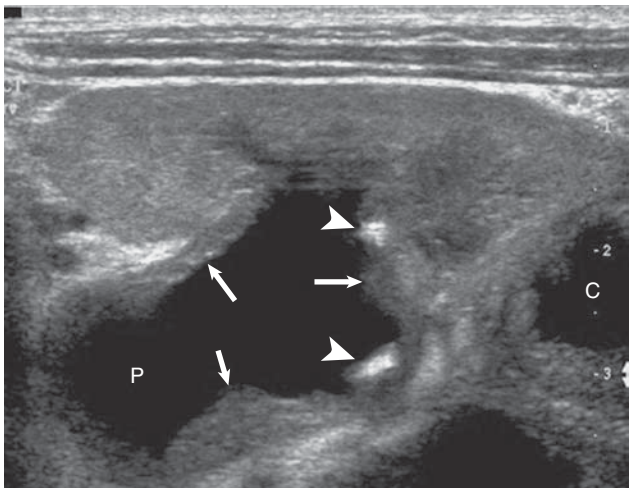

Figure 54-8 Thickened mucosa and calcifications. High-resolution transverse ultrasound scan of kidney shows mucosal thickening *(arrows)* of calyces and the pelvis *(P)*. There are calcifications of the wall of the calyx and pelvis *(arrowheads)*. A parenchymal cavity *(C)* is also shown. *(From reference 19, with permission of the American Institute of Ultrasound in Medicine.)*

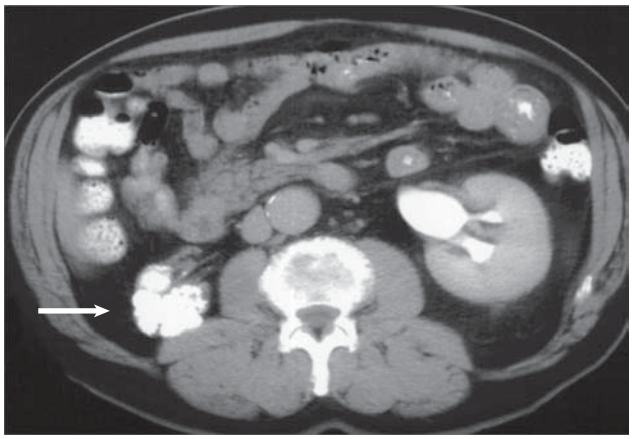

Figure 54-9 Calcified kidney. Contrast-enhanced CT image shows contracted calcified right kidney *(arrow)* and normal opposite side.

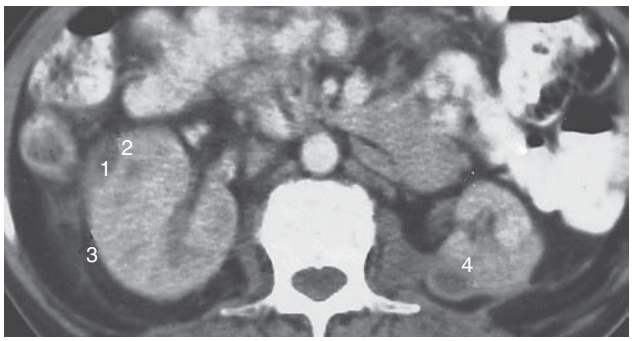

Figure 54-10 Renal tuberculosis. CT scan shows an enlarged left kidney with multiple cavities present bilaterally (marked *1, 2, 3,* and *4*). *(Courtesy Professor K. Sasidharan, Kasturba Medical College, Manipal, India.)*

Computed tomography (CT) is the most sensitive method for identifying renal parenchymal scarring, calcification, and cavitary lesions (Figs. 54-9 and 54-10). Cortical thinning is a common CT finding and may be either focal or global. These imaging modalities are helpful in the follow-up of patients with cavities or mass lesions in the kidney. Cystoscopy under general anesthesia helps visualize the mucosal lesions, the golf-hole ureteral orifice, or the efflux of toothpaste-like caseous material. Biopsy during the acute stage is avoided because of the risk of dissemination of TB.

Tuberculosis mimics numerous diseases. Chronic nonspecific urinary infections may be confused with renal TB, which is further confounded because secondary bacterial infection may complicate 20% of cases of renal TB. Absence of response to usual antibiotics should raise suspicion of urinary TB. Conditions causing recurrent painless hematuria, such as IgA nephropathy and schistosomiasis (see Chapter 56), are often misdiagnosed as TB in endemic areas. In interstitial cystitis, lower urinary symptoms similar to tuberculous cystitis may occur, but the urinalysis does not show gross pyuria, and cultures for acid-fast bacilli are negative. On radiologic examination, chronic pyelonephritis, renal papillary necrosis, medullary sponge kidney, calyceal diverticulum, renal carcinoma, xanthogranulomatous pyelonephritis, and multiple small renal calculi need to be differentiated from TB. In a few reported cases of pseudotuberculous pyelonephritis, caseating granulomas resembling TB were observed in the renal parenchyma, but no mycobacteria or other microorganisms were detected in the renal tissue or urine culture.[19]

NATURAL HISTORY

The prognosis of genitourinary TB depends on the host resistance and the load and virulence of the organism. In many cases, foci in the urinary tract remain dormant indefinitely. Progression occurs through formation of tuberculous granuloma, caseation, ulceration, and dystrophic calcification. Most manifestations result from the complications, which can be prevented by timely chemotherapy and appropriate surgical intervention when indicated. With the advent of effective chemotherapeutic measures, the long-term complications and sequelae of TB have decreased significantly.

TREATMENT

Genitourinary TB is usually amenable to medical treatment. Many antituberculous drugs reach the kidneys, urinary tract, urine, and cavitating lesions in high concentration, and there are fewer organisms in the lesions compared with cavitating lung lesions. A wide variety of antituberculous agents are available (Table 54-2).

A short-course regimen is recommended.[20] Treatment is started with daily rifampin (rifampicin) (600 mg), isoniazid (300 mg), and pyrazinamide (1500 mg) in the morning. Unless the culture sensitivity indicates otherwise, pyrazinamide is discontinued after 2 months, and isoniazid and rifampin are continued for another 4 months. If the patient is very sick with irritative bladder symptoms, streptomycin in daily doses of 1 g may be added during the first 2 months. However, if the patient is older than 40 years, the daily dose of streptomycin is reduced to 0.75 g with periodic monitoring for ototoxicity and vestibular toxicity.

If the probability of drug resistance is high, ethambutol in daily doses of 800 to 1200 mg may also be used in the first 2 months. Longer courses of antituberculous treatment ranging from 9 months to 2 years are useful in patients who do not tolerate pyrazinamide, those responding slowly to a standard regimen, those with miliary or central nervous system disease, and in children with multisite involvement.

Fixed-dose combinations of anti-TB drugs incorporating two or more drugs in the same tablet have the advantages of increased compliance, administration of adequate dose, minimization of inadvertent medication errors, and avoidance of drug resistance.

Antituberculous Drugs					
Drug	**Dose Form**	**Dosage**	**Side Effects**	**Mode of Action**	**Remarks**
Isoniazid	Tablet: 100 mg, 300 mg	5 mg/kg daily (oral) (maximum 300 mg/day)	Peripheral neuropathy, hepatitis, hypersensitivity reactions	Bactericidal for groups I and II	Pyridoxine (50 mg) prophylaxis necessary
Rifampin (Rifampicin)	Capsule or tablet: 150, 300, 450 mg	10 mg/kg daily (oral) (maximum 600 mg/day)	Hepatitis, febrile reactions, acute interstitial nephritis	Bactericidal for groups I, II, and III	—
Pyrazinamide	Tablet: 400, 500 mg	25 mg/kg daily (oral) (maximum 2 g/day)	Hepatotoxicity, hyperuricemia	Bactericidal for group II	Combination with aminoglycoside useful
Streptomycin	Powder for injection: 1 g	15 mg/kg daily IM (maximum dose 1 g; dose reduced in those age >40)	Ototoxicity, nephrotoxicity	Bactericidal for group I	—
Ethambutol	Tablet: 100, 400 mg	15-25 mg/kg daily (oral) (maximum, 2.5 g/day)	Optic neuritis (reversible), rash	Bacteriostatic for groups I and II	Used to inhibit development of resistant mutants; use with caution in renal failure.
Thiacetazone	Tablet: 150 mg	150 mg (oral) (not for intermittent therapy)	Rashes, exfoliative dermatitis, hepatic failure	Bacteriostatic and inhibits emergence of isoniazid resistance	Not used in renal failure
Ciprofloxacin	Tablet: 250, 500 mg	500-1000 mg (oral)	Hypersensitivity, drug interaction	—	Not used in children
Ciprofloxacin	Tablet: 200, 400 mg	400-500 mg (oral)	—	—	Not approved by FDA for tuberculosis
Capreomycin Kanamycin	—	15-30 mg/kg daily IM	Ototoxicity, nephrotoxicity	Bactericidal for group I	Avoided in older patients and those with renal failure

Table 54-2 Antituberculous drugs. The main drugs are listed with dosage form, dosage, side effects, and mode of action. *Mycobacterium tuberculosis* exists as three subpopulations. Group I is extracellular, occurs mainly in cavitating lesions, and responds to streptomycin, isoniazid, and rifampin. Group II resides intracellularly in macrophages, replicates slowly, and responds to pyrazinamide, isoniazid, or rifampin. Group III organisms exist within closed caseous lesions, survive better in neutral pH, replicate slowly, and respond best to rifampin. *FDA,* U.S. Food and Drug Administration; *IM,* intramuscularly.

During treatment, healing by fibrosis may lead to obstruction of one or both ureters, with hydronephrosis, parenchymal damage, and renal failure. Dehydration or salt depletion may occur from tubulointerstitial damage resulting in altered tubular function. Adrenal involvement may contribute to salt wasting. Oliguric acute kidney injury caused by allergic interstitial nephritis may occur in patients receiving intermittent rifampin therapy.

Surgical Treatment

The role of surgical treatment in patients with urinary TB is limited. For ureteral strictures, timely introduction of stents across the narrow segment may avoid the need for major surgical procedures. Two broad types of surgical treatments are considered.

Reconstructive surgery involves the correction of obstruction to the ureter by pyeloplasty, ureteroureterostomy, correction of reflux by ureteral reimplantation, and increasing the bladder capacity by augmentation cystoplasty, which involves anastomosis of an isolated segment of bowel to the contracted bladder.

Ablative surgery involves removal of the diseased parts together with the infected material containing the dormant organisms. The need for removal of a unilateral nonfunctioning kidney is controversial. Because prolonged antituberculous treatment for 18 to 24 months effectively sterilizes caseous and calcified masses of the tuberculous cement kidney, nephrectomy is advocated only in patients with secondary sepsis, pain, bleeding, uncontrollable hypertension, or continued positive urinary cultures. Tuberculous abscesses can be aspirated under ultrasound or CT guidance and antituberculous drugs directly instilled into the cavity.

Treatment Regimens in Special Situations

Women During Pregnancy and Lactation

Most antituberculous drugs are safe for use during pregnancy. However, streptomycin is ototoxic to the fetus and must be avoided. If a four-drug schedule is indicated, streptomycin is replaced by ethambutol. There is no contraindication to the use of these drugs during breastfeeding, and it is not necessary to isolate the baby from the mother. The baby should receive BCG immunization and isoniazid prophylaxis. Because rifampin interacts with the efficacy of oral contraceptives, women taking these agents together should be advised to take a higher dose of estrogen or to use alternative methods of contraception.

Patients with Liver Disease

The usual short-term (6-month) chemotherapy regimen can be used in patients with liver disorders if there is no evidence of chronic liver disease, hepatitis virus carrier state, past history of acute hepatitis, or excessive alcohol consumption. In chronic liver disease, isoniazid and two of the nonhepatotoxic drugs (streptomycin and ethambutol) can be used for 8 to 12 months. If rifampin is used, liver function should be closely monitored. Pyrazinamide is contraindicated. In those with acute hepatitis unrelated to TB or its therapy, it would be safer to defer the chemotherapy until the acute hepatitis has resolved.

If immediate treatment of TB during acute hepatitis is mandatory, streptomycin plus ethambutol for 3 months followed by isoniazid and rifampin for 6 months is advised.

Patients with Chronic Kidney Disease

In patients with CKD, isoniazid, rifampin, and pyrazinamide, which are eliminated by the biliary route, can be given in normal dosages. Those receiving isoniazid should also be given pyridoxine (50 mg/day) to prevent peripheral neuropathy. Because streptomycin and ethambutol are excreted by the kidney, dosage modification of these drugs is necessary in renal failure. Streptomycin (15 mg/kg) is administered every 24 to 72 hours for a GFR of 10 to 50 ml/min and every 72 to 96 hours for a GFR of less than 10 ml/min to maintain a therapeutic peak level of 20 to 30 µg/ml. Patients taking streptomycin who have a sense of fullness of the ear or have tinnitus or who are older than 45 should have an audiogram to detect ototoxicity early. For ethambutol, the dose is administered every 24 to 36 hours if GFR is 10 to 50 ml/min and every 48 hours if GFR is less than 10 ml/min. Monthly questioning for symptoms of visual dysfunction (alterations in visual fields, acuity, blue-green vision) with early referral for ophthalmic examination may identify ethambutol toxicity early, with potential reversibility.

Renal Allograft Recipients

A modified treatment regimen is recommended for renal allograft patients, with adjusted doses of isoniazid and ethambutol for 18 months, combined with ofloxacin (200 mg twice daily) for the first 9 months and pyrazinamide (750 mg twice daily) for the first 3 months.[21] Rifampin should be avoided in patients receiving a calcineurin inhibitor (CNI) because enzyme induction will make it more difficult to maintain adequate CNI blood levels. If rifampin is used in those receiving a non–cyclosporine-based immunosuppressive regimen, the maintenance dose of prednisolone should be doubled.

Acquired Immunodeficiency Syndrome

Short-term chemotherapy is sufficient for AIDS patients. If the follow-up cultures are positive, prolonged therapy for up to 2 years may be needed based on antibiotic sensitivity.

Patients Who Fail Treatment

Failure to show clinical or radiologic improvement with treatment may signify poor compliance, inadequate regimen and dosage, incorrect diagnosis, MDR TB, delayed response, or the paradoxical reaction known as "immune reconstitution inflammatory syndrome." This syndrome is characterized by unexpected worsening of symptoms or appearance of new lesions, including lymphadenopathy, serosal effusions, and pleural infiltrates. This syndrome is more common in those prescribed antiretroviral treatment for coexisting HIV and TB infections.[22]

Monitoring of Patients

After 2 months of intensive chemotherapy, urine is cultured for *M. tuberculosis* for 3 consecutive days. If cultures remain positive, sensitivity is done and treatment modified accordingly. After completion of treatment, all patients should have three consecutive early-morning samples of urine for *M. tuberculosis* culture, and this is repeated after 3 months and 1 year. Intravenous urography or ultrasound is repeated at the end of 2 months and at the completion of treatment to detect any evidence of obstruction. In cases of renal calcification, the patient should be evaluated yearly by three early morning samples of urine for culture of mycobacteria and by plain radiography of the abdomen for up to 10 years, because calcification may harbor *M. tuberculosis* and may progress to destruction of the kidney.

Considerable progress has been made in the areas of TB diagnostics, antituberculous drugs, and vaccines during the last decade. New antituberculous agents and several vaccines are in various phases of clinical trial. The global plan to eradicate tuberculosis is showing increasing promise.

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CHAPTER 55

Fungal Infections of the Urinary Tract

Carol A. Kauffman

Funguria is a frequent finding in hospitalized patients. Almost always, the organisms found in urine are *Candida* species, although several other yeasts, and less often, molds and endemic fungi, can also be found (Table 55-1). Candiduria is not a symptom, a sign, or a disease, but frequently it is a perplexing phenomenon for the physician to address. In reality, most patients with candiduria are asymptomatic and have colonization of the bladder or of an indwelling urinary catheter. The most difficult diagnostic problem is determining when *infection,* rather than colonization, is present. Diagnostic tests to define whether candiduria is related to colonization or infection have not been standardized; similarly, diagnostic studies to localize the site of infection to either the bladder or the kidneys are not well established. In contrast to the situation with candiduria, growth in urine of organisms such as *Blastomyces dermatitidis, Aspergillus* spp., and *Cryptococcus neoformans* almost always reflects disseminated infection. This chapter outlines an approach to the diagnosis and treatment of candiduria and other, less common fungal urinary tract infections (UTIs).

CANDIDA

Epidemiology

Candida species are common inhabitants of the perineum but are not found in urine in appreciable numbers in healthy hosts. However, a variety of predisposing factors allow these commensals to grow in the urine and in some cases, to invade the bladder or the upper urinary tract and cause infection. These factors are more frequently encountered in hospitalized patients, especially those in the intensive care unit (ICU).[1] In a recent point prevalence survey of positive urine cultures obtained from hospitalized patients, *Candida* species were found in almost 10% of specimens and were the third most common microorganism isolated from urine.[2]

Risk factors for candiduria, but not specifically for *Candida* UTI, include increased age, female gender, antibiotic use, urinary drainage devices, prior surgical procedures, and diabetes mellitus[3-5] (Table 55-2). In the largest surveillance study, urinary drainage devices, mostly indwelling urethral catheters, were present in 83% of patients who had candiduria.[3] In a multicenter study of patients in an ICU setting, independent risk factors associated with candiduria were age over 65, female gender, diabetes mellitus, prior antibiotic use, mechanical ventilation, parenteral nutrition, and length of hospital stay before ICU admission.[4] A case-controlled study that compared candiduria caused by *Candida glabrata* with that from *Candida albicans* found that *C. glabrata* was more common in patients with diabetes and in those who had received prior treatment with fluconazole.[5] Most patients in these studies had colonization and not infection with *Candida*.

Prospective controlled studies assessing risk factors for well-documented *Candida* UTI have not been performed because firm diagnostic criteria have not been established. However, clinical experience suggests that UTI is more common in diabetic patients and those with urinary tract obstruction.

Pathogenesis

Candida tends to cause disease by either the hematogenous or the ascending route. This contrasts with most UTIs caused by bacteria, in which infection ascends from bladder to the collecting system of the kidney. The pathogenesis of hematogenous seeding of *Candida* to the kidney has been studied with animal models.[6] Multiple microabscesses develop throughout the cortex, with the yeasts penetrating through the glomeruli into the proximal tubules, where they are shed into the urine (Fig. 55-1). Healthy animals eventually clear the infection, but immunocompromised animals do not. Consistent with the experimental studies, renal microabscesses have been identified at autopsy in most patients with invasive candidiasis. For ascending infection with *Candida,* obstruction is an important factor in some patients. Virulence factors of *Candida,* such as those that control adherence and biofilm formation, are also likely relevant, but have not been studied in the context of *Candida* UTI.[6,7]

A unique syndrome seen early after kidney transplantation is graft site candidiasis, which appears to result from contamination of the donor kidney during the harvest procedure.[8] Arteritis with aneurysm formation and rupture can result from direct fungal invasion into the arterial wall. Most patients lose the graft, and mortality is high.

Microbiology

Candida albicans accounts for 50% to 70% of all *Candida* urinary isolates, and *C. glabrata* for about 20% of isolates.[3] *Candida tropicalis* and *Candida parapsilosis* are less common, and other species are rarely isolated. Certain populations of patients have a predominance of *C. glabrata*. Older adults frequently have *C. glabrata* isolated from urine, but urine cultures from neonates rarely yield *C. glabrata*. In a prospective survey of candiduria in renal transplant recipients, *C. glabrata* represented 53% and *C. albicans* only 35% of isolates.[9]

It is important to know the species causing candiduria for therapeutic reasons. Resistance to fluconazole, the primary agent used for the treatment of *Candida* UTIs, is common among isolates of *C. glabrata* and in all isolates of *Candida krusei.* In contrast, almost all isolates of *C. albicans, C. tropicalis*, and *C. parapsilosis* are susceptible to fluconazole.

Clinical Manifestations

Most patients with candiduria are asymptomatic, and indeed, most do not have infection. A large prospective surveillance study of patients with candiduria noted that less than 5% of patients with

Fungal Genitourinary Tract Infections			
Fungal Infection	**Prostate**	**Bladder**	**Kidney**
Blastomycosis	+++	+	++
Histoplasmosis	+	+/–	++
Coccidioidomycosis	+	+/–	++
Aspergillosis	+/–	+/–	++
Mucormycosis	+/–	+/–	++
Cryptococcosis	++	+/–	+++
Candidiasis	++	++++	++++

Table 55-1 Fungal genitourinary tract infections. Shown is the relative frequency of the site of infection for various fungal organisms.

Risk Factors for Different Types of Candida Urinary Tract Infections	
Type	**Risk Factors**
Renal (hematogenous)	Neutropenia, recent surgery, central venous catheter, parenteral nutrition, antibiotics, dialysis
Lower urinary tract	Indwelling bladder catheter, older age, female, diabetes, obstruction, antibiotics, urinary tract instrumentation
Upper urinary tract	Older age, diabetes, antibiotics, obstruction, urinary tract instrumentation (e.g., nephrostomy tube, ureteral stent)

Table 55-2 Risk factors for candiduria.

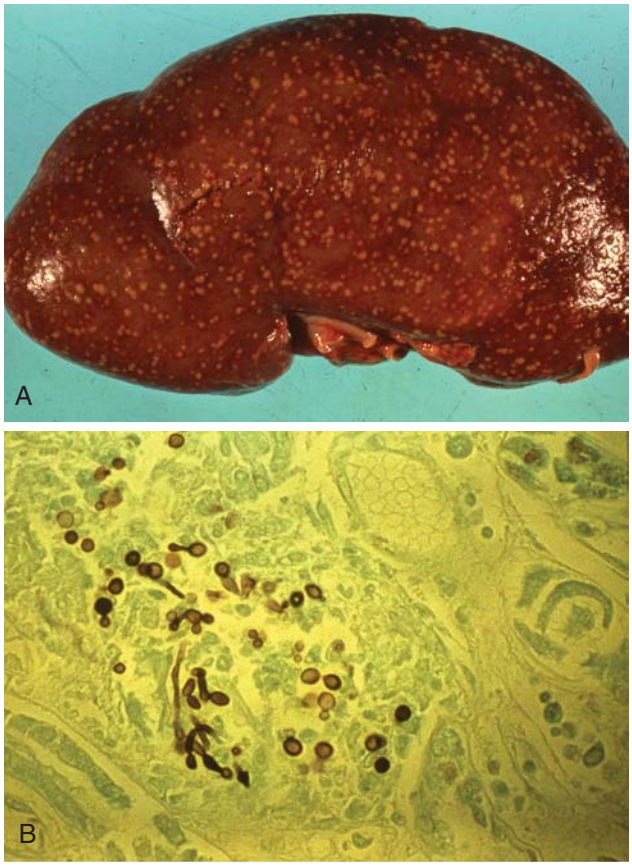

Figure 55-1 Hematogenous renal candidiasis. A, Multiple small abscesses are grossly obvious throughout the kidney. **B,** Histopathologic demonstration of a microabscess caused by *Candida albicans* in the cortex of the kidney (methenamine silver stain; yeast shown in *gray-brown color*).

candiduria had any symptoms suggesting UTI.[3] When patients have symptomatic cystitis or pyelonephritis, symptoms are indistinguishable from those noted with bacterial infections. Cystitis is manifested by dysuria, frequency, urgency, and suprapubic discomfort; patients with upper tract infection can present with fever, chills, and flank pain. Urinary tract obstruction occurs from formation of a bezoar or fungal ball in the bladder or the collecting system.

Patients who have had seeding of the renal parenchyma during an episode of candidemia manifest the symptoms and signs associated with invasive candidiasis and not UTI. Chills, fever, hypotension, and other manifestations of sepsis are often noted in patients who are candidemic.

Diagnosis

Major diagnostic difficulties are encountered in trying to differentiate contamination of a urine specimen from colonization of the bladder or an indwelling urethral catheter from invasive infection of the bladder or the kidney.[10] Contamination is most easily differentiated by simply repeating the urine culture to determine if candiduria persists. It may be necessary to obtain the second urine specimen by sterile bladder catheterization if the patient is unable to accomplish a clean-catch collection. In those patients who have an indwelling urethral catheter, the catheter should be replaced and a second urine specimen collected. For either of these circumstances, if the repeated culture yields no yeasts, no further diagnostic studies or therapeutic interventions are needed.

Distinguishing colonization from infection is not straightforward. Compared with bacterial UTIs, in which the diagnosis is based on appropriate symptoms combined with the findings of pyuria and quantitative bacterial counts, no studies have established the importance of quantitative urine cultures or pyuria for the diagnosis of *Candida* UTI.[11]

The role of quantitative urine cultures to differentiate upper tract infection from bladder colonization was assessed by investigators in the 1970s and unfortunately showed broad ranges of colony counts for both colonization and infection.[11] In patients who did not have indwelling catheters, documented renal infection was found with colony counts as low as 10^4 yeast colony-forming units per milliliter (cfu/ml). For patients who had indwelling catheters, colony counts between 2×10^4 and 10^5 cfu/ml or more were noted, and there was no correlation with biopsy-proven renal infection. A murine model of hematogenous renal candidiasis noted that renal involvement could be seen with any concentration of *Candida* in the urine.[12]

The techniques routinely used in most clinical laboratories for the detection of bacteria will also detect *Candida* in urine. However, *C. glabrata* grows more slowly than other species and more slowly than bacteria, and colonies may not appear for 48 hours, which is often after routine cultures of urine have been discarded. Laboratories should be notified if *C. glabrata* is a likely pathogen.

Pyuria is often not a helpful diagnostic criterion for infection in patients with candiduria. Concomitant bacteriuria is frequently noted in patients with candiduria and may be responsible for pyuria. In patients who have an indwelling bladder catheter, pyuria is routinely noted, whether or not infection is present. In patients who do not have an indwelling bladder catheter or bacteriuria, the presence of pyuria is helpful.

Imaging procedures, including abdominal ultrasound and computed tomography (CT), are essential to document obstruction at

any level in the urinary tract and to determine the presence of fungus balls in bladder or kidney (Fig. 55-2). In some patients, it is helpful to perform cystoscopy and biopsy of the bladder wall to determine whether inflammation is present and to evaluate the extent of invasion (Fig. 55-3).

Treatment with Systemic Antifungal Agents

Most patients who have candiduria do not need treatment with an antifungal agent. For patients who are asymptomatic, treatment should be given only to those who are at high risk for development of candidemia or in whom the presence of candiduria, regardless of symptoms, is likely to represent disseminated infection. The guidelines for the management of candidiasis published by the Infectious Diseases Society of America (IDSA) recommend treatment for patients about to undergo urologic procedures, very-low-birth-weight infants, and neutropenic patients[13] (Table 55-3). Patients who have candiduria and who are to undergo a urologic procedure are at increased risk for development of candidemia and should be treated with an antifungal agent a few days before and after the procedure. Candiduria in neutropenic patients and in very-low-birth-weight infants has a high probability of representing

Figure 55-2 Fungal hydronephrosis. Several fungus balls (dark round "holes" in the contrast dye) in the ureter and pelvis of the right kidney causing hydronephrosis.

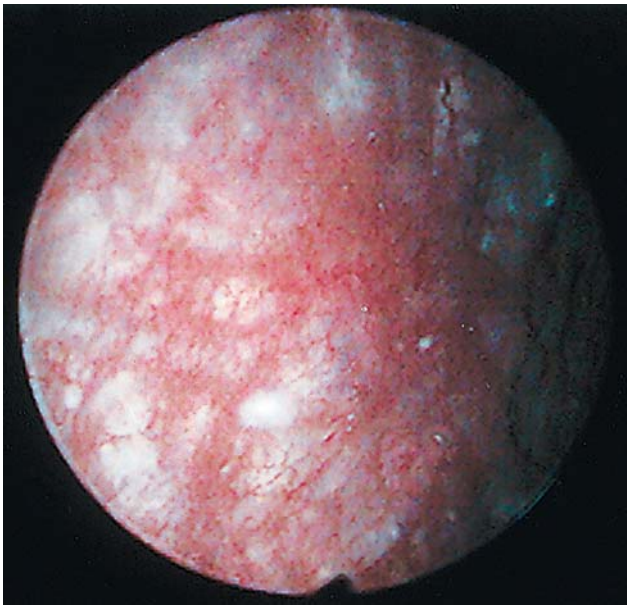

Figure 55-3 *Candida* cystitis. Cystoscopic appearance of extensive cystitis caused by *Candida krusei*.

Treatment Recommendations for *Candida* Urinary Tract Infections

Infection	Treatment	Other/Alternative Therapy
Asymptomatic candiduria	No treatment indicated except: Urologic surgery Low-birth-weight infant or neutropenic patient	 Treat a few days before and after the procedure with: Fluconazole, 200-400 mg daily, *or* Amphotericin B, 0.3-0.6 mg/kg/d Treat as for disseminated candidiasis/candidemia
Cystitis	Preferred: oral fluconazole, 200 mg daily × 14 days*	Alternatives include: Amphotericin B, 0.3-0.6 mg/kg/d × 1-7 days Flucytosine, 25 mg/kg q6h × 7-10 days†
Pyelonephritis	Preferred: oral fluconazole, 200-400 mg daily × 14 days	Alternatives include: Amphotericin B, 0.5-0.7 mg/kg/d × 14 days Flucytosine, 25 mg/kg q6h × 14 days
Renal (hematogenous)	Treat as for disseminated candidiasis/candidemia	—
Fungus balls	Surgical removal Fluconazole, 200-400 mg daily until resolved	Alternatives include: Amphotericin B, 0.5-0.7 mg/kg/d Flucytosine, 25 mg/kg q6h
Prostatitis Epididymo-orchitis	Surgical drainage Fluconazole, 400 mg daily until resolution noted on imaging studies	Alternatives include: Amphotericin B, 0.5-0.7 mg/kg/d

Table 55-3 Treatment recommendations for candiduria and *Candida* urinary tract infections (UTIs). *Fluconazole dosage in renal failure: creatinine clearance (Cr Cl) 20-50 ml/min, reduce dose by 50%; CrCl <20 ml/min, reduce dose by 75%; *q6h,* every 6 hours. †Flucytosine dosage in renal failure: CrCl 20-40 ml/min, reduce dose to 25 mg/kg every 12 hours; CrCl <20 ml/min, reduce dose to 25 mg/kg every 24 hours.

disseminated candidiasis; thus, these groups also should be treated with an antifungal drug. Asymptomatic candiduria in the renal transplant patient does not warrant systemic antifungal treatment unless obstruction is present or symptoms suggestive of local or systemic infection develop.

In non–high-risk patients who have asymptomatic candiduria, removal of an indwelling urinary catheter will eradicate candiduria in many patients.[3] If catheterization cannot be discontinued, the existing catheter should be removed and a new one inserted. This will often eradicate candiduria transiently, but it is highly likely that the organisms will return within a short time. Relief of obstruction, whether it is present in the upper or lower urinary tract, is essential for the long-term eradication of *Candida* from the urinary tract.

Patients who have symptoms suggestive of cystitis or pyelonephritis, and in whom bacteria as well as *Candida* are found in the urine culture specimen, should be treated initially with an antibacterial agent. If no bacteria are present, treatment with an antifungal drug is appropriate. Eradication of the organism with antifungal therapy is more likely if the indwelling catheter is also removed.[14] Oral fluconazole, which is an azole antifungal agent and is excreted as active drug in the urine, is the agent of choice (see Table 55-3). A loading dose of 400 mg should be given, followed by 200 mg daily for 14 days.[13,15] Fluconazole does not effectively treat *C. krusei* infections, and many *C. glabrata* infections also do not respond to fluconazole.

The possibility of drug-drug interactions should be evaluated before fluconazole is prescribed. Phenytoin, warfarin, cyclosporine, tacrolimus, and sulfonylurea agents are a few of the drugs for which serum concentrations will increase and may reach toxic levels after the addition of fluconazole. Azoles should be used with caution in patients on drugs that prolong the QTc interval.

The other available azole agents, itraconazole, voriconazole, and posaconazole, are not excreted into the urine as active drug. Whether tissue concentrations might be high enough to treat invasive kidney or bladder infections is not known, but there is little clinical experience to suggest that they will be effective.[15]

Intravenous (IV) amphotericin B deoxycholate is effective in treating *Candida* UTIs but should be reserved for patients who have upper tract infection or for whom fluconazole therapy has failed, which will be predominantly those who have *C. glabrata* infection. Because of its inherent nephrotoxicity, IV amphotericin B must be used judiciously in patients who have renal dysfunction. The recommended dosage is 0.3 to 0.7 mg/kg/day for 1 to 7 days, although this may be extended to 2 weeks for those with complicated upper tract infection.[13] The dose used depends on renal function and number of days infusions will be given; for example, some clinicians have had success with 0.3 mg/kg daily for 3 days, whereas others use a single dose of 0.7 mg/kg. Infusion-related side effects are seen in some patients, even when low dosages are used, and can include rigors, fever, nausea, vomiting, and headache.

Lipid formulations of amphotericin B are not recommended for treatment of fungal UTIs. The decreased nephrotoxicity that results from the addition of the lipid component likely also precludes the drug's effectiveness by failing to achieve adequate levels in the urinary tract.[15]

One of the few uses of flucytosine is for the treatment of *Candida* UTIs. Flucytosine, which is excreted into the urine in high concentrations as active drug, should be used only when fluconazole is not tolerated or the organism is fluconazole resistant. The usual dosage of flucytosine is 25 mg/kg orally every 6 hours for 7 to 10 days.[15] Most species of *Candida,* with the exception of *C. krusei,* are susceptible to flucytosine, but resistance emerges quickly when this agent is used alone. Serious adverse effects of flucytosine include bone marrow suppression and hepatotoxicity. These effects are dose related, and the risk increases greatly with renal failure (see Table 55-3).

The echinocandins (caspofungin, micafungin, and anidulafungin) have minimal or no excretion into the urine as active drug. The tissue concentrations achieved with these agents may be adequate to treat invasive *Candida* infections of the bladder or kidney, but clinical data are limited.[16] Therefore, echinocandins currently cannot be recommended for the treatment of *Candida* UTIs.

Local Antifungal Administration

Continuous bladder infusion of amphotericin B, 50 mg in 1 liter of sterile water through a triple-lumen catheter, is sometimes used to treat *Candida* bladder infection. Bladder irrigation clears candiduria more quickly than systemic antifungal agents.[17] However, the effect is brief, and recolonization occurs within 1 to 2 weeks. Amphotericin B bladder irrigation is rarely required as a strategy given the need for catheter placement and the availability of more convenient treatment options.[18] The one exception might be lower tract infection with azole-resistant *C. krusei* or *C. glabrata*.

In the patient with kidney obstruction caused by a fungus ball, irrigation through a percutaneous nephrostomy tube with amphotericin B is recommended, in addition to systemic antifungal therapy with fluconazole.[13] Absorption of amphotericin B does not occur, and direct infusion is not nephrotoxic. Surgical or endoscopic removal of the fungus ball is essential to eradicate the infection.

Localized *Candida* Infections

Prostatitis and prostatic abscess caused by *Candida* species present with symptoms that are similar to those of bacterial prostatic infection. The initial presentation may be urinary retention; physical examination reveals a tender prostate, and imaging can show either discrete abscesses or diffuse inflammation. Treatment is drainage if an abscess is present, and fluconazole, which achieves excellent concentrations in the prostate, for several months until the infection has resolved.[19] Epididymo-orchitis is less common and usually presents as a tender scrotal mass. Surgical drainage or orchiectomy is required, along with fluconazole therapy until resolution has occurred.

OTHER YEASTS

Cryptococcus neoformans infection in immunosuppressed hosts, especially patients with acquired immunodeficiency syndrome (AIDS), is a systemic illness with involvement of many organs, including the genitourinary (GU) tract. In autopsy series, kidney involvement has been noted in 25% to 50% of patients who died of cryptococcosis, but symptoms rarely are referable to the GU tract. The prostate is frequently infected and can be a reservoir for persistent *C. neoformans* infection. Isolated prostatitis and epididymo-orchitis have been reported in the absence of systemic cryptococcosis.[20] The diagnosis is usually made at the time of biopsy of a mass or nodule; granulomatous inflammation is typically seen. Treatment of localized GU tract cryptococcal infection is fluconazole, 400 mg daily, for 6 to 12 months.

Saccharomyces cerevisiae has been described rarely as a cause of UTI. The presentation is the same as for *Candida* species. In clinical microbiology laboratories that do not identify yeasts in urine to the species level, this organism will not be differentiated from *Candida*. *S. cerevisiae* is often resistant to fluconazole, and successful treatment may require amphotericin B.

ASPERGILLUS AND OTHER MOLDS

The urinary tract is an uncommon site of infection with molds. However, individual case reports have noted genitourinary infections caused by a variety of molds, including the Mucorales (e.g., *Rhizopus, Mucor*), *Aspergillus, Penicillium*, and *Paecilomyces*.[21] The most common mold infection is aspergillosis. Hematogenous spread to the kidney with invasive disease in immunosuppressed patients results in numerous renal microabscesses and infarcts. This may be an incidental finding in light of massive dissemination at autopsy. Patients who have symptomatic UTI usually present with urinary tract obstruction from masses of fungal elements causing fungal balls, which can be visualized on CT scan or ultrasound. Treatment is surgical removal of the obstructing mass, often nephrectomy, and systemic antifungal therapy for the specific mold. Mortality is extremely high.

ENDEMIC FUNGI

All of the major endemic mycoses have been reported to infect the GU tract. For all of these organisms, infection is by hematogenous spread to the GU tract. For upper tract infection, treatment is the same as that for disseminated infection. The treatment of focal infection, which is more likely to involve the lower GU tract, is usually surgical removal of the infected tissue combined with antifungal therapy.

Blastomyces dermatitidis has the greatest propensity to cause symptomatic infection. In patients with disseminated blastomycosis, involvement of the GU tract occurs in as many as a third of cases and usually manifests as prostate or epididymal infection.[22] In most patients, this involvement is discovered incidentally when urine cultures yield the organism or when a biopsy is performed for a prostatic or epididymal mass.

Symptomatic GU tract involvement with histoplasmosis is uncommon. However, at autopsy, kidney lesions are often found in patients who have disseminated histoplasmosis.[23] Patients are usually asymptomatic in regard to urinary symptoms. Individual cases of testicular abscesses, epididymitis, and prostate nodules have been reported.

Coccidioidomycosis rarely causes symptomatic UTI. However, autopsy series of cases of disseminated coccidioidomycosis have noted kidney involvement in more than 50% of cases.[24] The finding of *Coccidioides* species in the urine in such patients is not uncommon. Localized infection, presenting as abscesses or mass lesions of the epididymis or prostate, also occurs in patients with disseminated coccidioidomycosis.

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CHAPTER 56

The Kidney in Schistosomiasis

Rashad S. Barsoum

Schistosomiasis is a parasitic disease usually acquired by teenagers, often leading to complications that may extend into the fourth and fifth decades of life. It was known to the ancient Egyptians as "the bloody urine disease"[1] and is also known as *bilharziasis* in honor of its discoverer, Theodor Bilharz, the German physician who practiced in Egypt in the 1850s.

The life cycle of the parasite is shown in Figure 56-1. Infection is acquired through contact with contaminated waters in the ponds and slow-flowing canals originating from certain rivers. Cercariae enter through the skin or mucous membranes and migrate through the lymphatics and blood circulation into the portal or perivesical venous system, where they mature into sexually differentiated adult worms and live in almost continuous copulation. Females leave the males only to lay eggs, traveling against the blood flow, aiming at the rectal or bladder mucosa. The ova are driven out by visceral contraction during defecation or urination in the respective excreta. Contact with fresh water within a couple of days allows the eggs to hatch, releasing miracidia, which infect specific snails. In this "intermediate" host, the organisms mature asexually into cercariae, which are eventually released, searching for their "definitive" host, usually humans and occasionally apes and cattle. The snail demography defines the endemicity and frequency of schistosomiasis in different geographic regions. Because this is largely influenced by climatic factors such as temperature and humidity, it is possible to accurately monitor the global epidemiology of schistosomiasis by satellite remote sensing.[2]

According to World Health Organization estimates, about 200 million inhabitants of 76 countries on five continents are infected, and an additional 600 million are at risk. Of the infected subjects, 60% are symptomatic, 10% have serious sequelae, and 1% die of the disease each year, mainly in China, the Philippines, Egypt, Brazil, northern Senegal, and Uganda.

Three species are mainly responsible for almost all the morbidity from the disease, namely, *Schistosoma haematobium* throughout Africa and adjacent regions; *Schistosoma mansoni* in Africa, South America, and the Caribbean islands; and *Schistosoma japonicum* in the Far East (Fig. 56-2). The other four significant human-pathogenic schistosomal species (*Schistosoma intercalatum, Schistosoma mekongi, Schistosoma guineensis, and Schistosoma mattheei*) have a patchy distribution in certain geographic locations, hence their limited impact on the global epidemiology of schistosomiasis.

S. haematobium affects the urinary tract, whereas *S. mansoni* and *S. japonicum* affect the colon and rectum, ultimately reaching the liver and inducing periportal fibrosis. Sporadically, all three species cause "metastatic lesions" when ova are driven by the bloodstream to the lungs, brain, spinal cord, heart muscle, eyes, and other sites.[3] Overall morbidity is variable and depends on the virulence of the infective strains, host resistance, environmental factors, and standards of primary medical care. For example, chronic lower urinary tract disease among infected subjects is reported to vary from 2% in Nigeria in the west of Africa to 52% in Tanzania in the east.[4]

PATHOGENESIS

Schistosomes cause morbidity through two major mechanisms: (1) local reactions around the ova deposited in different tissues and (2) systemic effects attributed to the host's response to circulating antigens released from the worms or the ova (Fig. 56-3).[4,5]

The local reaction is a cell-mediated immune response to soluble egg antigens diffusing out of trapped ova through micropores in the eggshell. The initial response is innate, being driven by tissue macrophages, and involves natural killer cells, neutrophils, and complement. This response is followed by a specific immune response orchestrated by T helper (Th) lymphocytes.

The schistosomal granuloma is composed of mononuclear cells, eosinophils, neutrophils, basophils, and fibroblasts, which are recruited and activated by a variety of Th lymphokines as well as specific chemoattractants of parasitic origin (Fig. 56-4). These cells are involved in the elimination of the parasite by direct phagocytosis (monocytes), lymphocytotoxicity (T lymphocytes), antibody-dependent cytotoxicity (eosinophils), and antibody- and complement-dependent cytotoxicity (neutrophils). Later, the granuloma is modulated by gradual switching from Th1 to Th2 activation, largely mediated by a change in the monokine profile that favors release of interleukin (IL)–4, which is associated with a phenotypic change of the committed tissue macrophages. At this stage, the intensity of the inflammatory reaction is reduced, and progressive fibrosis is induced largely through the release of IL-4, IL-5, IL-10, somatostatin, and transforming growth factor β. Further on, tolerance to the parasite is achieved by an established population of regulatory T cells, which develop under the combined influence of host- and parasite-derived mediators. With the final extinction of the inflammatory reaction, granulomas in the bladder, lower ureters, and seminal vessels heal with dystrophic calcification.[6,7]

The systemic immune response is primarily a humoral reaction to circulating schistosomal antigens, which originate mainly from the worm's digestive enzymes (gut antigens), with a minor contribution from the tegument and ova. The gut antigens consist of a positively charged glycoprotein and a negatively charged proteoglycan (circulating cationic antigens and circulating anionic antigens, respectively). These antigens are present in most of the schistosomal immune complex–mediated lesions, particularly in glomeruli.[8] The antibody response is biphasic, reflecting the successive Th1 and Th2 stages of lymphocyte activation. In the Th1 stage, B cells tend to synthesize IgM, IgG1, and IgG3 under the influence of IL-2. During the Th2 phase, IgG2, IgG4, and IgA predominate; these have a limited ability to fix complement and may even block its deposition, hence their importance in modulating the granulomas.[4,6]

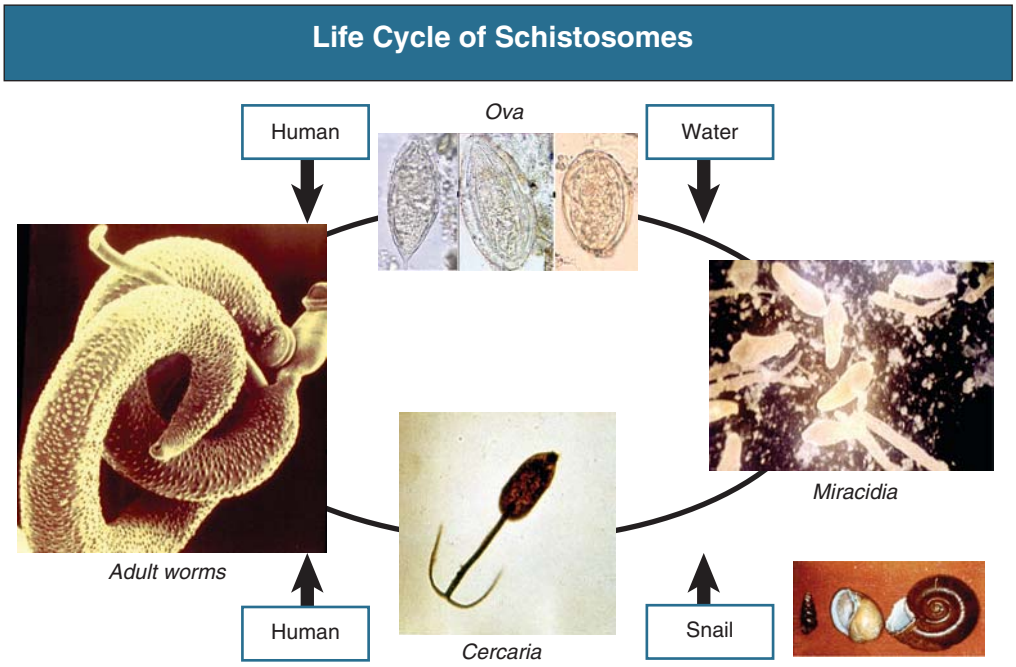

Figure 56-1 Life cycle of schistosomes.

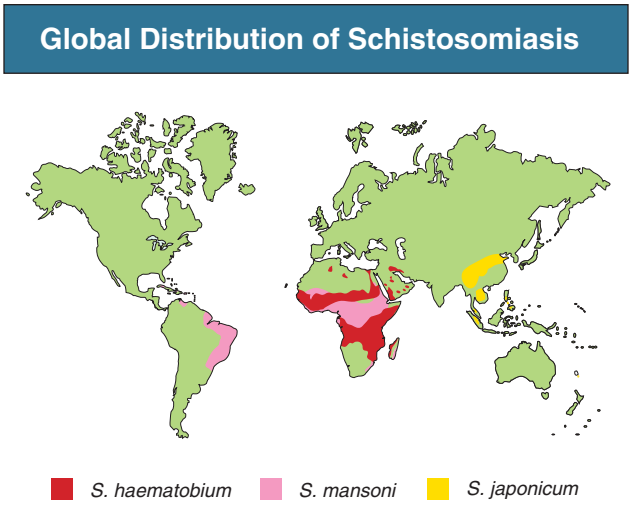

Figure 56-2 World map showing the geographic distribution of the main pathogenic schistosomes.

CLINICAL MANIFESTATIONS

Schistosomal lesions in the urinary system mirror the two major pathogenetic mechanisms. On one hand, there are local lesions, mostly affecting the lower urinary tract, caused by the local granulomatous response to *S. haematobium* ova.[9] On the other hand are those lesions caused by immune complex deposition in the glomeruli, usually associated with hepato-intestinal *S. mansoni* and, less commonly, urogenital *S. haematobium* infections.[10] Although glomerular lesions can be readily induced by *S. japonicum* in experimental animals,[11] this species does not seem to cause significant kidney disease in humans.

Lower Urinary Tract Schistosomiasis

The lower urinary tract and adjacent genital structures are the primary sites of *S. haematobium* infection. Clinical disease starts by the coalescence of multiple granulomas that form small "pseudotubercles" in the bladder mucosa (Fig. 56-5). These may consolidate to form sessile, occasionally pedunculated masses or ulcerate, leading to painful terminal hematuria, the most typical presenting symptom. Hematuria may vary from microscopic (40% to 100% in different reports) to gross (0% to 97%).[12] Ulcers eventually heal by fibrosis, with calcified granulomas under the atrophic and dirty mucosa, leading to the characteristic cystoscopic appearance of sandy patches and also the radiologic appearance of linear bladder calcifications in 2% to 62% of cases.[12] Similar lesions may occur in the lower ureters, bladder neck, seminal vesicles, and other organs in the vicinity (Fig. 56-6).

The bladder lesions predispose to secondary bacterial infection, particularly with *Pseudomonas* or *Proteus* species, usually following instrumentation. *Proteus* infection is notorious for favoring stone formation, which further complicates the scenario. The subsequent fibrotic process may involve the bladder neck, leading to outflow obstruction, or the vesicoureteral junction, leading to ureteral obstruction or vesicoureteral reflux. Involvement of the detrusor is a late event that may interfere with the motor function of the bladder, leading to an atonic or a hyperirritable viscus. Eventually, the bladder becomes a deformed, contracted, and calcified organ that accommodates a very small amount of urine that it can hardly void.

Bladder Cancer

Chronic bilharzial cystitis is precancerous. In a study of almost 10,000 Egyptian patients with bladder cancer, schistosomal association was confirmed in 55.3%. The predominant lesions were transitional cell carcinoma (65.8%) and squamous cell carcinoma (28.4%).[13] The tumor, particularly when of the squamous cell type, remains localized for a long time before spreading to the surrounding pelvic tissues or a distant site, thanks to the occlusion of lymphatics by the preceding fibrotic process.

Associated infection with human papillomavirus is encountered in about one fourth of cases, which suggests an etiologic role in malignant transformation.[14] Specific p53 gene mutations were detected in one third of cases.[15] This may be attributed to neutrophil-generated reactive oxygen molecules, cleavage of conjugated urinary carcinogens, or production of nitrosamines by bacterial enzymes.[16]

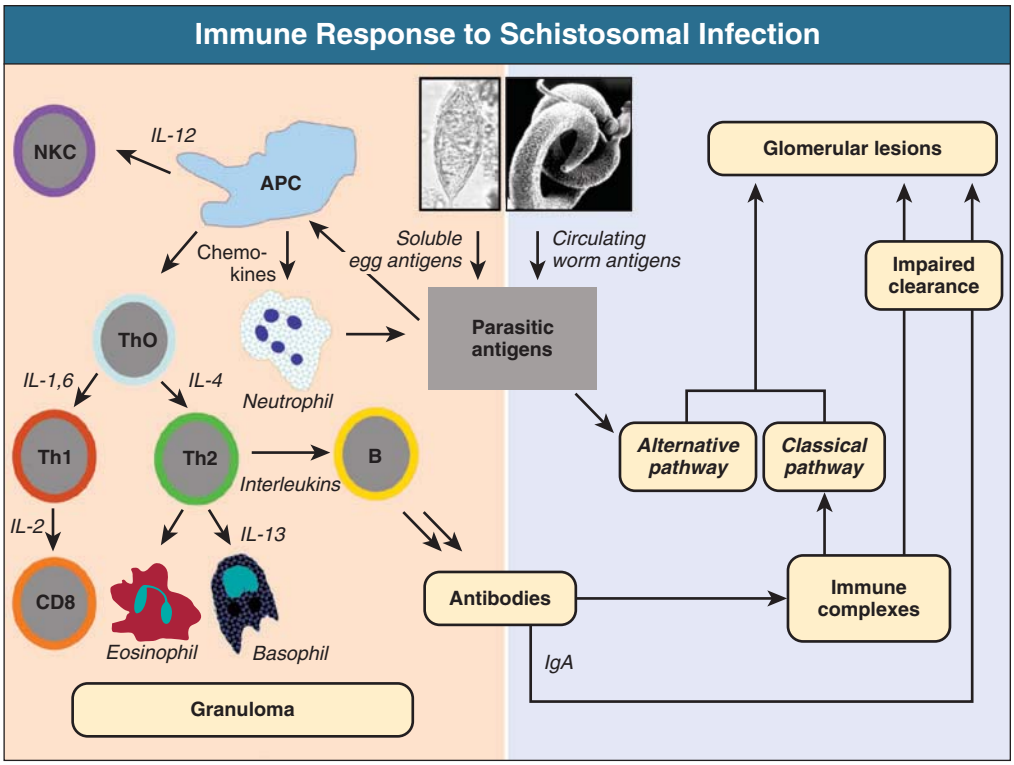

Figure 56-3 Immune response to schistosomal infection. The local immune response to deposited ova leading to granuloma formation is shown on the left; all cells shown in the diagram, in conjunction with antibodies or complement, participate in eventual parasite elimination (see text). The systemic immune response is shown on the right; note the important role of impaired clearance of schistosomal antigens and IgA in the development of glomerular lesions. *APC,* Antigen-presenting cell; *IL,* interleukin; *NKC,* natural killer cell.

Figure 56-4 *Schistosoma haematobium* granuloma. Note the egg's terminal spike, which identifies *S. haematobium,* and the distortion of shell from proteases and oxidants released by the local neutrophil infiltration. (Hematoxylin-eosin; ×500.)

Development of malignancy is suspected when the symptoms of chronic cystitis exacerbate, along with recurrence of hematuria many years after the initial presentation and the passage of small pieces of necrotic tissue with urine (necroturia). A characteristic radiologic sign is the irregular 'eating up' of the bladder calcification on a plain radiograph. Cystography shows the tumor mass as an irregular filling defect or bladder ulcer. Cystoscopy shows the tumor and provides the means for a histologic diagnosis (Fig. 56-7).

Human Immunodeficiency Virus Infection

Several recent studies have established an epidemiologic link between schistosomiasis and human immunodeficiency virus (HIV). It has been shown that women and men with lower urinary schistosomiasis were at a significantly increased risk of acquiring, and subsequently transmitting HIV to their sexual partners. The immunologic perturbation induced by schistosomiasis seems to accelerate the progression and spread of HIV infection in endemic areas.[17]

Upstream Consequences

Although ureteral strictures and calcifications are common, the hypertrophied upper ureteral musculature usually overcomes the lower obstruction, thereby limiting the upstream consequences. Nevertheless, hydronephrosis and progressive renal failure may develop when there is extensive ureteral scarring, in the presence of stones or secondary bacterial infection, or when the vesicoureteral junction is incompetent (Fig. 56-8). The frequency of upper urinary tract disease from *S. haematobium* is variably reported from different geographic regions—for example, from less than 10% in Niger to 48% in Cameroon.[10]

Interstitial Nephritis

Chronic pyelonephritis is the eventual outcome of complicated *S. haematobium* infection, resulting from obstruction, reflux, and bacterial infection. Granulomas have occasionally been seen in the renal interstitium but tend to be discrete and of no functional significance (Fig. 56-9). Immune-mediated tubulointerstitial nephritis has been described with *S. mansoni* in humans,[18] but the role of immune mechanisms remains questionable in *S. haematobium* pyelonephritis.

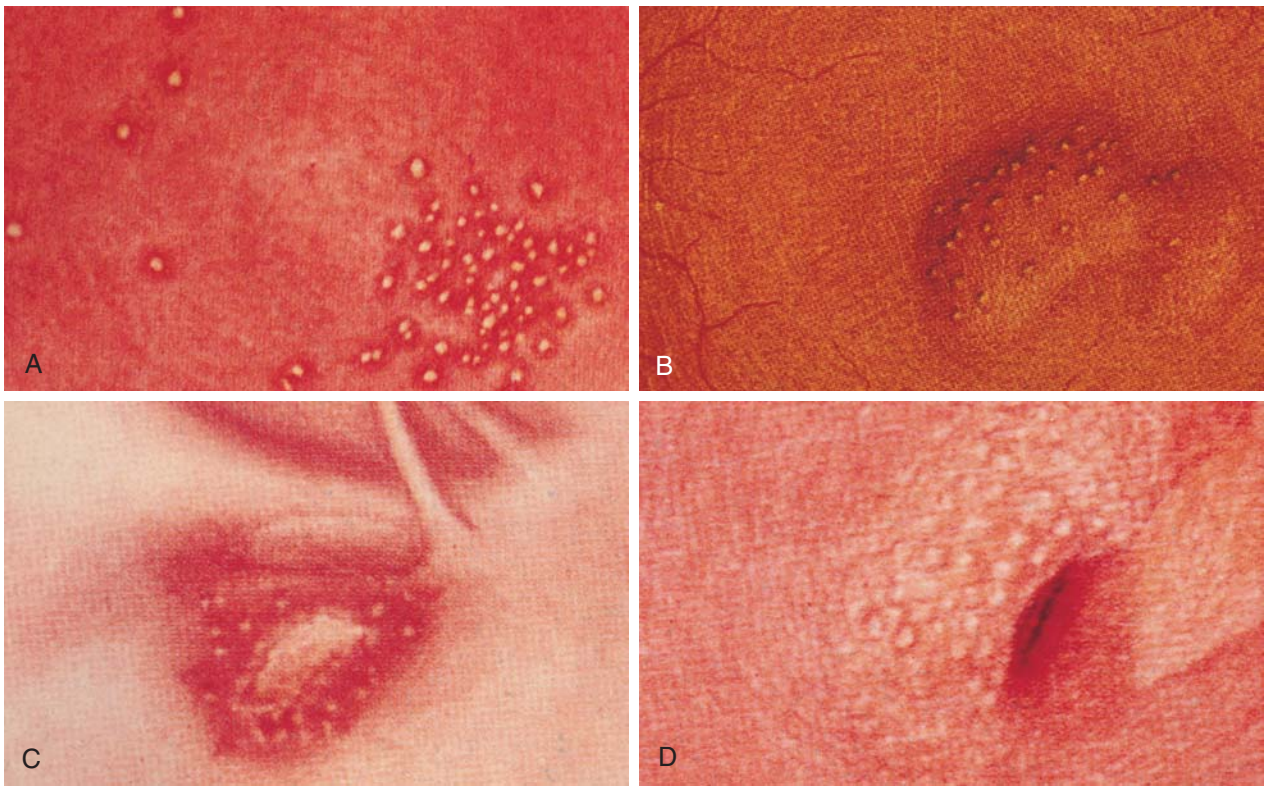

Figure 56-5 **Cystoscopic appearances in urinary schistosomiasis. A,** Pseudotubercles. **B,** Sessile mass covered by pseudotubercles. **C,** Ulcer surrounded by pseudotubercles. **D,** Sandy patches. *(Courtesy Professor Naguib Makar.)*

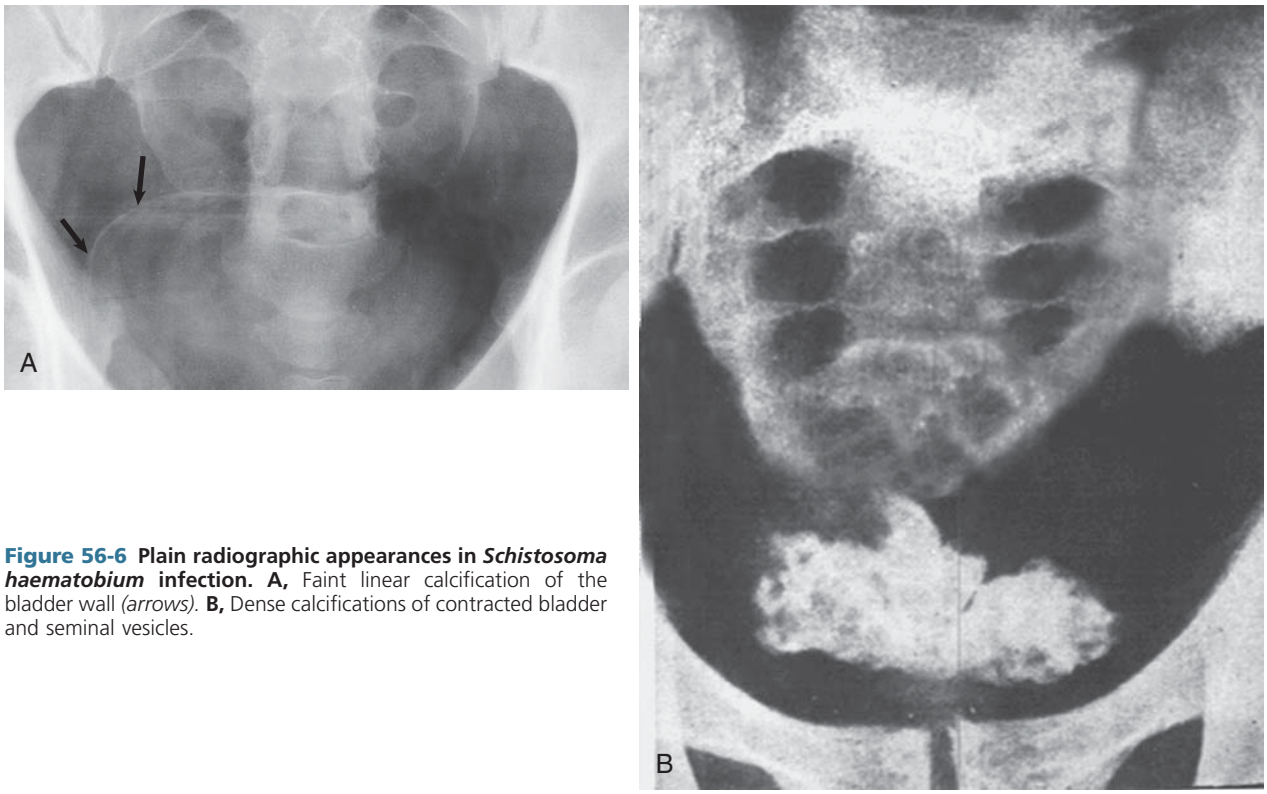

Figure 56-6 **Plain radiographic appearances in *Schistosoma haematobium* infection. A,** Faint linear calcification of the bladder wall *(arrows).* **B,** Dense calcifications of contracted bladder and seminal vesicles.

Figure 56-7 Bilharzial bladder cancer.

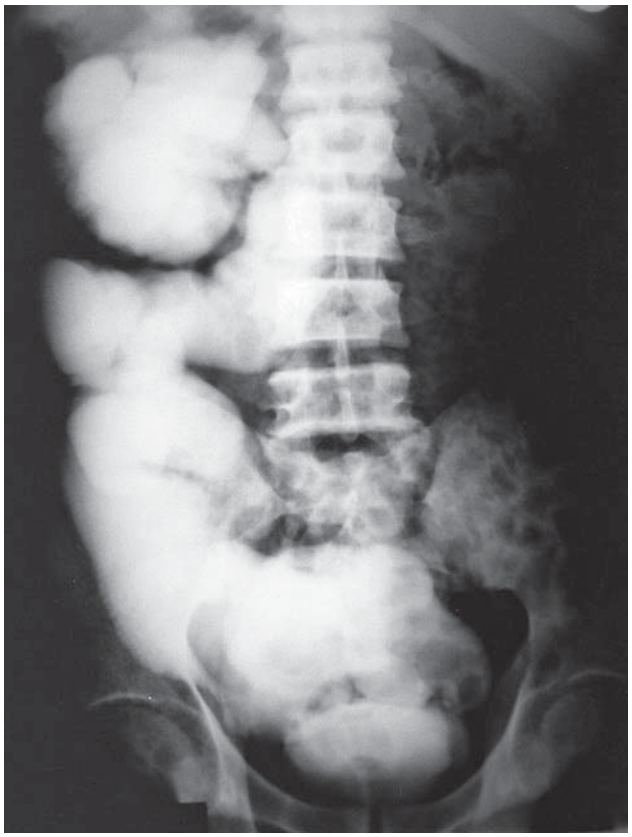

Figure 56-8 Ascending cystogram showing right megaureter caused by vesicoureteral reflux.

The typical pathologic picture is that of a deformed kidney with calyceal dilation, distortion, and atrophic parenchyma. Dense interstitial infiltration, fibrosis, and periglomerular scarring are present. The glomeruli may show ischemic collapse or other schistosomal lesions, such as proliferative glomerulonephritis (GN) or amyloidosis.

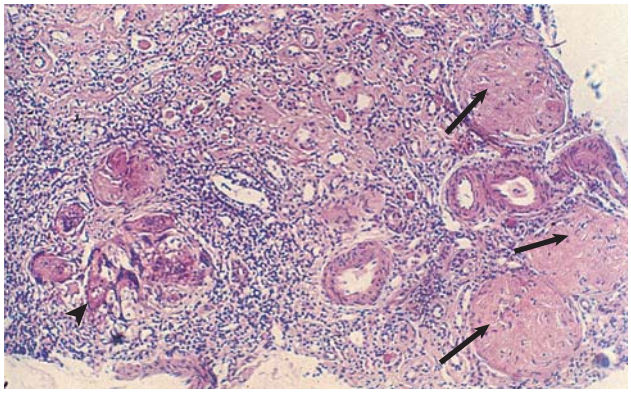

Figure 56-9 Schistosomal chronic interstitial nephritis. Note the dense cellular infiltration and fibrosis, atrophic dilated tubules, and thickened vessels. Three glomeruli heavily infiltrated with amyloid are seen on the right side *(arrows);* a schistosomal granuloma is seen in the lower left corner *(arrowhead).* (Hematoxylin-eosin stain; original magnification ×75).

The clinical picture is that of chronic tubulointerstitial nephritis (see Chapter 64), often associated with residual manifestations of lower urinary tract involvement. Hypertension is a late feature, being checked by concomitant tubular salt wastage. Anemia and osteodystrophy may be disproportionately severe because of the associated secondary distal tubular acidosis and nutritional deficiency in endemic areas.

Glomerulonephritis

Immune complex–mediated GN has been described in experimental[11] and human[10] infection, mainly with *S. japonicum* and *S. mansoni*. The latter species accounts for most clinically significant disease in humans. *S. haematobium* GN is rare and usually subclinical, though a small epidemic of acute nephritis was reported in an Egyptian village where the infection had been recently introduced as a result of change in the agricultural irrigation system.[19]

Schistosomal gut antigens are present in circulating immune complexes as well as in the immune deposits in mesangial, subendothelial, and intramembranous locations. The presence of liver fibrosis is critical because it results in impaired hepatic clearance of schistosomal antigens and immune complexes. These are mostly generated within the portal venous system, which accommodates the adult worms. Evidence of autoimmune reactivity has also been reported, but its potential pathogenetic role is ill-defined.

Most patients are 20- to 40-year-old men with evidence of hepatosplenic schistosomiasis. Renal involvement is asymptomatic in up to 40% of those, being identified by accidental or surveillance urinalysis, which may display various grades of proteinuria, or abnormal sediment. Some 15% of those with hepatosplenic schistosomiasis have overt GN, with proteinuria and microhematuria on presentation, with or without the nephrotic syndrome, hypertension, and impaired kidney function. Liver function test results are often normal. A polyclonal gammopathy is seen in most cases, whereas a monoclonal IgM response is seen in those with associated hepatitis C virus (HCV) infection and cryoglobulinemia. Rheumatoid factor activity and anti-DNA antibodies are detected in 5% to 10% of cases, particularly in association with *Salmonella* infection (see later discussion), but they do not correlate with clinical severity. Rheumatoid seropositivity is detected in much higher titers when HCV infection is associated.[20]

Six histologic classes of schistosomal GN have been proposed (Table 56-1 and Fig. 56-10).[10,20] Class I (mesangial proliferative), class

Classification of Schistosomal Glomerulonephritis

Class	Histology	Immunofluorescence	Etiologic Agent	Prevalence	Clinical Findings	Treatment of Renal Disease
I	Mesangial proliferative GN	IgM, C3 Schistosomal gut antigens	*S. haematobium* *S. mansoni* *S. japonicum*	27%-60% of asymptomatic patients, 10%-40% of patients with renal disease	Microhematuria Proteinuria	May respond to antiparasitic treatment
II	Diffuse proliferative exudative GN	C3, *Salmonella* antigens	*S. haematobium* *S. mansoni* + *Salmonella* species	*Salmonella* infections Reduced serum C3	Acute nephritic syndrome, toxemia	May respond to treatment of *Salmonella* and schistosomal infections
III	Membranoproliferative GN	IgG, IgA, C3, schistosomal antigens	*S. mansoni (S. haematobium*?)	7%-20% of asymptomatic patients and in 80% of patients with overt renal disease	Hepatosplenomegaly, nephrotic syndrome, hypertension, renal failure	No
IV	Focal segmental glomerulosclerosis	IgM, IgG (occasionally IgA)	*S. mansoni*	11%-38%	Hepatosplenomegaly, nephrotic syndrome, hypertension, renal failure	No
V	Amyloid	AA protein	*S. mansoni* *S. haematobium*	16%-39%	Hepatosplenomegaly, nephrotic syndrome, hypertension, renal failure	No
VI	Cryoglobulinemic GN	IgM, C3	*S. mansoni* + hepatitis C virus	Unknown	Hepatosplenomegaly, nephrotic syndrome, purpura, vasculitis, arthritis, hypertension, renal failure	Interferon + ribavirin, corticosteroids, immunosuppression, plasma exchange

Table 56-1 Classification of schistosomal glomerulonephritis. *GN,* Glomerulonephritis.

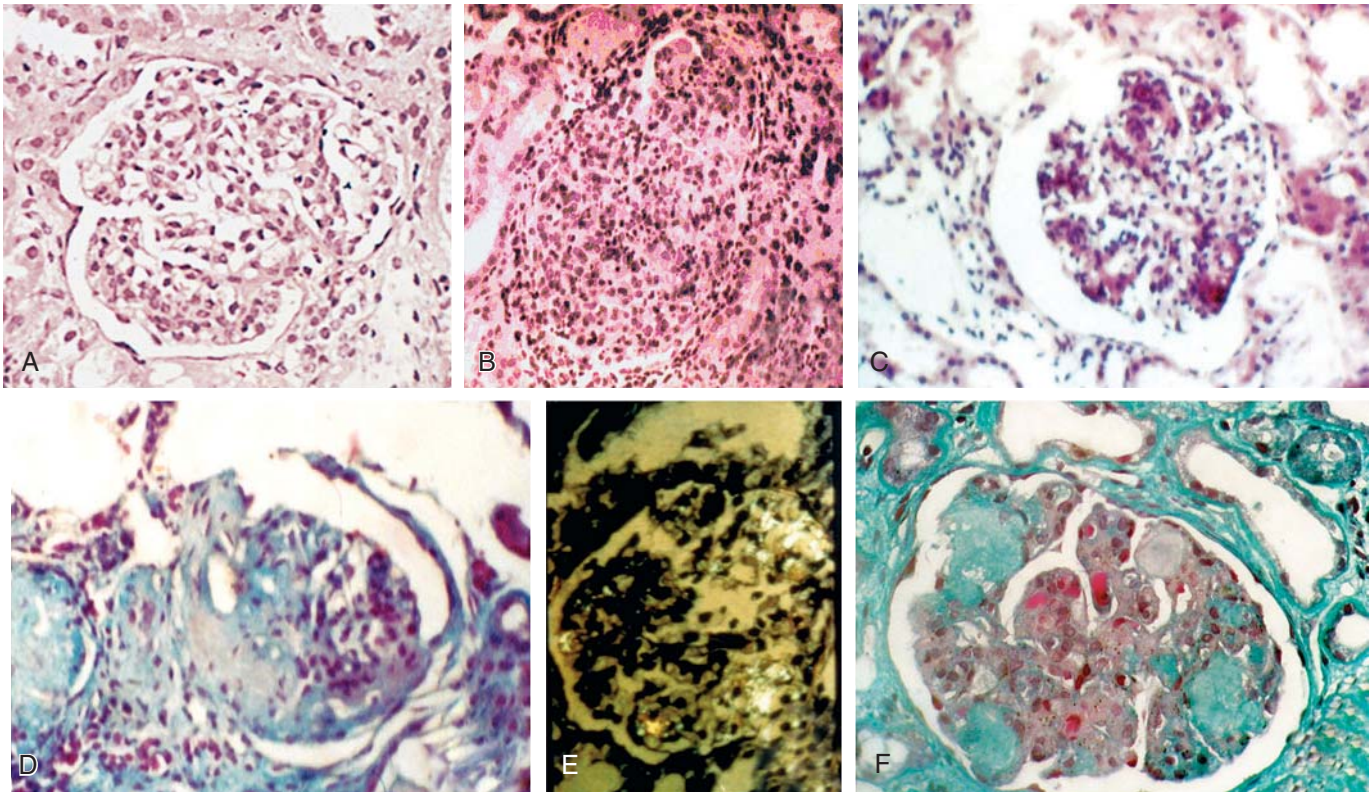

Figure 56-10 Schistosomal glomerulopathy. A, Mesangial proliferative glomerulonephritis (GN), hematoxylin-eosin stain (class I). **B,** Schistosoma- and *Salmonella*-associated exudative GN, hematoxylin and eosin stain (class II). **C,** Membranoproliferative (mesangiocapillary) GN type I, hematoxylin and eosin stain (class III). **D,** Focal segmental glomerulosclerosis, Masson trichrome stain (class IV). **E,** Green birefringence under polarized light in a glomerulus with mesangial proliferation in a patient with mixed *Schistosoma haematobium and Schistosoma mansoni* infection, Congo red stain (class V). **F,** Amyloid deposits and cryoglobulin capillary thrombi (red stain) in a glomerulus displaying focal mesangial proliferation in a patient with schistosomal hepatic fibrosis and associated hepatitis C virus infection (class VI).

III (membranoproliferative), and class IV (focal segmental proliferative and sclerosing) result from the deposition of immune complexes representing different stages in the evolution of "pure schistosomal" hepatosplenic disease. The main deposits in class I are schistosomal antigens, IgM, and C3; and in class III and class IV, IgG and IgA, usually without schistosomal antigens. The IgA deposits parallel the severity of proteinuria and mesangial proliferation. Impaired hepatic clearance and increased mucosal synthesis of IgA have been documented in those patients.[21] Whereas class I lesions are seen in most asymptomatic cases, class III and class IV are usually symptomatic and progressive, even with eradication of the parasitic infection.

Class II (diffuse proliferative and exudative) is associated with urinary or biliary coinfection with *Salmonella* strains, usually *Salmonella paratyphi* A in Africa and *Salmonella typhimurium* in Brazil, which are attached to specific receptors in the tissues of adult schistosomes. C3 and *Salmonella* antigens have been detected in the glomerular capillary walls and the mesangium. In these patients the clinical presentation is typical of acute postinfectious GN, associated with manifestations of *Salmonella*-related toxemia (fever, exanthema, and severe anemia).

Serum amyloid A protein deposits are detected by special stains or electron microscopy in up to 15% of biopsy samples from patients with class III and class IV, whereas AA-amyloidosis may be the predominant lesion (class V) in less than 5% of patients with clinically overt schistosomal GN. It occurs with heavy, often mixed infection regardless of the anatomic site. Minimal amyloid deposits do not seem to alter the clinical presentation or prognosis, but typical class V lesions are grossly nephrotic and relentlessly progressive.

A class VI lesion was more recently described in patients with hepatosplenic schistosomiasis and HCV infection.[20] This association is common, particularly in Egypt, where it is believed that the virus was acquired many decades earlier, when intravenous injections were used for mass treatment of schistosomiasis. Some soft evidence suggests that the virus may be transmitted with the infected cercariae. The lesion consists of a mixture of mesangial proliferation, amyloid deposition, fibrinoid necrosis, and cryoglobulinemic thrombi in the glomerular capillaries with tubular casts. Patients have chronic hepatitis, cirrhosis, nephrotic syndrome, cryoglobulinemic skin vasculitis, polyarthritis, and rapidly progressive renal failure associated with severe protein-calorie malnutrition.

DIAGNOSIS

Schistosoma haematobium Urinary Tract Disease

The bedside diagnosis of lower urinary schistosomiasis is easily made, particularly in patients with the typical pattern of painful terminal hematuria after exposure to fresh river waters in an endemic area. Diagnosis is more difficult when the history of exposure is less convincing (e.g., swimming pools) or when the clinical presentation is atypical (such as bacterial pyelonephritis, typhoid, or amyloidosis).

The diagnosis is made by finding ova in a fresh urine sample, which is easy because of their abundance, large size, and typical appearance with terminal spike (see Fig. 56-4). Live ova, containing mobile miracidia, indicate active infection, whereas dead, calcified ova may continue to be shed from fibrotic lesions for many months or even years.

Serologic diagnosis is based on finding circulating schistosomal antigens or antibodies by gel diffusion, precipitation, complement fixation, chromatography, immunoelectrophoresis, indirect hemagglutination, microfluorometry, radioimmunoassay, or various forms of enzyme-linked immunosorbent assay (ELISA) techniques. The circumoval precipitin test is most frequently used in clinical laboratories. These techniques are useful in confirming the diagnosis in the absence of ova, which occurs with old infections when the worms are sterile but continue to release their antigens. Serologic tests are also useful in assessing the response to treatment because titers usually become negative within 3 to 6 months of complete eradication of infection.

The radiologic appearances of bladder and seminal vesicle calcification are so typical that no further confirmatory tests are needed in an endemic area. Cystoscopic findings are equally pathognomonic although seldom required. Early pseudotubercles are easily distinguished from mycobacterial infection by their size and the surrounding mucosal pathologic changes. The presence of sandy patches with associated masses, polyps, and even neoplasms makes the diagnosis. Tissue biopsy confirms the parasitic nature of the lesions. Different imaging techniques (e.g., ultrasound, intravenous urography, voiding cystography) are useful in the diagnosis of upstream complications, including obstruction and reflux (see Chapter 60).

The main differential diagnosis for urinary schistosomiasis is tuberculosis, which also causes hematuria, strictures, back pressure, and chronic kidney disease. This differential can be resolved with appropriate parasitologic and bacteriologic techniques (see Chapter 54).

Schistosoma mansoni Glomerulonephritis

Overt glomerular disease in patients with hepatosplenic schistosomiasis is suspected in those who develop hypertension, nephrotic or nephritic syndrome, or chronic kidney disease. Occult glomerular disease is indicated by the presence of abnormal urinary sediment or kidney function. Although renal biopsy is essential for the diagnosis and classification, none of the lesions is pathognomonic unless schistosomal antigens are detected, which is unusual in clinically overt cases when sought with conventional immunofluorescence. Identification of *S. mansoni* eggs in the stools (Fig. 56-11) or submucosal rectal biopsy samples supports the diagnosis. Concomitant *Salmonella* or HCV infection can be detected by appropriate microbiologic tests. The various serologic abnormalities described are of limited diagnostic value, except the high rheumatoid factor, monoclonal IgM expansion, and low C4 that are typical of class VI.

Other glomerular disorders associated with hepatic fibrosis, such as secondary IgA nephropathy and hepatic glomerulosclerosis,

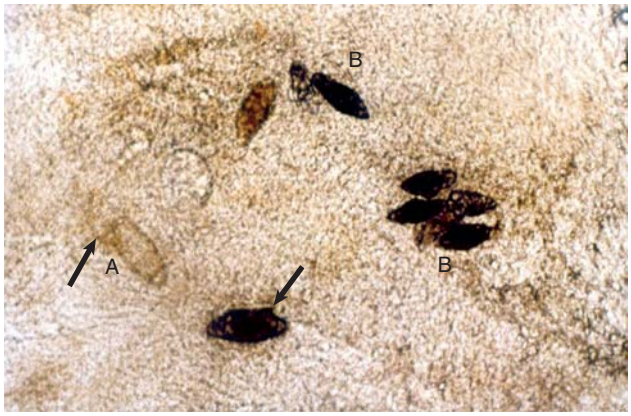

Figure 56-11 Stool smears showing living *(A)* and dead *(B) Schistosoma mansoni* ova. Species are identified by the lateral spike *(arrows).*

should be considered in the differential diagnosis. However, in both these conditions the renal lesions are relatively mild, mainly with microhematuria at presentation but rarely with nephrotic-range proteinuria or impaired renal function. The glomerular deposits are mostly mesangial, in contrast to those seen in schistosomiasis, in which subendothelial and intramembranous deposits may also be present.

TREATMENT

Schistosoma haematobium Urinary Tract Disease

S. haematobium is susceptible to antimony compounds, organophosphates (metrifonate), and niridazole, but the current drug of choice is praziquantel, the most effective and least toxic. It is administered as a single oral dose of 40 mg/kg body weight. Antiparasitic treatment cures the early bladder disease, yet it has no effect on sandy patches or other fibrotic lesions. Ureteral distention with radiologic evidence of hydronephrosis may be reversed in a few weeks after successful treatment.

Antibacterial therapy usually controls acute episodes of cystitis and pyelonephritis. However, it must be combined with simultaneous eradication of parasitic infection if still active, especially when the urinary bacterial infection is a result of typhoid *(Salmonella typhi)*.

Chronic fibrotic lesions are difficult to treat. Surgery or the placement of stents may be necessary for the relief of an obstructive lesion. However, particular caution is required in dealing with the vesicoureteral junction to avoid induction of reflux. Several plastic procedures are available to restore the distorted ureteral, bladder, or urethral anatomy. Associated bacterial infections may require long-term low-dose antibiotics.

Regular dialysis in such patients can be difficult owing to the negative effects of chronic infection; the associated schistosomal lesions in the liver, lungs, and other organs; and the comorbid impact of undernutrition, viral infection, or malignant disease. The same factors reflect on the outcome of renal transplantation, with the additional risk for urinary leakage, which is many-fold higher than usual owing to the presence of fibrotic granulomas and anatomic distortion in the bladder wall. Reinfection with *S. haematobium* has also been described in patients living in an endemic area.[22]

Schistosoma mansoni Glomerulonephritis

S. mansoni is more resistant to treatment and may require higher doses of praziquantel (40 to 60 mg/kg body weight) or the use of oxamniquine (single dose of 15 mg/kg body weight in South America or two doses of 15 mg/kg body weight given 12 hours apart in Africa). Nevertheless, eradication of the parasite can be curative only in classes I and II. In class II, it must be combined with antibiotics for the control of *Salmonella* infection (usually ampicillin and cotrimoxazole). Antischistosomal therapy (praziquantel or oxamniquine) and immunosuppressive therapy are ineffective in all other classes of schistosomal GN.[10]

Dialysis may be difficult in those who reach end-stage renal disease because of the frequent presence of esophageal or gastric varices that carry the risk for bleeding with anticoagulation for hemodialysis. Endoscopy is essential before the start of regular hemodialysis, with prophylactic sclerotherapy if necessary. Although peritoneal dialysis is a viable option in some cases, it is relatively contraindicated in those with significant ascites because of the risk for excessive protein loss in the effluent.

Renal transplantation is a viable option in those who develop end-stage renal disease, in the absence of major risk factors such as viral infection, undernutrition, or hepatic insufficiency. Uncomplicated residual hepatic fibrosis in the recipient does not seem to significantly modify the pharmacokinetics of the immunosuppressive agents used in transplant recipients. However, variations in cyclosporine blood levels have been noted[15] and attributed to altered absorption of the drug. Associated viral hepatitis may have a considerable impact on the protocols of donor selection and prophylactic immunosuppression and on the eventual outcome (see Chapters 102 and 105).

Recurrence of schistosomal GN has been described in a few patients,[23] suggesting the persistent release of antigens from living worms. Though not an evidence-based practice, many authorities recommend the administration of a single dose of praziquantel to recipients known to have been previously infected with the parasite.

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CHAPTER 57

Glomerular Diseases Associated with Infection

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GENERAL CHARACTERISTICS OF GLOMERULAR DISEASES ASSOCIATED WITH INFECTION

The observation of dark scanty urine in the convalescent period of scarlet fever is more than two centuries old. At the beginning of the last century, Clemens von Pirquet, on the basis of clinical observations, postulated that the disease resulted from antibodies that instead of having beneficial effects were pathogenic—an insight that opened the field of immune-mediated renal disease.

Today, the incidence of infection-related glomerulonephritis (GN) is declining in developed countries, and usually the disease is associated with older individuals and debilitating conditions such as diabetes, malignant neoplasia, acquired immunodeficiency syndrome (AIDS), and alcoholism. The prognosis in elderly individuals is poor, with less than 25% recovering full renal function. In recent years there has been a tendency for an increase in GN associated with *Staphylococcus* (IgA dominant) and fewer cases associated with *Streptococcus,* but a wide variety of pathogens have been reported (Box 57-1). In general, the infection-related GNs have a better prognosis than other forms of GN, but in adult patients with other comorbid factors they carry a significantly higher risk of chronic kidney disease (CKD).[1]

Histologic Patterns and Pathogenesis

The histologic patterns and the most typical infectious diseases associated with them are shown in Table 57-1. Mesangial proliferative GN is usually acute and self-limited. Microscopic hematuria and non-nephrotic proteinuria are present in association with deposits of IgG, IgM, and C3. Serum complement may be transiently decreased. Diffuse proliferative GN is also acute and self-limited if the infection is eradicated. IgG, IgM, and C3 deposits are prominent in the mesangium and glomerular capillaries, and electron-dense deposits are present in mesangial, subendothelial, and subepithelial locations. Staphylococcal infections, particularly methicillin resistant, may induce diffuse proliferative GN with crescent formation and exclusive or predominant IgA deposition. Membranoproliferative GN (MPGN) is commonly observed with chronic infections. The clinical presentation is usually with severe proteinuria, microscopic hematuria, and variable degrees of hypertension. Immunoglobulins and C3 deposits are present. In the setting of liver disease (as in *Schistosoma mansoni* infection), IgA may be a predominant component of the immune deposits. Membranous nephropathy (MN) is associated with chronic infections and may manifest as the nephrotic syndrome. Finally, vasculitis may develop in association with viral (especially hepatitis B virus [HBV] and human immunodeficiency virus [HIV]) or bacterial (rarely *Streptococcus*) infections.

Infection-related GN, especially when it is immune complex associated, occurs more frequently and has a worse prognosis in conditions in which there is difficulty clearing the infection or immune complexes. These conditions include HIV infection, infections acquired in the neonatal period (when tolerance is often induced, such as is observed with HBV infection), chronic liver disease, diabetes, and chronic alcoholism.

Glomerulonephritis associated with infections usually results from glomerular deposition of immune complexes containing bacterial antigens, but other mechanisms may also occur. Staphylococcal infections may cause GN induced by bacterial wall superantigens that induce a nonspecific polyclonal immunoglobulin response. Focal segmental glomerulosclerosis (FSGS) with glomerular collapse (collapsing glomerulopathy) may occur with HIV or parvovirus B19 infection. The hemolytic uremic syndrome (HUS) may result from verotoxin-producing *Escherichia coli* or *Shigella* species (see Chapter 29). Amyloidosis may result from chronic infections such as tuberculosis, leprosy, and schistosomiasis. Interstitial nephritis manifested as acute renal failure may result from several viral (especially Epstein-Barr virus [EBV]) or bacterial (especially *Legionella*) infections. Hantavirus can also induce a hemorrhagic fever–renal failure syndrome in which infection of the interstitial capillaries and tubules leads to acute renal failure (see Chapters 69 and 70).

BACTERIAL INFECTIONS

Poststreptococcal Glomerulonephritis

Epidemiology

Poststreptococcal glomerulonephritis (PSGN) is more common in males (2:1) and usually affects children 2 to 14 years old. Certain strains of group A *Streptococcus pyogenes* are nephritogenic: impetigo caused by streptococci of M types 47, 49, 55, and 57 and upper respiratory infections with types 1, 2, 4, and 12.[2] More recently, ingestion of unpasteurized milk contaminated with group C *Streptococcus (Streptococcus zooepidemicus)* has caused clusters of cases and at least one large epidemic.[3] The risk of nephritis in epidemics may range from 5% in throat infections to as high as 25% in M type 49 pyoderma. The risk of PSGN is reduced by early antibiotic treatment. A genetic predisposition is suggested because there is an association of PSGN with HLA-DR4 and HLA-DR1 and higher attack rates in siblings than expected for the general population.

Poststreptococcal glomerulonephritis is becoming less common in industrialized countries and, instead of affecting predominantly children, now occurs more commonly in debilitated elderly individuals, alcoholics, diabetics, and intravenous drug users. The reduction in incidence of PSGN likely relates to improvement in public health, more rapid and frequent use of antibiotics, and perhaps the common practice of fluorination of water, which reduces the expression of virulence factors in cultures of *S. pyogenes.* Nevertheless, PSGN remains common in developing countries, where it may have an incidence of 9.3 to 9.8 cases per 100,000 population,[4] and it represents a major problem in indigenous populations. For example, in

Australia more than 95% of the cases occur in aboriginal tribes in remote locations.[5]

Pathogenesis

Two nephritogenic streptococcal antigens have been identified: nephritis-associated plasmin receptor (NAPLr), which was characterized as glyceraldehyde-3-phosphate dehydrogenase (GAPDH); and streptococcal pyrogenic exotoxin B (SPEB) and its more immunogenic precursor, zymogen. GAPDH and SPEB have been demonstrated in renal biopsy specimens of acute PSGN, and antibody titers to both these antigens are elevated in most convalescent sera.[2] GAPDH has been localized in areas of the glomeruli with plasmin-like activity, suggesting a local direct mechanism of glomerular inflammatory damage, but it is not co-localized with complement or immunoglobulin.[6,7] In contrast, SPEB is co-localized with both complement and IgG, suggesting a participation in the immune-mediated glomerular damage.[8] SPEB is the only putative streptococcal nephritogenic antigen that so far has been demonstrated in the subepithelial electron-dense deposits known as humps, the most typical histologic lesion of acute PSGN (Fig. 57-1). In studies from Latin America and central Europe, SPEB but not GAPDH is usually detectable in renal biopsy specimens of PSGN patients.[9] In contrast, GAPDH was present in PSGN in a study of Japanese patients.[6,7] These contrasting results raise the possibility that different streptococcal antigens are capable of inducing acute nephritis in different ethnic groups. Indeed, a study of the group C *S. zooepidemicus* strain that caused the epidemic outbreak in Brazil revealed an absence of the gene related to SPEB, which documents that this antigen was not involved in that epidemic.[9]

Poststreptococcal glomerulonephritis is thought to occur when persistent streptococcal infection results in antigenemia and the development of circulating immune complexes that primarily deposit in the subendothelial and mesangial locations to initiate an inflammatory cascade with local complement activation and the recruitment of neutrophils and monocytes-macrophages. Subepithelial immune deposits (humps) develop when cationic antigens (e.g., SPEB) are involved and result from dissociation of immune complexes in the subendothelial space with transit and re-formation on the outer aspect of the glomerular basement membrane.

Several issues remain unresolved. For example, immune complex disease generally results in activation of the classical complement pathway, yet in most cases, C4 levels are normal and only C3 is found in the deposits. This could be explained by the presence of antigens (such as GAPDH) that activate the alternative pathway. In some patients, C3Nef IgG antibodies that are capable of activating the alternative complement pathway have been demonstrated in sera. Activation of the mannose-binding lectin complement pathway by bacterial antigens has been postulated (see Chapter 16), but individuals genetically unable to activate this pathway may still develop PSGN.

Finally, the role of autoimmune mechanisms remains to be clarified. Rheumatoid factors (especially IgG rheumatoid factor) and

Some Infectious Agents Associated with Renal Disease

Bacterial

Streptococcus (group A, *Streptococcus viridans*), *Staphylococcus (aureus, epidermidis), Salmonella (typhi, paratyphi), Escherichia coli, Leptospira, Treponema pallidum, Neisseria* species, *Mycobacterium leprae, Yersinia enterocolitica, Coxiella burnetii, Brucella abortus, Listeria monocytogenes*

Viral

Hepatitis A, B, and C; human immunodeficiency virus, varicella-zoster, parvovirus B19, cytomegalovirus, mumps, influenza, Epstein-Barr virus, coxsackievirus, and enteric cytopathic human orphan (ECHO) virus

Fungal

Histoplasma capsulatum, Candida

Protozoal

Plasmodium (*falciparum, malariae, vivax,* and *ovale*); *Trypanosoma, Toxoplasma*

Helminthic

Schistosoma (mansoni, haematobium), Wuchereria bancrofti, Trichinella spiralis; filariae *(Onchocerca volvulus, Loa loa)*

Box 57-1 Some infectious agents associated with renal disease.

Renal Syndromes Associated with Infection

Clinical Presentation	Time Course	Pathologic Findings	Examples
Subclinical, microhematuria non-nephrotic proteinuria	Acute	Mesangioproliferative GN	Typhoid fever, *Plasmodium falciparum* PSGN
Acute nephritic syndrome	Acute	Diffuse proliferative GN	PSGN
Acute kidney injury, nephrotic syndrome	Acute, chronic	Diffuse proliferative GN, crescents 1. IgM, IgG dominant 2. IgA dominant	1. Endocarditis, PSGN 2. Methicillin-resistant *Staphylococcus aureus*
Nephrotic syndrome and reduced GFR	Chronic	1. MPGN type I ± cryoglobulins 2. Focal segmental glomerulosclerosis	1. Hepatitis C virus, infected AV shunts 2. HIV, parvovirus
Nephrotic syndrome	Chronic	1. Membranous nephropathy 2. Amyloid	1. Hepatitis B virus 2. Leprosy, *Schistosoma,* kala-azar
Acute kidney injury, systematic symptoms, arthralgias, skin ulcers	Acute, chronic	Vasculitis, crescents, tubulointerstitial inflammation, atrophy and fibrosis	Hepatitis B virus, HIV
Hemolytic uremic syndrome	Acute	Arteriolar thickening and occlusion, microthrombi, capillary wall thickening	*Escherichia coli* O157:H7
Decreased renal function, non-nephrotic proteinuria, eosinophilia	Acute, chronic	Interstitial nephritis	Epstein-Barr virus, legionnaires' disease, Hantavirus, kala-azar

Table 57-1 Renal syndromes associated with infection. *AV,* Arteriovenous; *GFR,* glomerular filtration rate; *GN,* glomerulonephritis; *HIV,* human immunodeficiency virus; *MPGN,* membranoproliferative glomerulonephritis; *PSGN,* poststreptococcal glomerulonephritis.

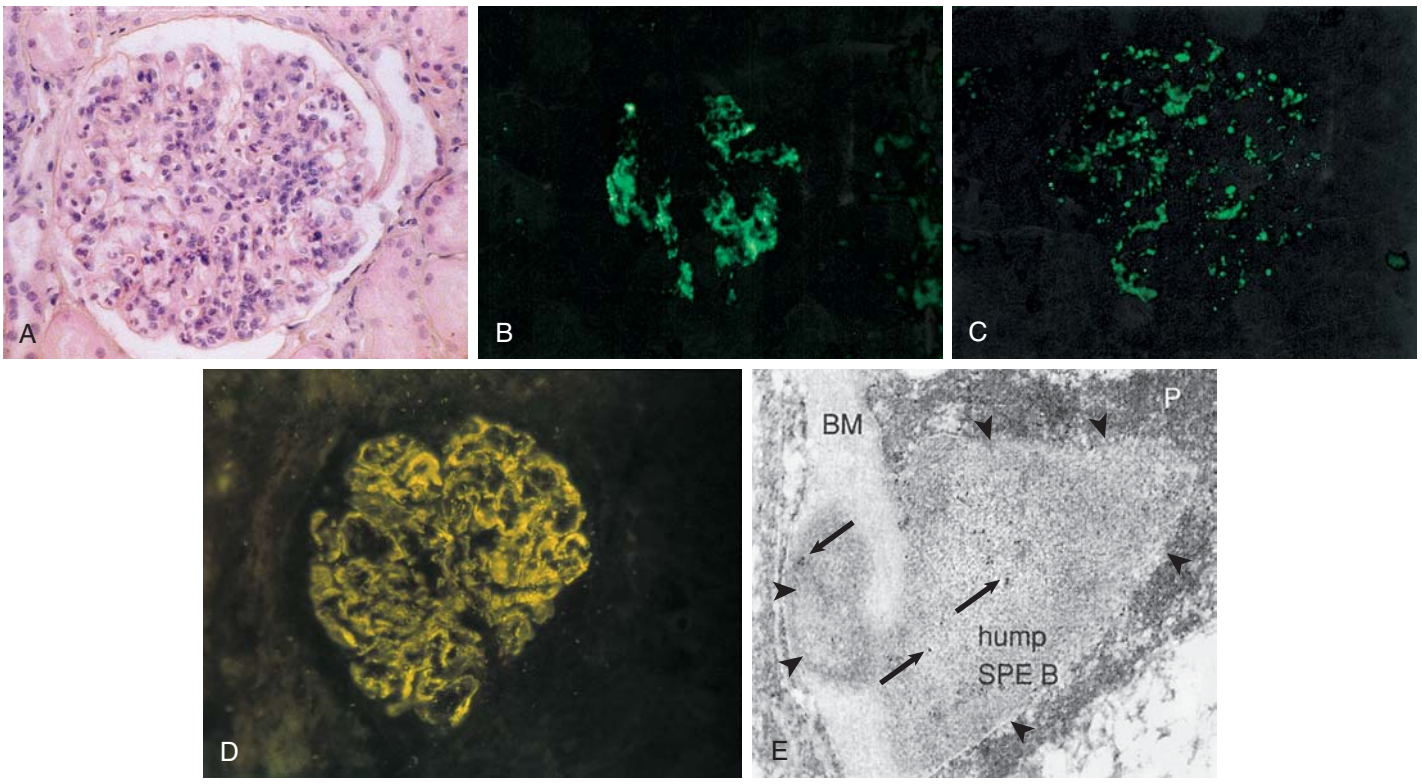

Figure 57-1 Poststreptococcal glomerulonephritis (GN). A, A diffuse proliferative and exudative GN can be seen with light microscopy. **B** to **D,** Immunofluorescence showing the mesangial (**B**), starry sky (**C**), and garland (**D**) patterns. **E,** Immune electron microscopy showing the characteristic subepithelial electron-dense deposits (humps) *(arrowheads),* inside which streptococcal pyrogenic exotoxin B (SPE B) is demonstrated *(arrows)* (immunogold staining). *BM,* Basement membrane; *P,* podocyte. *(Reprinted with permission from reference 8.)*

cryoglobulins are found in the serum of one third of patients in the first week of the disease. Rheumatoid factors (antibody to IgG) have been shown in one third of the renal biopsy specimens and in the eluate from the kidney in a fatal case. Anti-IgG reactivity may result from the loss of sialic acid from autologous IgG due to streptococcal neuraminidase (sialidase) or from binding of the Fc fragment of IgG to type II Fc receptors in the streptococcal wall.[2] Anti-IgG antibody, induced by streptococcal IgG Fc-binding protein, may play a role in the renal accumulation of IgG-containing complexes.[10] Additional manifestations of autoimmune reactivity include the anti-C1q antibodies, particularly in severe cases, and rarely anti-DNA reactivity, antineutrophil cytoplasmic antibody (ANCA), and autoimmune hemolytic anemia.[2]

Pathology

Renal biopsy shows a diffuse endocapillary GN with proliferation of mesangial and endothelial cells (see Fig. 57-1). There is glomerular and interstitial infiltration of monocytes and lymphocytes. Glomerular accumulation of neutrophils is common and is termed exudative GN. Glomerular immune deposits of C3 (100% of the cases), IgG (62%), IgM (76%), and properdin and the terminal membrane attack complex C5b-C9 (85% of the cases, usually co-deposited with C3) are seen in glomerular capillary loops and in the mesangium. A seminal work by Sorger and colleagues[11] described three patterns of immunofluorescence in the glomeruli and their clinical correlations: the mesangial pattern of irregular and heavy immune deposits, the starry sky pattern of deposits scattered in mesangium and in capillary walls, and the garland pattern formed by gross deposits in the capillary loops (see Fig. 57-1). The garland pattern is clinically relevant because it is associated with heavy proteinuria and a large number of electron-dense subepithelial immune deposits. Ultrastructural studies demonstrate the subepithelial humps, which are typical, although not pathognomonic of PSGN because they may also be observed in postinfectious GN of other causes (classically endocarditis-associated GN secondary to *Staphylococcus* infection), cryoglobulinemia, and lupus nephritis. Recent reports have called attention to the identification of NAPLr antigen in biopsies with features of MPGN, raising the possibility of a more varied histologic presentation on PSGN than previously recognized.

Glomerulonephritis resolves by apoptosis of the excess cells. Residual renal injury is common, and biopsy specimens obtained years later show variable degrees of focal glomerulosclerosis and mesangial expansion even in the absence of clinical disease. The prognostic significance of these changes is undetermined.

Clinical Manifestations

Most patients give a history of a previous streptococcal infection, although it has often resolved at presentation. The incubation period is longer after skin infections (several weeks) than after throat infections (2 weeks).

The classic presentation is acute nephritic syndrome. Hypertension is found in 80% of patients. Edema occurs in 80% to 90% of cases and is the chief complaint in 60%; yet ascites is distinctly unusual. Primary sodium retention is the cause of expanded intravascular volume, hypertension, and edema. Plasma renin activity and aldosterone are reduced and natriuretic peptide levels are increased. Hematuria is universal and in 30% of cases is macroscopic. The nephrotic syndrome may occur at the onset in 2% of the children and 20% of adults. Rapidly progressive renal failure, resulting from extracapillary crescent formation, occurs in less than 1% of patients. Increments in serum creatinine occur in 25% to 40% of the children and in up to 83% of adults.

Positive cultures for *Streptococcus* are obtained in 10% to 70% of the cases during epidemics and in about 20% to 25% of sporadic cases. Antistreptolysin O (ASO) titers are increased in more than two thirds of patients with PSGN after throat infections, and anti-DNAse B titers are elevated in 73% of the post-impetigo cases. The streptozyme panel (which measures antibodies to four antigens, anti-DNAse B, antihyaluronidase, ASO, and antistreptokinase) is more sensitive, and the result is positive in more than 80% of patients. Antibody titers to GAPDH and SPEB/zymogen, although more sensitive and specific,[2,4] are not clinically available.

Serum C3 levels are depressed in more than 90% of patients in the first week of disease and return to normal in less than 2 months. Levels of C4, a measure of classical complement pathway activation, may be normal. Serum IgG and IgM are elevated in 80% of the cases, and in contrast with another poststreptococcal disease, rheumatic fever, IgA is normal. Cryoglobulins, elevated rheumatoid factor, and anti-C1q antibodies are present in up to one third of patients in the acute phase. Subclinical disease, manifested by microscopic hematuria and fall in serum complement, occurs four to five times more frequently than clinically overt disease and often involves siblings of index cases. On occasion, whole families have various manifestations of PSGN; it is therefore important to inquire about a history of streptococcal infections and signs of nephritic syndrome among family members.

Management

Renal biopsy is not routinely indicated in PSGN but may be required to confirm the diagnosis in the presence of unusual clinical features, such as nephrotic proteinuria, decreased C3 levels lasting for more than a month (suggests lupus or hypocomplementemic MPGN), or increasing renal dysfunction (suggests crescentic GN).

Management includes culture and treatment of any remaining streptococcal infection. Early antibiotic treatment is likely to prevent PSGN.

Treatment is with penicillin IM (a single intramuscular [IM] injection of 1.2 million units of benzathine penicillin in adults or half this dose in small children) or oral penicillin, or erythromycin (in patients allergic to penicillin) or cephalosporins. Oral treatments should be given in doses every 6 hours for 7 to 10 days.[12]

Treatment of the acute nephritic syndrome includes restriction of fluid and sodium intake and the use of loop diuretics to treat circulatory congestion. An oral long-acting calcium antagonist is usually sufficient to control hypertension. Nitroprusside is used in exceptional cases with hypertensive encephalopathy. Dialysis (either hemodialysis or peritoneal dialysis) is required in 25% to 30% of adults but seldom in children.

Rare complications of acute PSGN include cerebral vasculitis, cerebral vasogenic edema, and posterior reversible leukoencephalopathy. The last is manifested by mental disturbances, visual hallucinations, headache, and convulsions and may be confused with hypertensive encephalopathy. The diagnosis requires the use of magnetic resonance imaging studies.

Anecdotal reports suggest that the rare patients with crescentic GN associated with PSGN may benefit from pulse methylprednisolone therapy, and if spontaneous improvement is not observed in 2 weeks, this therapy may be tried. The prognosis of crescentic PSGN is significantly better than that of crescentic GN from other causes, but complete recovery may be expected in less than half the cases.

Prognosis

Most children with PSGN recover. In older patients, there are higher acute complication rates including a higher prevalence of renal impairment (60% to 70%), congestive heart failure (40%), nephrotic proteinuria (20%), and mortality (25%).[4] Deficiency of complement regulatory proteins (such as factor H–related protein 5) may represent a risk factor for the development of CKD in these patients.[13]

After recovery, mild proteinuria (<500 mg/day) and microscopic hematuria may persist for up to 1 year without worsening the long-term prognosis. Nevertheless, some individuals, especially adults, may have persistent impaired renal function, proteinuria, or hypertension. However, end-stage renal disease (ESRD) occurs in less than 1% of the children observed for one to two decades after the acute attack.[4]

Certain epidemics have reported a high incidence of chronicity, perhaps because of a predominantly adult population.[14] Risk factors for the development of CKD include an onset with nephrotic-range proteinuria, older age, and coexistent diabetic nephropathy and metabolic syndrome.[15]

Endocarditis-associated Glomerulonephritis

The epidemiology of infective endocarditis has changed in the last three to four decades, especially in industrialized countries. Instead of being a disease that affects predominantly young adults with rheumatic heart disease, it now is seen in older patients and in patients at risk, a category that includes drug users, patients with prosthetic valves and implantable devices, patients with HIV infection, and patients who develop health care–associated bacteremia. *Staphylococcus aureus* and *Staphylococcus epidermidis* are the most common pathogens in hospital-acquired infective endocarditis, whereas *Streptococcus* infections are more frequent in community-acquired and native valve endocarditis.[16] Nevertheless, the incidence of methicillin-resistant *S. aureus* (MRSA) causing community-acquired endocarditis is increasing.[17] Gram-negative bacteria (*Enterococcus faecalis, E. coli, Brucella,* and *Proteus*) less frequently cause infective endocarditis. Culture-negative infective endocarditis is usually caused by *Bartonella* species and *Tropheryma whipplei.*[18]

In a survey of 62 patients with infective endocarditis in whom renal tissue was available for study, biopsy and autopsy material demonstrated GN in 26%; localized infarcts, half of which were septic, in 31%; and interstitial nephritis, mostly attributable to antibiotics, in 10%. Cortical necrosis was found in 10% of the patients.[19] The most common GN was diffuse proliferative, followed less frequently by focal GN, MN, and MPGN type I. Crescent formation is found in about half of the proliferative GN forms. Widespread deposition of IgM, IgG, and C3 and electron-dense subendothelial, mesangial, and subepithelial deposits (which resemble poststreptococcal humps) are usually evident. In subacute endocarditis, focal segmental proliferative lesions with fibrinoid necrosis or capillary thrombi and mesangial immune deposits may be present. Variable degrees of cellular infiltration and atrophy and fibrosis may be seen in tubulointerstitial regions. Intense eosinophilic infiltration should suggest another diagnosis, such as acute interstitial nephritis secondary to antibiotics.[19]

The pathogenesis of endocarditis-associated GN involves the deposition of immune complexes containing bacterial antigens in the glomeruli, a mechanism similar to that proposed for PSGN. Cryoglobulins (polyclonal, i.e., type III) are present in 50% of patients and may be found in glomeruli. Some bacteria (classically MRSA) express superantigens that can also activate T cells directly and lead to a polyclonal gammopathy and immune complex GN (see later).

Clinical Manifestations and Diagnosis

Patients often have fever, arthralgias, anemia, and purpura. Rarely, infective endocarditis may manifest as primary renal disease without

characteristic systemic symptoms. Classic findings in endocarditis, such as Osler nodes, Janeway lesions, and splinter hemorrhages, are seldom seen, and the diagnosis may be missed until autopsy in 38% of the patients.[20]

The renal manifestations usually are microscopic hematuria and mild proteinuria (except in patients with membranous GN, which may have proteinuria in the nephrotic range), with or without mild impairment in renal function (except in patients with renal vasculitis, in which renal failure is common). A rapidly progressive clinical course or nephrotic syndrome is unusual. Decreased C3 and C4 levels (consistent with activation of the classical complement pathway), high titers of rheumatoid factor, circulating immune complexes, and type III cryoglobulins are common findings. These serologic findings are observed in 50% of patients with infective endocarditis and in a higher proportion of patients with endocarditis-associated GN, although complement levels may be normal in superantigen-mediated GN.

The differential diagnosis includes antibiotic-associated nephrotoxicity, interstitial nephritis, and embolism. Embolism may originate from the left side of the heart or from the right if the foramen ovale is patent. Microscopic or large emboli may occlude small or large vessels, the latter observed with fungal or *Haemophilus* endocarditis. Large emboli may produce flank pain, hematuria, and pyuria; microemboli produce local infarcts and microabscesses that give the kidney the classic "flea-bitten" appearance. Interstitial nephritis is often associated with fever, eosinophilia, and eosinophiluria (see Chapter 62). Unfortunately, endocarditis-associated GN may also cause fever, and eosinophiluria can complicate crescentic nephritis of any etiology.

Antibiotic treatment usually results in complete eradication of endocarditis with correction of serologic abnormalities, but microscopic hematuria, proteinuria, and elevation of serum creatinine may persist for months after eradication of the infection. Early diagnosis, risk stratification, and prompt start of antibiotic therapy are critical for improving the prognosis.[21] Normalization of C3 levels during therapy correlates with a good outcome. In patients with crescentic GN, pulse corticosteroid therapy and plasma exchange have been used in addition to effective antibiotic therapy, but the value of these treatments remains undefined. The overall mortality of bacterial endocarditis is 20% and increases to 36% in patients who develop renal failure.[22]

Staphylococcal Infections with Glomerular IgA Deposition

In 1995, Koyama and co-workers[23] described a novel form of severe GN that was associated with methicillin-resistant staphylococcal infections and included renal impairment, nephrotic proteinuria, and variable degrees of crescent formation. There was IgA-dominant or co-dominant deposition in association with other immunoglobulin and complement deposits, and the patients had increased serum IgA levels and specific T cell receptor V_{β}^{+} subsets during the course of the disease. They postulated that staphylococcal superantigens were involved in the pathogenesis. The frequency of this condition is undefined, but it represents 1.6% of adult kidney biopsies in one institution.[24]

Clinical and Pathologic Characteristics

In a recent review,[25] IgA-dominant postinfectious GN was four times more frequent in males and the average age was 60 years. Underlying diabetes was present in 55% of the patients, and diabetic glomerulosclerosis frequently coexisted. The most common site of infection was the skin. Acute or rapidly progressive renal failure and proteinuria in the nephrotic range were present in half the patients, and gross hematuria in 20%. However, milder clinical courses occur as well. Complement levels are low in almost 70% of the patients.

Renal biopsy reveals endocapillary proliferative and exudative (63%), mesangial proliferative GN (33%), or crescentic (4%) GN. Typically C3 staining is intense, in contrast with IgA nephropathy.[25] Interstitial fibrosis and tubular atrophy may be mild or severe. Electron microscopy shows electron-dense deposits in the mesangium in the glomerular basement membrane and in subendothelial areas (Fig. 57-2). Large subepithelial electron-dense deposits are reported in some series.[26]

Pathogenesis

Infection-related IgA-dominant GN is associated with methicillin-resistant or methicillin-sensitive *S. aureus* infections in most patients.[25] The pathogenesis may involve staphylococcal superantigens that bind directly to the major histocompatibility complex class II molecules on antigen-presenting cells, which then engage the V_{β} T cell receptor region.[23] The result is an intensive T cell activation with generation of cytokines that activate in B cells a polyclonal IgG and IgA response. Researchers have identified an *S. aureus* cell envelope antigen that is co-localized with the glomerular IgA deposits.[27] Mild elevations in serum IgA levels occur in some patients, suggesting activation of a selective IgA response. Whether staphylococcal antigens are involved in the pathogenesis of IgA nephropathy (see Chapter 23) is a possibility that deserves further study.

Differential Diagnosis and Treatment

Antibiotic treatment of IgA-dominant *Staphylococcus*-related GN may lead to recovery of renal function. Corticosteroid treatment is contraindicated, at least while there is active infection, which makes it important to establish its differential diagnosis with IgA nephropathy, in which corticosteroids may be indicated in severe cases (see Chapter 23). Characteristics that may be helpful in the differential diagnosis with IgA nephropathy are the association with staphylococcal infection (in contrast with upper respiratory infection in IgA nephropathy), the frequent occurrence of hypocomplementemia, massive proteinuria (rare in IgA nephropathy), and intense C3 deposits in the renal biopsy.

Shunt Nephritis

Atrioventricular shunts used to relieve increased intracranial pressure may become infected in about 6% of adult patients.[28] GN may develop in 0.7% to 2% of infected atrioventricular shunts; this may occur 2 months to many years after insertion. The infective organisms are usually *S. epidermidis* and *S. aureus* and less frequently *Propionibacterium acnes,* diphtheroids, *Pseudomonas,* or *Serratia.* In contrast with atrioventricular shunts, ventriculoperitoneal shunts are rarely complicated with GN.

Patients have insidious low-grade fever, arthralgias, weight loss, anemia, rash, hepatosplenomegaly, hypertension, and signs of increased intracranial pressure. Microscopic hematuria is present in 90% of patients, and proteinuria is often in the nephrotic range. Serologic findings include positive rheumatoid factor titers, cryoglobulinemia, and decreased serum C3, C4, and CH50 levels. Raised C-ANCA titers may be found. Eosinophilia in the cerebrospinal fluid, which is a sign of a malfunctioning shunt, may be helpful for the diagnosis.

Renal histology shows MPGN type I in nearly 60% of the cases and non-IgA mesangial proliferative GN in the remainder. IgM, IgG, and C3 deposits are present in the glomerular capillary and mesangium.

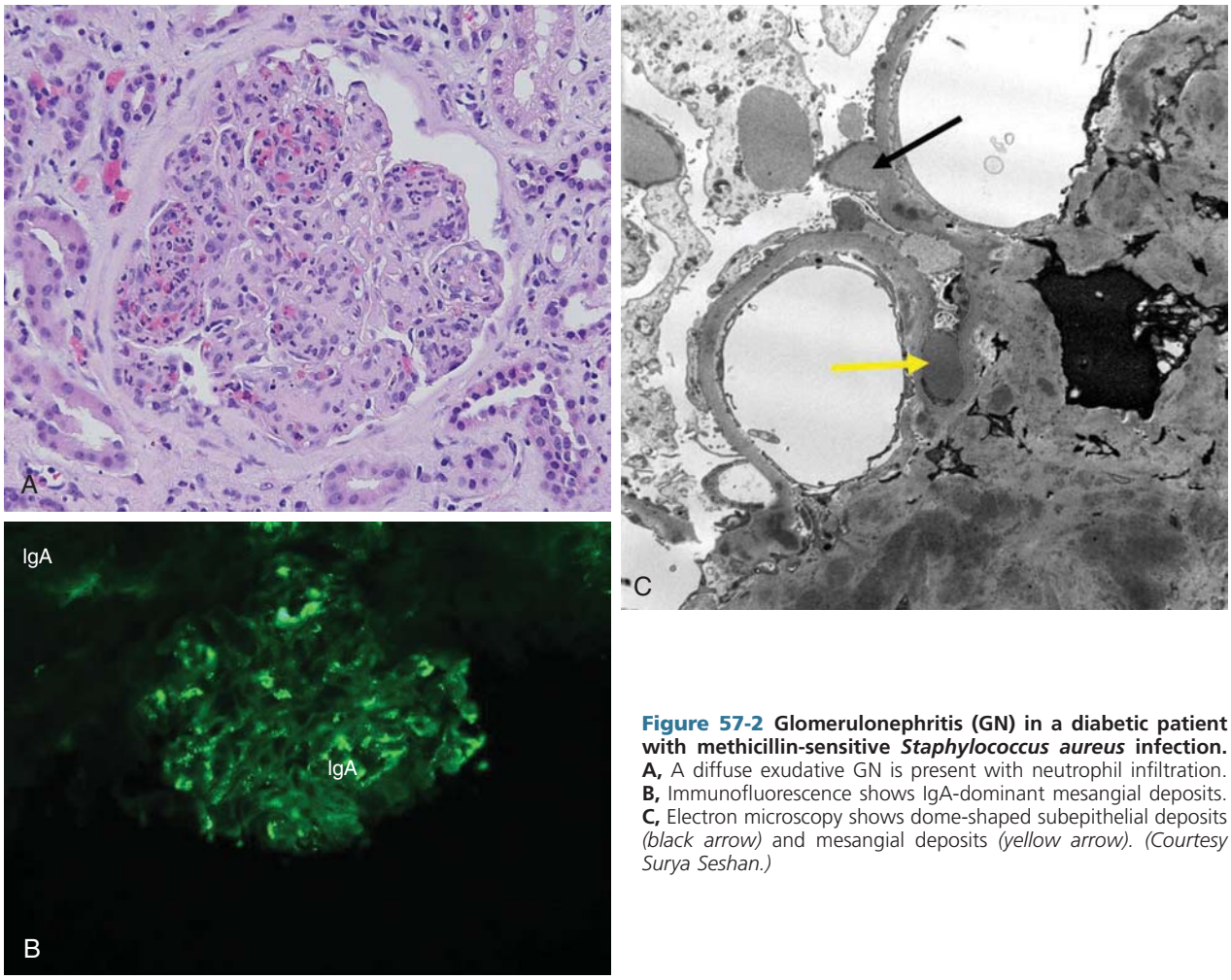

Figure 57-2 Glomerulonephritis (GN) in a diabetic patient with methicillin-sensitive *Staphylococcus aureus* infection. **A,** A diffuse exudative GN is present with neutrophil infiltration. **B,** Immunofluorescence shows IgA-dominant mesangial deposits. **C,** Electron microscopy shows dome-shaped subepithelial deposits *(black arrow)* and mesangial deposits *(yellow arrow). (Courtesy Surya Seshan.)*

Treatment requires antibiotic therapy and the prompt removal of the infected atrioventricular shunt, which is usually replaced by a ventriculoperitoneal shunt. Delay in diagnosis and in removal of the shunt worsens the prognosis of the renal lesion. In the event that dialysis is required, hemodialysis is the preferred modality because peritonitis complicating chronic peritoneal dialysis carries the risk of meningitis in patients with a ventriculoperitoneal shunt. Complete recovery occurs in more than half of the patients; persistent urinary abnormalities have been found in 22% and ESRD in 6% of the patients.

Glomerulonephritis Associated with Other Bacterial Infections

Osteomyelitis and intra-abdominal, pelvic, pleural, and dental abscesses can be associated with GN. Infection usually has been present for several months before it is diagnosed. Renal disease may vary from mild urinary abnormalities to rapidly progressive GN, but the most frequent presentation is nephrotic syndrome. Unlike with other infection-associated GN, complement levels are often normal. Renal histology reveals MPGN, diffuse proliferative GN, or mesangial proliferative GN. Crescents may be present. Antibiotic treatment may result in recovery of renal function if it is started early.

Congenital and secondary (or early latent) syphilis may be associated with GN. In congenital syphilis the presenting sign is anasarca 4 to 12 weeks after birth. Nephrotic syndrome may be the primary clinical manifestation (as opposed to the more classic triad of rhinitis, osteochondritis, and rash). In acquired syphilis, renal involvement occurs rarely. In adults the presentation is with nephrotic syndrome or occasionally with an acute nephritic picture. Serologic test results for syphilis are positive (rapid plasmin reagin, Venereal Disease Research Laboratory [VDRL], and fluorescent treponemal antibody absorption test). MN is the most common renal pathologic process, but diffuse proliferative GN with or without crescents, MPGN, and mesangial proliferative GN have also been observed. Treponemal antigens have been identified in the immune deposits. Syphilitic GN responds to antibiotic treatment, although remission may not occur for 4 to 18 months.

Acute typhoid fever from *Salmonella typhi* is characterized by fever, splenomegaly, and gastrointestinal symptoms. In severe cases patients may develop shock and acute renal failure as a part of disseminated intravascular coagulation or HUS, but these complications are rare. Overt mesangial proliferative GN occurs occasionally, but microscopic hematuria and mild proteinuria may be present in 25% of the patients.[29] GN may also occur in patients with schistosomiasis and coexisting *Salmonella* infection of the urinary tract (see Chapter 56).

Leprosy (*Mycobacterium leprae* infection) is associated with proteinuria and renal dysfunction in 3% to 5% of the patients.[30] In autopsy studies, renal findings include GN (5% to 14% of the patients, usually MPGN or diffuse proliferative GN with IgG, C3, IgM, IgA, and fibrin deposits), interstitial nephritis (4% to 54%), or amyloidosis (4% to 31%).[31] It remains controversial whether GN is more common in lepromatous leprosy than in tuberculoid leprosy.

Nephrotic syndrome is the usual clinical presentation. Response of glomerular disease to treatment of leprosy is variable. Multidrug therapy may be associated with liver failure and CKD in more than 20% of the patients.[32]

Pneumococcal pneumonia may rarely be associated with microhematuria and proteinuria, especially if treatment is delayed. Both diffuse proliferative GN and MPGN have been reported, and pneumococcal antigen is present in the immune deposits. Rarely, pneumococcal pneumonia can also be associated with HUS as a result of unmasking of the Thomsen-Friedenreich antigen in glomeruli by pneumococcal neuraminidase, which then allows preformed antibodies to bind and to elicit an immune response.

Gastroenteritis caused by *Campylobacter jejuni* may be associated with mesangioproliferative or diffuse proliferative GN. GN may also occur with other bacterial infections, including those with *E. coli, Yersinia,* meningococcus, and *Mycoplasma pneumoniae.*

VIRAL INFECTIONS

Viral infections may cause acute GN (hepatitis A virus [HAV], parvovirus B19, measles, EBV), chronic GN (HBV, hepatitis C virus [HCV], HIV, parvovirus B19), and interstitial nephritis (Hantavirus, influenza virus, dengue, BK virus, coronavirus, cytomegalovirus [CMV], HAV). The most common infections are those associated with HBV, HCV, and HIV. Pathogenetic mechanisms include deposition or *in situ* formation of exogenous (viral) immune complexes; autoantibody formation directed toward endogenous antigen modified by viral injury; virus-induced release of proinflammatory cytokines, chemokines, adhesion molecules, and growth factors; and direct cytopathic effects of viral proteins.[33]

Hepatitis A Virus–Associated Renal Disease

Acute kidney injury (AKI) may develop in 6% to 8% of the patients with hepatitis A infection, and most of them fully recover.[34] Less frequently, interstitial nephritis or immune complex–related diffuse proliferative GN with immunoglobulin and C3 deposits may occur. Patients with the latter may have nephritic or nephrotic syndrome. Recovery from GN usually coincides with the improvement of hepatitis.

Hepatitis B Virus–Associated Renal Disease

Hepatitis B virus is a DNA virus of the Hepadnaviridae family, which has the human as its only known natural host. It is estimated that there are 350 million people with chronic HBV infection in the world, most of whom do not know they are infected.[35] Hepatitis develops as a result of immune reactivity directed toward infected hepatocytes.

Acute HBV infection may cause nausea, vomiting, fever, hepatomegaly, and a short-lived serum sickness–like syndrome: urticaria or maculopapular rash, neuropathy, arthralgia or arthritis, microscopic hematuria, and non-nephrotic proteinuria.[36] Renal biopsy, if it is performed at this time, shows a mesangial proliferative GN. The clinical picture resolves spontaneously as the hepatitis improves.

Whereas acute HBV infection may resolve uneventfully, more than 90% of infected infants, 25% to 50% of the children infected between the ages of 1 and 5 years, and 6% to 10% of older children and adults develop chronic infection (defined as persistence of HBsAg-positive serology but negative for IgM antibodies to HBV core antigen). Vertical transmission (maternal-infant at birth) is usually present in endemic areas, such as China and Southeast Asia. Horizontal transmission occurs through contamination with blood or by direct contact with mucous membranes. In Europe and the United States, the prevalence is lower, and most carriers acquire the infection as adolescents or adults by horizontal transmission as a consequence of drug abuse, blood transfusions, or sexual relations. HBV carriers may have a variety of renal syndromes.[37]

Hepatitis B Virus–Associated Membranous Nephropathy

Membranous nephropathy may occur in chronic HBV carriers. Children show a male predominance and often have asymptomatic proteinuria or nephrotic syndrome, microscopic hematuria, and normal renal function, often with minimal evidence of liver disease. The prognosis is usually good, and spontaneous remission is common in association with the appearance of anti-HBe antibodies in circulation. Adults might also develop nephrotic syndrome, but often have impaired kidney function and clinically apparent liver disease and are at greater risk for progression to renal failure. Decreased C3 and C4 levels are found in less than half of the patients. Renal histology is consistent with MN, but mesangial immune deposits may also be present, in contrast with idiopathic MN. Virus-like particles have been identified in various areas of the glomeruli. HBeAg can often be demonstrated in the immune deposits by immunohistochemistry.[33]

Hepatitis B Virus–Associated Membranoproliferative Glomerulonephritis

Membranoproliferative glomerulonephritis is the most common glomerular lesion in adult HBV carriers. Cryoglobulinemia may be present, especially if there is concurrent infection with HCV. Chronic liver disease is usually present but may be clinically asymptomatic. Nephrotic or non-nephrotic proteinuria, often associated with microhematuria, is common. Biopsy shows typical type I MPGN, and HBsAg is occasionally shown in the immune deposits.

Mesangial Proliferative Glomerulonephritis with IgA Deposits

There are several reports of IgA nephropathy in HBV infection. It is possible that this is a consequence of chronic liver disease with impaired clearance of IgA circulating immune complexes, leading to hepatic IgA nephropathy (see Chapter 23).

Treatment of Hepatitis B Virus–Associated Glomerulonephritis

Treatment is aimed at eradication of HBV virus. Interferon-alfa (5 million units daily for 6 months) or pegylated interferon-alfa may result in remission, especially in HBV-associated MN. Lamivudine (100 mg orally once daily for 52 weeks) has also been reported to clear HBV virus and to induce remission in HBV-associated MN. A reduction of the dose is necessary when the glomerular filtration rate (GFR) is reduced below 50 ml/min/1.73 m^2. If the GFR is 30 to 49 ml/min/1.73 m^2, the initial dose is 100 mg, and this is followed by 50 mg orally daily; if the GFR is 15 to 29 ml/min/1.73 m^2, the initial dose is the same and subsequent does are reduced to 25 mg daily. In patients with ESRD, the initial dose is 35 mg followed by 10 mg daily.[38] Entecavir and adefovir dipivoxil may provide an alternative, but the nephrotoxicity of adefovir is a deterrent, although the risk is low at standard dosages if kidney function is normal.[38] Recent reports have drawn attention to viral breakthrough after prolonged lamivudine administration, resulting from mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the nucleotide binding that might lead to the aggravation of renal disease in HBV-associated GN patients. Another potential complication of therapy

is the development of membranous nephropathy after several months of pegylated interferon-α2a treatment.

It has been argued that corticosteroid and immunosuppressive agents should not be used because they are ineffective and may delay or prevent seroconversion and accelerate the progression of liver disease. However, a recent meta-analysis of 12 clinical trials with 317 patients found that combined antiviral and immunosuppressive therapy can improve the proteinuria in HBV-GN patients without altering HBV replication or damaging liver and renal function.[39]

The prevailing view has been that treatment is not required for children with HBV-associated MN because the majority of them undergo spontaneous remission. However, clearance of HBV DNA and HBeAg has been achieved in about half of the children in controlled studies, with a higher incidence of resolution of the proteinuria in the treated group. Because HBV-associated MN may rarely progress to ESRD in children, it is reasonable to treat when proteinuria is severe or there is progression of kidney disease.

Polyarteritis Nodosa

Hepatitis B virus–related vasculitis (HBV-related polyarteritis nodosa [PAN]) has become progressively rarer and is observed primarily in adult men who acquire HBV infection from drug use or blood transfusion, usually less than 12 months after a mild attack of hepatitis. It is almost never observed in children and is rare in areas of the world where HBV infection is acquired at birth or in childhood, such as in Asia.

The typical patient with HBV-related PAN shows signs of serum sickness preceding and during a mild or asymptomatic attack of hepatitis, unlike HBV-associated serum sickness, which resolves spontaneously with clearing of the HBsAg. In these patients the disease progresses to involve numerous organs. It typically involves medium-sized arteries and may have a variety of presentations, including myocardial ischemia, mesenteric angina, cerebral ischemia, and mononeuritis multiplex. Renal vasculitis is manifested by microhematuria, nephrotic or non-nephrotic proteinuria, and renin-dependent hypertension. Manifestations are in general similar to those observed in noninfectious PAN, but patients with HBV-associated PAN more frequently have peripheral neuropathy, abdominal pain, cardiomyopathy, orchitis, hypertension, and renal vessel involvement, whereas pulmonary and cutaneous manifestations are rare, compared with patients with non–HBV-related PAN.[40] Rapidly progressive GN, as seen in microscopic polyangiitis, is infrequent in HBV-related PAN.[40]

The pathogenesis of HBV-associated PAN is thought to be a result of the deposition of HBsAg–anti-HBs immune complexes in the arterial wall, which results in a subsequent inflammatory reaction with the activation of complement. The vessels often show a predominance of IgM and HBsAg, suggesting that the injury is mediated by HBsAg-IgM complexes. Serologic tests reveal HBsAg and anti-HBc antibodies. Serum complement is usually normal, and ANCAs are absent.

Diagnosis requires the detection of circulating HBsAg in association with either histologic or angiographic evidence of vasculitis. Renal biopsy studies demonstrate vascular lesions, which are typically panmural and in different stages of development. Variable degrees of fibrinoid necrosis, fibrin deposition, and leukocyte infiltration are present. HBsAg, IgM, and occasionally IgG are deposited in the vessel wall. Angiographic studies demonstrating narrow segments and saccular or fusiform aneurysms in celiac or renal arteries have higher diagnostic yield than biopsies.

Liver biopsy demonstrates chronic active or persisting hepatitis or, rarely, acute hepatitis. The kidney biopsy, in addition to the arteriolar lesions, may show relatively preserved glomeruli with variable degrees of collapse in the glomerular tuft, likely resulting from ischemic changes. In contrast with idiopathic microscopic polyangiitis, necrotizing lesions with crescent formation are rare. Mesangial proliferative GN, diffuse proliferative GN, MPGN, and MN have all been reported.

Treatment consists of a short course of corticosteroids (prednisone 1 mg/kg/day for 2 weeks) and plasma exchange (9 to 12 exchanges during 3 weeks) followed by interferon-alfa therapy or lamivudine.

Hepatitis C Virus–Associated Renal Disease

Hepatitis C virus, an RNA virus of the Flaviviridae family, is a common cause of chronic hepatitis, cirrhosis, and hepatoma. An estimated 170 million people in the world are chronically infected with HCV; there are nine genetically distinct genotypes, of which the most common is genotype 1. Chronic HCV infection can also be associated with the development of several types of glomerular disease. The most common is MPGN with or without cryoglobulinemia, and this entity is discussed in Chapter 21. HCV may also be associated with MN, especially in kidney transplant patients.

The clinical and histologic findings are similar to those observed in idiopathic MN except that HCV RNA and anti-HCV antibodies are present in the blood. Other reported associations include fibrillary GN, focal glomerulosclerosis (especially in African Americans), and thrombotic microangiopathy with anticardiolipin antibodies (especially after kidney transplantation). The pathogenesis of these lesions involves the deposition of immune complexes in the glomeruli, and recently it has been described that Toll-like receptor 3 could have a pathogenic role, thus suggesting a link between viral infection and GN.[41] Combined antiviral therapy and immunosuppression (cyclophosphamide or rituximab with corticosteroids) may be the treatment of choice for patients with severe renal disease—that is, nephrotic syndrome with or without progressive renal failure—or disease that is refractory to anti-HCV therapy alone.[42] HCV infection may represent a risk factor for graft failure, and pretransplant interferon therapy has been recommended.[43]

Human Immunodeficiency Virus–Associated Renal Disease

Human immunodeficiency virus infection may be associated with myriad renal complications, one of the most common of which is HIV-associated nephropathy. A discussion of HIV-associated nephropathy and other HIV-associated renal disorders is provided in Chapter 58.

Other Virus-Associated Renal Disease

Polyomavirus nephropathy caused by BK virus is an increasingly recognized complication in renal transplantation and can be a cause of decreased renal function. It is described in detail in Chapter 105.

Cytomegalovirus infection may occur in renal transplant recipients, in whom it can infect tubular cells and macrophages in the interstitium, resulting in the characteristic intracytoplasmic "owl-like" inclusions. Whereas there is some evidence that this may be a cause of tubular dysfunction, there is no evidence that this results in glomerular injury. Rarely, however, in nontransplant patients CMV has been reported to cause a diffuse proliferative GN with immune deposits containing CMV antigens. In addition, a rare report has linked CMV infection with collapsing glomerulopathy and ESRD in patients not infected with HIV.

Parvovirus B19 is a single-stranded DNA virus with marked tropism for the erythroid precursor cells. In conditions in which there is increased destruction or decreased production of red cells, as in kidney transplantation and in sickle cell disease, parvovirus infection may cause aplastic anemia. In patients with sickle cell disease, parvovirus-induced aplastic crises are occasionally followed by nephritic or nephrotic syndrome, assumed to be the result of immune complex deposition. Diffuse proliferative GN, MPGN, and collapsing focal glomerulosclerosis (with similarities to heroin- and HIV-associated nephropathy) have been attributed to parvovirus B19 infection, and some studies but not others have detected viral DNA in kidney biopsy specimens. Granular deposition of C3 and IgG in capillary walls and subendothelial deposits have been found. Studies have also suggested a relationship between renal parvovirus infection and chronic allograft nephropathy.[44]

Many viral infections, including varicella, mumps, adenovirus, coxsackievirus, and influenza, can be associated with transient microscopic hematuria, non-nephrotic proteinuria, and a mesangial proliferative GN or diffuse proliferative GN in which viral antigens can be identified in the mesangium. Measles may also cause a diffuse proliferative GN but is better known for its unique ability to induce remission in patients with minimal change disease with nephrotic syndrome.

Dengue hemorrhagic fever, currently the most prevalent mosquito-borne urban viral infection worldwide, may be caused by four serotypes of the Flaviviridae virus family. The clinical manifestations, reflecting increased vascular permeability, include fever, headache, generalized muscle pain, gastrointestinal symptoms, and, in severe cases, bleeding manifestations and shock. The most common renal complication is AKI. Acute endocapillary GN with IgG, IgM, and C3 deposits presenting with hematuria, proteinuria, and renal failure has been reported in dengue patients.

Mild renal abnormalities can also be observed in acute EBV infection, with microhematuria and proteinuria in 10% to 15% of cases. Acute interstitial nephritis is the most common renal complication of this viral infection, but diffuse proliferative GN and MPGN may also occur. Replicating EBV was localized not only to infiltrating macrophages but also to renal proximal tubular cells, which were shown to express the CD21 receptor for EBV.[33]

PARASITIC INFECTIONS

Kidney involvement is fairly common in different parasitic diseases. With the exception of schistosomiasis, malaria, filariasis, and leishmaniasis, such involvement is usually mild, transient, and often masked by the manifestations of the primary disease (Table 57-2).

Malaria

Malaria, caused by a protozoan of the genus *Plasmodium* and acquired through the sting of infected *Anopheles* mosquitoes, is a major world health problem, with 300 to 500 million cases and 1.5 to 2.7 million deaths each year (Fig. 57-3). About 90% of the cases occur in Africa, India, Southeast Asia, and Latin America. Malaria can also be acquired by blood transfusions (prevalence among blood donors in a teaching hospital in Nigeria was 32%), by transplantation of infected donor organs, and by the bite of infected vectors introduced in aircraft ("airport malaria").[45,46] Four major species are responsible for malaria. *Plasmodium falciparum* is usually associated

Renal Lesions in Parasitic Infection

	Glomerular Lesions	Tubulointerstitial Lesions	Amyloidosis	Local Tissue Infestation	Acute Kidney Injury	Post-transplant Disease
Schistosomiasis						
*S. haematobium**	MesPGN	+++	++	Granulomas		+
*S. mansoni**	MesPGN, DPGN, MPGN, FSGS	+	++	Granulomas		+
S. japonicum	MesPGN	+				
S. mekongi		+++				
Malaria						
*P. malariae**	MPGN					
*P. falciparum**	DPGN, MPGN	+			++	+
Filariasis						
Onchocerciasis*	MCD, MesPGN, MPGN					+
Loiasis	MN, MesPGN					
Bancroftiasis	MesPGN, MPGN, DPGN			Chyluria		
Dirofilariasis	MPGN (dogs), MN (dogs, cats)					
Brugia malayi	MesPGN, MPGN, DPGN					
Kala-azar*	DPGN (human), MPGN (dogs)	++	++	Interstitial	+	+
Trichinosis	MesPGN					
Strongyloidiasis	MesPGN					
Echinococcosis	MPGN			Hydatid cysts		
Opisthorchiasis*	MesPGN	++	+		++	
Chagas disease*	MesPGN (mice)					
Babesiosis	MesPGN				++	+
African trypanosomiasis	MesPGN (monkeys, mice)					
Toxoplasmosis*	MesPGN	+				

Table 57-2 Renal lesions in parasitic infection. All conditions documented in humans unless otherwise indicated. *DPGN,* Diffuse proliferative glomerulonephritis; *FSGS,* focal segmental glomerulosclerosis; *MCD,* minimal change disease; *MPGN,* membranoproliferative glomerulonephritis; *MesPGN,* mesangial proliferative glomerulonephritis; *MN,* membranous nephropathy. *Parasitic antigens or specific antibodies detected in the glomeruli.

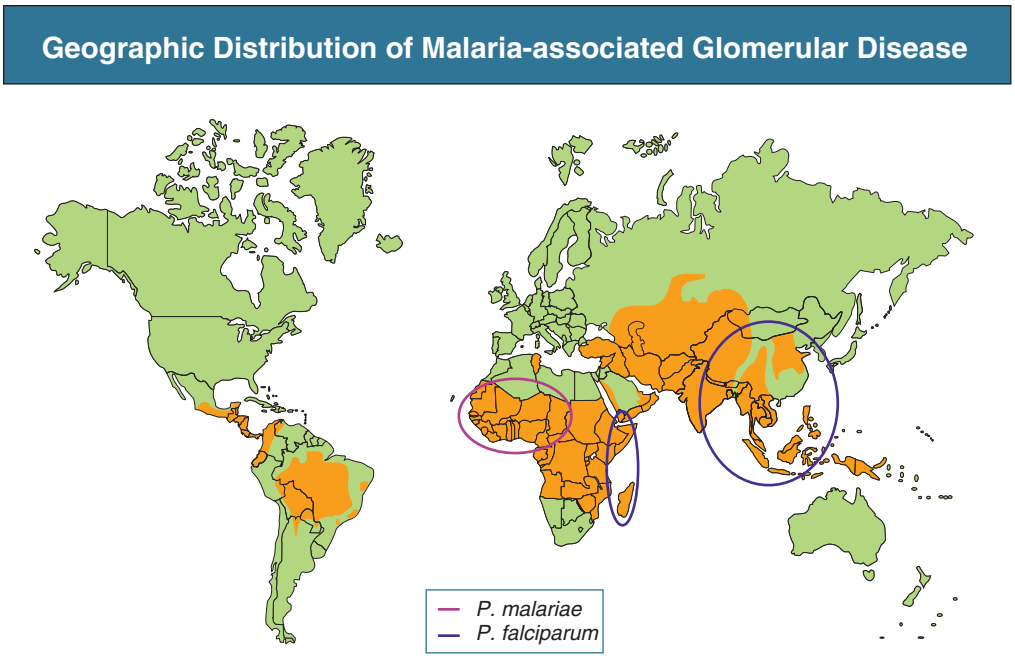

Figure 57-3 Geographic distribution of malaria-associated glomerular disease. Although malaria is endogenous to many areas of the world *(shaded orange)*, the major areas where malaria-associated glomerular disease has been reported *(ringed)* and their respective species are shown.

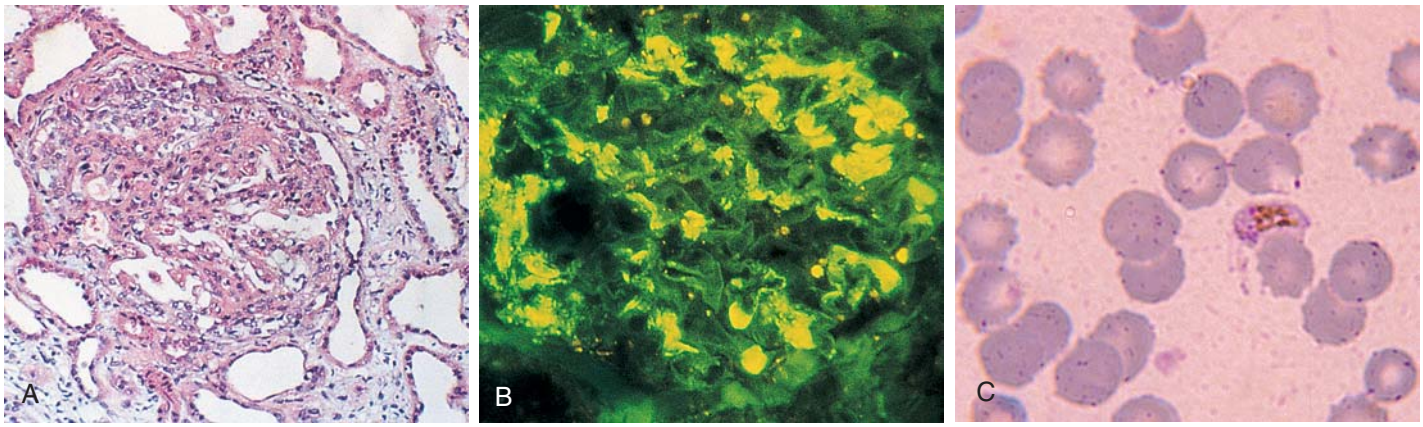

Figure 57-4 Glomerulonephritis (GN) associated with *Plasmodium falciparum* malaria. A, Light microscopy shows a mesangial proliferative GN. **B,** Immunofluorescence may reveal *P. falciparum* antigens in a mesangial pattern. **C,** Peripheral blood smear confirms acute *P. falciparum* infection, with banana-shaped gametocytes and multiple ring forms in erythrocytes. *(**A** reprinted with permission from reference 50; **B** and **C** courtesy V. Boonpucknavig.)*

with heavy parasitemia because it invades red blood cells of any age. Because all red cells can be infected, *P. falciparum* malaria may be associated with AKI and multiple organ failure. This entity is discussed in more detail in Chapter 70.

The immune response to malaria is highly sophisticated, being adapted to the multiplicity of parasitic antigens, which vary with successive generations of the parasite's life cycle, as well as those generated by parasitized red cells. Malarial antigens activate the immune system by initial interaction with the monocytes, as well as direct activation of the alternative complement pathway. Monocyte activation upregulates T helper 1 (Th1) and subsequently Th2 lymphocytes, leading to the secretion of respective chemokines and cytokines. Infected red cells are at least partly responsible for switching the immune response to the Th2 profile, through the preferential expression of certain surface antigens.[46,47]

Acute malaria-associated GN may occur with *P. falciparum* or *Plasmodium vivax* infection.[48] Transient urinary abnormalities such as mild proteinuria and microhematuria are encountered in 25% to 50% of patients; a full-blown nephritic syndrome with hypertension, edema, and impaired kidney function is uncommon. Serum complement C3 and C4 may be reduced in such cases. Renal biopsy typically shows endocapillary proliferation with mesangial expansion and infiltration with pigment-laden macrophages and parasitized red cells. Platelet-fibrin thrombi and patchy necrosis of the tubules may be associated. Immunofluorescence shows granular deposition of IgM, C3, malarial antigens, and occasionally IgG.[46] Dense immune complex deposits, containing plasmodial antigens, are seen with electron microscopy (Fig. 57-4).

Another malarial species, *Plasmodium malariae,* infects only aging erythrocytes and is therefore associated with a less severe form of malaria (quartan malaria). Epidemiologic studies suggest that chronic quartan malaria may be associated with a corticosteroid-resistant nephrotic syndrome, referred to historically as tropical nephritis[49] and more recently as tropical nephrotic syndrome. The disease typically affects children, usually 4 to 8 years old, and only rarely adults. It causes heavy proteinuria and overt nephrotic

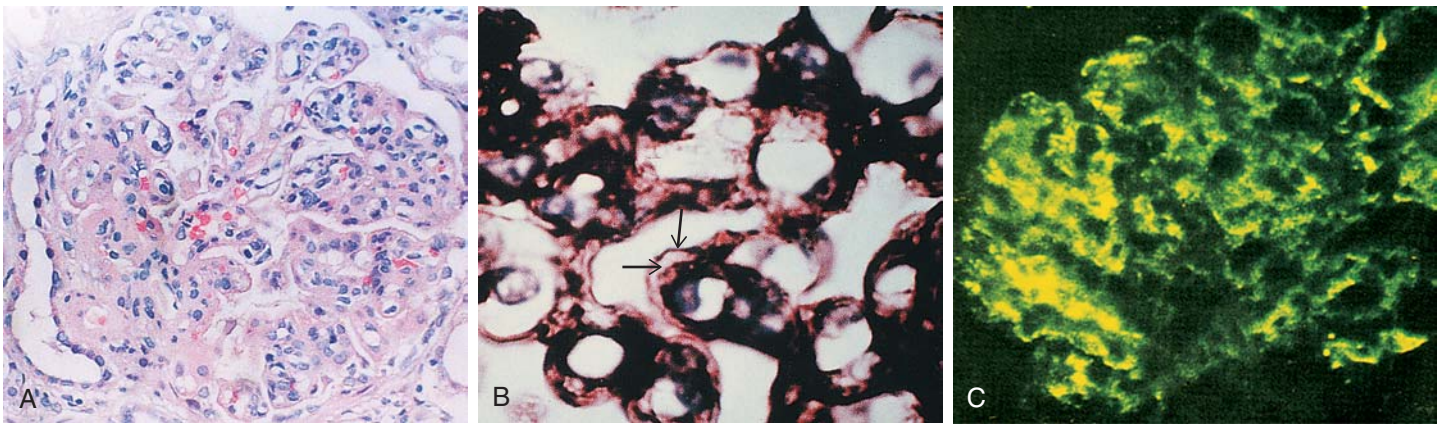

Figure 57-5 Quartan malarial nephropathy. A, Light microscopy shows a sclerosing membranoproliferative glomerulonephritis. **B,** Silver stain shows a double contour *(arrows)* of the basement membrane. **C,** Malarial antigens are present on immunofluorescence. *(From reference 50.)*

syndrome, late-onset hypertension, and progressive kidney impairment. Despite the severe hypoproteinemia, blood cholesterol is often normal, presumably because of associated nutritional deficiency. Renal biopsy shows MPGN with intramembranous lacunae (from reabsorption of immune complexes). Immunofluorescence shows coarsely granular IgG, IgM, and C3 deposits, and electron microscopy displays subendothelial deposition of dense material (Fig. 57-5).[50] As mentioned earlier, the disease is steroid resistant and progresses to end-stage CKD in a few years, even with successful treatment of the malarial infection, which is often attributed to the involvement of autoimmune mechanisms in progression.

The identity of quartan malarial nephropathy as a specific disease entity is largely based on experimental and epidemiologic evidence.[45] Most impressive is the declining incidence of steroid-resistant nephrotic syndrome in Nigeria with the control of malaria; but simultaneous improvement of health care in general may have the same effect.

The lack of hard evidence continues to invite challenges to the presumed cause-and-effect relationship between malaria and CKD.[51] The most significant argument is the inconsistency of the immunohistochemical profile in different geographic regions. Even at an epidemiologic level, it is not understood why quartan malarial nephropathy is limited to Nigeria among the West African countries and Uganda in the East, despite similar endemicity of the same malarial species in neighboring countries. Concomitant infection with other parasites (e.g., schistosomiasis) or viral infection (e.g., EBV) may be involved in the pathogenesis of kidney injury, thereby having a potential influence on geographic variations. The recently discovered *APOL1* gene mutations in African Americans may turn out to be a risk factor in this context, yet this possibility remains to be investigated.

Filariasis

Filariae are nematodes that infect humans as well as several animal species. Of hundreds of known filarial parasites, eight species affect humans. Only three, *Wuchereria bancrofti, Onchocerca volvulus,* and *Loa loa,* are associated with kidney disease. Like all filarial species, these are transmitted by arthropod vectors, namely black flies and mosquitoes.

W. bancrofti affects more than 90 million people mainly in sub-Saharan Africa, Southeast Asia, India, and the Pacific Islands. It is responsible for several clinical syndromes, the best known of which include tropical eosinophilic pneumonia, elephantiasis, and chyluria. The latter has typically been blamed for the occurrence of proteinuria, hypoproteinemia, and even hematuria in infected patients. It was not until the late 1970s that the urinary abnormalities in a small proportion of patients were attributed to parenchymal kidney disease, mesangial proliferative GN being the predominant lesion. Immune complex deposits containing worm antigens were demonstrated in the glomeruli a few years later.[52] Acute proliferative and exudative GN with eosinophilic predominance was occasionally described in association with *W. bancrofti* infection.[53]

Bancroftiasis is often associated with bacterial infection, usually staphylococci and certain streptococci, the impact of which in the pathogenesis of "filarial" GN is unclear. Even less understood is the role of rickettsiae-like bacteria, *Wolbachia,* recently discovered within filarial nematodes and blamed for activation of innate immune pathways.[54]

O. volvulus is less widely spread, yet it affects 21 million people in West Africa, particularly Cameroon, Burkina Faso, and Ghana, as well as in Central and South America, with a few foci in Southern Arabia and Yemen. The adult worms settle in the subcutaneous tissues, leading to a variety of skin manifestations including papular and lichenified dermatitis, hyperpigmentation and depigmentation, and atrophy. It also parasitizes the inguinal lymph nodes, which causes obstruction of the scrotal lymphatics, leading to a characteristic "hanging scrotum." Onchocercosis is associated with a number of immune-mediated manifestations, the most significant of which are keratitis, anterior uveitis, and optic atrophy. These lesions may lead to blindness in large populations living around the rivers where the mosquito vector breeds, hence the term "river blindness."

In a large study of 1011 infected individuals in Cameroon, proteinuria was over fivefold more frequent than in controls.[55] Steroid-resistant nephrotic syndrome with progressive kidney impairment was the usual clinical presentation in this and other series. Minimal change, MPGN, and chronic sclerosing GN lesions were most often encountered on renal biopsy. Subendothelial and mesangial immune complexes containing IgM, IgG, and C3. Onchocercal antigens were detected by immunofluorescence, and mesangial electron-dense deposits by electron microscopy. Onchocercal GN is known to recur in transplanted kidneys.[45]

L. loa is the least prevalent of nephritogenic filariae, being localized in Central America, where about 3 million individuals are infected. Like *Onchocerca, L. loa* lives in the subcutaneous tissues; infection may lead to transient and nonerythematous swellings on the extremities, particularly overlying the joints (Calabar swellings). These may be associated with localized pain, pruritus, and urticaria.

Adult worms may be seen migrating under the conjunctiva. Kidney disease associated with this infection includes membranous nephropathy and less commonly MPGN and FSGS.[56]

Leishmaniasis

Leishmaniae are obligatory intracellular protozoa that infect 12 million humans and many animals. The latter serve as reservoir hosts, the types of which vary according to geographic location: dogs in the Mediterranean and China, rodents in Africa, and foxes in Brazil and Central Asia. Humans may serve as a reservoir for transmission, particularly in India. Infection is transmitted by female sand flies *(Phlebotomus)*. Of 30 known leishmanial species, 21 are pathogenic to humans, the best known being *Leishmania donovani, Leishmania infantum, Leishmania chagasi, Leishmania tropica, Leishmania major, Leishmania mexicana,* and *Leishmania braziliensis*.

Kidney involvement may occur only with visceral leishmaniasis (kala-azar), the systemic illness induced by *L. donovani* in Bangladesh, China, India, Nepal, and Sudan; by *L. infantum* in North Africa and southern Europe; and by *L. chagasi* in Latin America. The disease is characterized by fever, malaise, anorexia, weight loss, and massive hepatosplenomegaly. Generalized lymphadenopathy may occur in a few geographic locations. Although many reports have described different frequencies and profiles of CKD in visceral leishmaniasis, the global incidence remains unknown. Urinary concentration and acidification defects are present in one third of the patients.[57] Reported lesions include chronic interstitial nephritis, MPGN, and renal amyloidosis.[58] The latter has been most frequently described in patients with associated HIV infection.[59] Leishmania-induced AKI has been mostly reported in children with visceral leishmaniasis,[60] and reactivation of leishmaniasis is a potential complication in transplant patients.[61]

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CHAPTER 58

Human Immunodeficiency Virus Infection and the Kidney

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Human immunodeficiency virus (HIV) infection is the defining infectious disease of our era. The 2012 UNAIDS report estimated that there are 35.3 million people living with HIV infection and 2.3 million new infections[1]; there have been 16 million deaths since the start of the epidemic. With regard to nephrologic issues, HIV-1 infection is associated with glomerular and tubulointerstitial disease, and patients with HIV infection are also at risk for nephrotoxicity from antiretroviral therapy (ART) as well as from other medications. Coinfections with other pathogens, in particular hepatitis B virus (HBV) and hepatitis C virus (HCV), can complicate the clinical picture. Acute kidney injury (AKI) and interstitial nephritis, resulting from medication and opportunistic infection, are not uncommon. As patients with HIV disease live longer with ART, patients are experiencing the complex, interacting effects of HIV infection itself, ART, and the worldwide diseases of development, including atherosclerosis, metabolic syndrome, type 2 diabetes, and end-stage renal disease (ESRD). Patients with HIV disease and chronic kidney disease (CKD) and ESRD, those undergoing chronic dialysis therapy, and those undergoing kidney transplantation face particular issues and concerns.

In addition to HIV-1, HIV-2 can cause immunodeficiency but rarely causes kidney disease. In this chapter, we use HIV to refer to HIV-1.

HUMAN IMMUNODEFICIENCY VIRUS–ASSOCIATED KIDNEY DISEASE

The evaluation of AKI or CKD in a patient with HIV infection resembles that in other settings: history, focused particularly on medication use and other infections; physical examination; examination of the urine sediment; serum and urine chemistries; and, in many cases, renal imaging studies. Urine chemistries may include 24-hour timed or spot urine measurement of protein and albumin (for suspected glomerular disease), glucose, phosphate, and uric acid (for suspected proximal tubular disease). Indications for kidney biopsy include AKI without clear associated cause, especially with a nephritic sediment; nephrotic proteinuria; clinical evidence of thrombotic microangiopathy (TMA); and unexplained CKD. In the past, some clinicians argued that nephrotic proteinuria in an individual of African descent is likely to be HIV-associated collapsing glomerulopathy (CG) and that a biopsy is not necessary. The widespread use of ART in the current era makes this decision less tenable, and renal biopsy appears to be indicated to guide prognosis and therapy, particularly when substantial proteinuria is present.

GLOMERULAR DISORDERS

Human Immunodeficiency Virus–Associated Collapsing Glomerulopathy

Human immunodeficiency virus infection is associated with various glomerular disorders (Table 58-1). The classic glomerulopathy of HIV infection is CG. The pathologic changes were described in early reports as focal segmental glomerulosclerosis (FSGS) and more recently as HIV-associated nephropathy (HIVAN), but the latter term has also been used to describe other glomerular pathologic processes associated with HIV infection.

Etiology and Pathogenesis

Human immunodeficiency virus–associated CG occurs with both acute infection and chronic infection; in the latter case, it is associated with higher viral RNA levels and lower CD4 T lymphocyte counts. It appears that HIV can infect glomerular and tubular cells, setting up a chronic and possibly latent infection.[2] Specific HIV accessory proteins such as Vpr and Nef can damage renal cells independent of direct infection. In transgenic mice, the expression of HIV-1 accessory protein Vpr or Nef in podocytes is associated with progressive CKD, leading to ESRD, loss of podocyte differentiation markers, and features suggestive of human CG and segmental glomerulosclerosis. Transgenic mouse experiments also suggest that HIV-1 gene products are toxic to tubular epithelial cells, resulting in apoptosis and blocking cell proliferation.

Host factors also determine susceptibility to HIV-associated CG, especially in individuals of African descent when compared with those of European descent. This 20-fold predilection was originally linked with genetic polymorphisms in MYH9, encoding myosin heavy chain 9, a component of nonmuscle myosin IIA. More recently, much of the risk attributed to *MYH9* genetic variation has been shown to more closely associate with coding-region polymorphisms in *APOL1* (encoding apolipoprotein L1), which is in linkage disequilibrium with *MYH9* polymorphisms. Apolipoprotein L1 is a constituent of high-density lipoprotein. The ApoL1 codon-changing variants confer an odds ratio of 29, a strikingly high effect for a complex disease.[3] It remains unknown whether these *APOL1* polymorphisms cause CKD, and by what molecular mechanism. Nevertheless, homozygosity or dual heterozygosity for two risk alleles (labeled G1 and G2) are observed in approximately 50% of African Americans with HIV-associated CG, compared with only 12% of African American controls. It is interesting to note that these variants appear to protect individuals from African sleeping sickness caused by *Trypanosoma brucei rhodesiense,* and this may explain the

Kidney Diseases Associated with HIV Infection

	Entity	Frequency	Associations
Glomerular	Collapsing glomerulopathy	Common	African descent; particularly advanced HIV disease
	Immune complex glomerulonephritis	Common	European, Asian descent, and black Africans in Africa
	Thrombotic microangiopathy	Uncommon	
	Membranoproliferative glomerulonephritis, with or without cryoglobulin-associated vasculitis	Rare*	Hepatitis C; enfuvirtide
	Membranous nephropathy	Rare*	Hepatitis B
	Fibrillary and immunotactoid glomerulopathies	Rare*	
	Amyloid nephropathy (AA type)	Rare*	
	Minimal change nephropathy	Rare*	Nonsteroidal anti-inflammatory medication
Tubular	Acute kidney injury	Moderately common	Aminoglycosides, cidofovir foscarnet
	Proximal tubule injury (Fanconi syndrome)	Moderately common	Tenofovir, adefovir, cidofovir, didanosine
	Diabetes insipidus	Uncommon	Amphotericin, tenofovir, didanosine, abacavir
	Chronic tubular injury	Moderately common	Amphotericin, cidofovir, adefovir, tenofovir
	Crystal nephropathy	Uncommon	Indinavir, atazanavir; sulfadiazine, ciprofloxacin, intravenous acyclovir
Interstitial	Interstitial nephritis	Uncommon	Allergy to β-lactam, sulfa, ciprofloxacin, rifampin, proton pump inhibitor, allopurinol, phenytoin; also causes of crystal nephropathy listed above
			BK virus; generally advanced disease
			Immune reconstitution inflammatory syndrome; generally advanced disease; following initiation of ART

Table 58-1 Kidney diseases associated with human immunodeficiency virus (HIV) infection. Shown are diseases that are associated with HIV infection or its treatment. *ART,* Antiretroviral therapy. *Certain glomerular diseases are commonly associated with other viral infections or may occur on an idiopathic basis; a true association with HIV disease is uncertain or doubtful. Collapsing glomerulopathy is notable for glomerular, tubular, and interstitial disease but is classified under glomerular disease for simplicity.

rapid rise in allele frequency in certain African populations, particularly West African populations, that has occurred during the past 40,000 years.[4,5]

Clinical Manifestations

Patients with HIV-associated CG typically present with laboratory abnormalities, including proteinuria and renal impairment; some patients present with edema, although edema is less common than with other conditions associated with nephrotic range proteinuria or with uremia. Imaging studies may reveal increased kidney size despite reduced glomerular filtration rate (GFR) and, in some cases, increased echogenicity; this unusual feature is shared with diabetic nephropathy and amyloid nephropathy. However, no radiologic features predict the renal histology, and renal biopsy is required for diagnosis.

Pathology

Human immunodeficiency virus–associated CG is indistinguishable from idiopathic CG, with pathologic changes in glomeruli (proliferation and dysregulation of podocytes or podocyte stem cells, together with glomerular collapse), tubules (acute and chronic injury, sometimes with microcystic tubular changes), and interstitium (chronic inflammation, fibrosis) (Fig. 58-1). Both HIV-associated CG and idiopathic CG may cause tubuloreticular inclusions within dilated endosomal compartments within glomerular endothelial cells, which is believed to be a marker for cytokine (interferon) injury. Some pathologists diagnose classic FSGS in the setting of HIV infection, and others see this rarely; it is unclear whether these differences are a result of population differences or of different diagnostic standards in distinguishing FSGS from CG. Some patients with progressive loss of kidney function (e.g., from immune complex glomerulonephritis [ICGN] or interstitial nephritis) may develop adaptive FSGS from the consequence of glomerular hyperperfusion and hyperfiltration.

Diagnosis and Differential Diagnosis

Diagnosis of HIV-associated CG is made by renal biopsy. Among individuals of African descent, nephrotic proteinuria and low CD4 count are consistent with HIV-associated CG; plasma HIV RNA of less than 400 copies/ml suggests another disease. Among individuals of African descent, other possible diagnoses include primary or adaptive FSGS (although a pathogenic role for HIV cannot be excluded in conferring susceptibility) and arterionephrosclerosis (see later). In all individuals, diabetic nephropathy and HIV-related ICGN should be considered (see later discussion and Table 58-1).

Treatment

Human immunodeficiency virus–associated nephropathy is an indication for the initiation of ART in patients who are not currently receiving these medications; this is regardless of T-lymphocyte count.[6] It is reasonable to extend this recommendation to HIV-associated ICGN, despite an absence of specific evidence.

In the era before ART therapy, HIV-associated CG progressed rapidly, with patients reaching ESRD in months to a few years. The marked decline in HIV-associated ESRD in the United States after the introduction of ART in 1995 suggests that effective control of viral replication with ART may prevent HIV-associated CG. Retrospective studies also suggest that ART treatment of HIV-associated CG may prolong renal survival.[7] The Development of Anti-Retroviral Therapy in Africa (DART) study, conducted in Uganda and Zimbabwe, demonstrated improvement of kidney function of 2 to 6 ml/min/1.73 m^2 after 4 to 5 years of ART.[8] Other studies suggest that ART is most effective when it is initiated before the onset of severe renal disease.[9-12] In a few cases, regression of histologic lesions with ART has been demonstrated.[12,13] The current guidelines from the Infections Disease Society of America suggest starting ART when HIVAN is diagnosed, if therapy was not used before.[14] The guidelines do not address the role of ART in other renal histologies, but

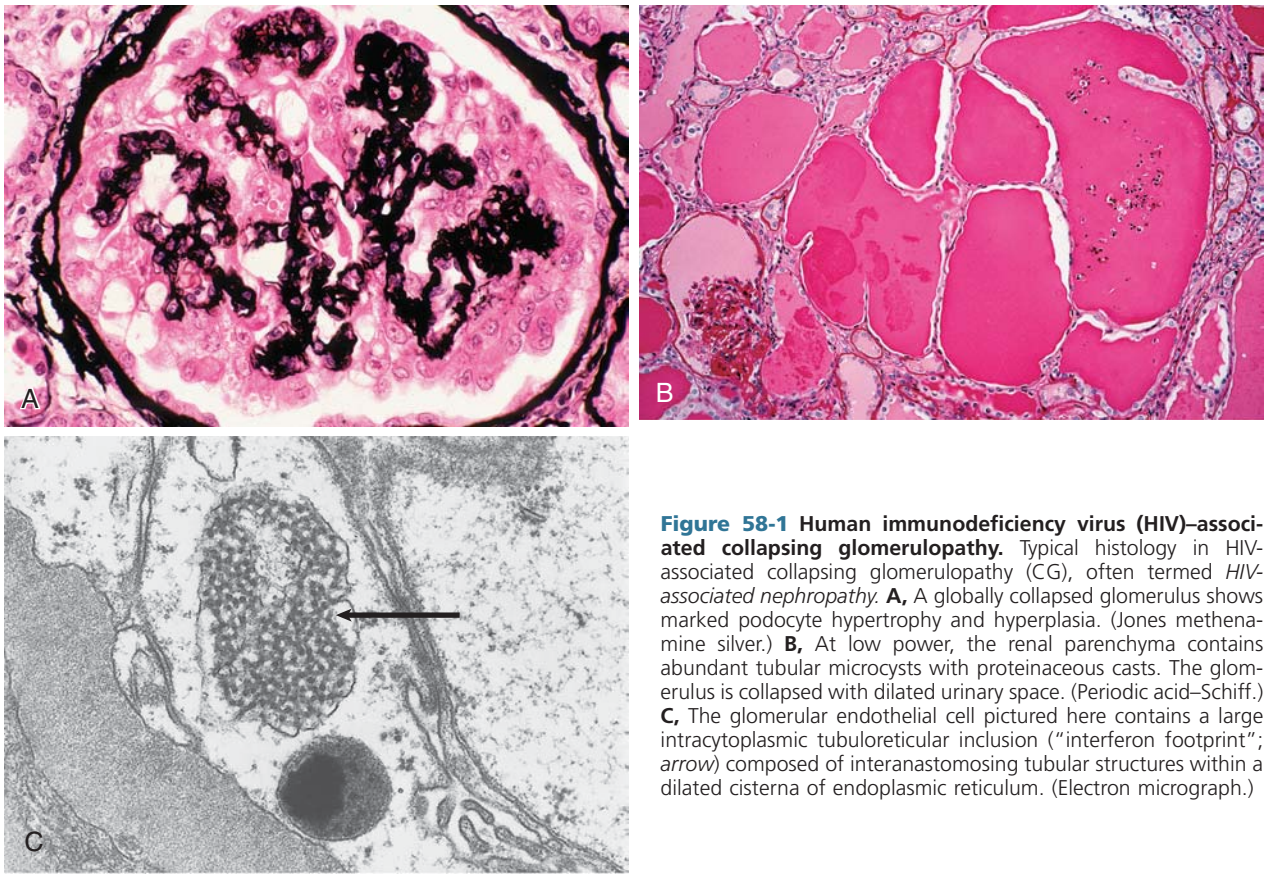

Figure 58-1 Human immunodeficiency virus (HIV)–associated collapsing glomerulopathy. Typical histology in HIV-associated collapsing glomerulopathy (CG), often termed *HIV-associated nephropathy.* **A,** A globally collapsed glomerulus shows marked podocyte hypertrophy and hyperplasia. (Jones methenamine silver.) **B,** At low power, the renal parenchyma contains abundant tubular microcysts with proteinaceous casts. The glomerulus is collapsed with dilated urinary space. (Periodic acid–Schiff.) **C,** The glomerular endothelial cell pictured here contains a large intracytoplasmic tubuloreticular inclusion ("interferon footprint"; *arrow*) composed of interanastomosing tubular structures within a dilated cisterna of endoplasmic reticulum. (Electron micrograph.)

the authors believe it is prudent to initiate ART for any glomerular disease that is plausibly linked to HIV infection.

Treatment of HIV-associated renal disease also includes standard therapies for CKD, including control of blood pressure to below 130/80 mm Hg and the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Nonrandomized studies in HIV-associated renal disease suggest benefit from these interventions, but randomized controlled studies have not been performed. Several nonrandomized studies have suggested a benefit from corticosteroid therapy, but because the efficacy appears to be modest and often short-lived, this is not considered standard therapy.

Natural History

Progression of CKD is more rapid in HIV-infected individuals of African descent, probably reflecting the effect of the *APOL1* variants.[9] This is of particular relevance to the African population in sub-Saharan Africa that has the highest prevalence rates of HIV infection.

Patients with HIVAN may also progress to ESRD in spite of ART.[15,16] Predictors of progression are a high degree of chronic damage on histology[15] as well as severe renal dysfunction at baseline, high-grade proteinuria, and presence of large numbers of sclerotic glomeruli.[16] Concomitant use of renin-angiotensin blockade results in improved renal survival.[16]

Human Immunodeficiency Virus–associated Immune Complex Glomerulonephritis

In populations of European and Asian ancestry, the most common glomerular disease associated with HIV disease is ICGN; this is true among developed countries (e.g., European Union) and developing countries (e.g., Thailand). HIV-associated ICGN is also seen in populations of African descent.[17] The pathogenesis of HIV-associated ICGN is not well understood. In some cases, immune complexes include HIV antigens. Other cases may represent generalized polyclonal B-cell expansion that accompanies HIV disease. Clinically, patients typically present with nephrotic proteinuria and hematuria that are clinically indistinguishable from HIV-associated CG. Renal biopsy findings may vary from mesangial proliferative glomerulonephritis (GN) to focal or diffuse proliferative GN with endocapillary proliferation (Fig. 58-2). In some cases, changes consistent with HIV-associated CG may also be present, and tubuloreticular inclusions may be present within glomerular capillary endothelial cells. Immune deposits may be in mesangial, subendothelial, and in some cases subepithelial locations and may include IgG and IgM or IgG, IgM, and IgA (so-called "full house deposits"), often with C3. These forms resemble lupus nephritis, although lupus serologic test results are typically negative. Patients who have coinfection with HCV may manifest membranoproliferative glomerulonephritis (MPGN), with double glomerular capillary basement membrane contours. Other patients may have only mesangial IgA deposits, and this is observed especially in the setting of microhematuria and non-nephrotic proteinuria, resembling idiopathic IgA nephropathy. The long-term outcome of HIV-associated ICGN is not well defined but appears to be more favorable when histologic changes resemble IgA nephropathy as opposed to lupus-like GN. There are few studies of therapy; presumably, control of HIV infection and conservative measures to control blood pressure and proteinuria are indicated.

OTHER GLOMERULAR DISORDERS

In addition to HIV-associated CG, FSGS, and HIV-associated immune complex disease, mentioned earlier, other glomerular

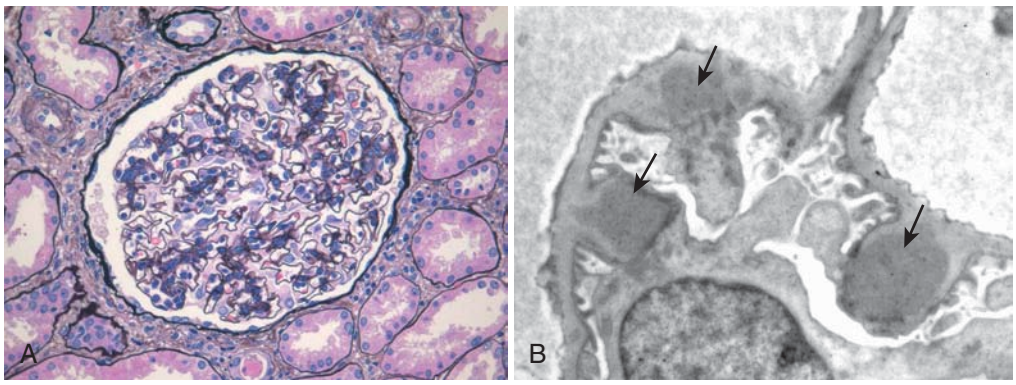

Figure 58-2 Human immunodeficiency virus (HIV)–associated GN. This HIV-infected patient presented with microhematuria and non-nephrotic proteinuria with normal renal function. Renal biopsy shows mild mesangial expansion **(A),** with mesangial and paramesangial deposits, together with varying numbers of subepithelial-based deposits *(arrows),* resulting in the "ball-and-cup" appearance **(B).** *(Courtesy Professor Stewart Goetsch, University of the Witwatersrand, Johannesburg, South Africa.)*

disorders have been seen with HIV infection. TMA may occur with HIV infection and is associated with lower CD4 cell counts, higher viral burden, and acquired immunodeficiency syndrome (AIDS). Membranous nephropathy (MN), fibrillary GN, immunotactoid GN, and amyloidosis have also been reported in HIV infection, but a causal role for HIV infection has not been firmly established.

ARTERIONEPHROSCLEROSIS

As HIV has become a chronic disease, extending over a period of decades, it has become apparent that chronic HIV disease is associated with premature aging, affecting various organ systems. In the kidney, this takes the form of arterionephrosclerosis, which is the constellation of arterial intimal thickening, medial hypertrophy, and duplication of the internal elastic lamina, together with global glomerulosclerosis, and is traditionally ascribed to hypertension. However, increasing evidence suggests that afferent arteriolar lesions may not only predispose to glomerulosclerosis by altering renal autoregulation, but may also have a role in the pathogenesis of hypertension. In this view, arteriosclerosis is a disorder associated with genetic mutations (e.g., *APOL1*), metabolic disorders (e.g., diabetes, obesity, hyperlipidemia, metabolic syndrome, and HIV infection), and chronic inflammation (smoking, oxidative stress, hemodynamic shear stress, and renin-angiotensin system activation).[18] Many of these factors arise as result of lifestyles, activity patterns, diets, and habits that have been adopted throughout the world. Certain of these pathogenic factors are exacerbated in HIV infection and its therapy, including chronic inflammation, metabolic disorders, and premature aging. In a recent series of biopsies performed on HIV patients in the United States, isolated arteriosclerosis with glomerulosclerosis was the most common single pathology noted,[19] and this is a trend that is likely to grow stronger.

TUBULAR DISORDERS

Human immunodeficiency virus infection is associated with several tubular disorders, many of which are secondary to drugs commonly used in this disease (see Table 58-1).[20] HIV-associated AKI, as defined by the AIDS Clinical Trials Group, is a creatinine concentration equal to or greater than 1.5 mg/dL or an increase of 1.3-fold over the upper limit of normal, that resolves within 3 months.[21] Most HIV-associated AKI occurs outside hospitals, with major causes being pre-renal or post-renal impairment (including obstruction as a result of prostate disease, kidney stone, or crystalluria), medication toxicity (including interstitial nephritis caused by antibiotics or indinavir, tubular injury caused by tenofovir or other agents, and statin-associated rhabdomyolysis), and less commonly acute presentations of glomerular diseases. Risk factors for HIV-associated AKI include male sex, black race, low CD4 count, high viral load, diabetes, CKD, and hepatic disease.[22]

Proximal tubular injury is moderately common, manifesting as various combinations of glycosuria, phosphaturia (sometimes associated with clinically significant hypophosphatemia), uricosuria, proteinuria, and aminoaciduria. Diabetes insipidus may also be present, indicating that the distal nephron is also involved. The most common cause is tenofovir, which is taken up by proximal tubular cells by one or more organic anion transporters and causes mitochondrial injury (mitochondrial depletion, enlargement, and dysmorphic changes) and also inhibits DNA repair and replication.[23,24] A mild decrease in GFR has also been associated with tenofovir use, but usually it is not severe enough for treatment to be discontinued.[23] Although three controlled studies have suggested minimal nephrotoxicity (perhaps 1%) when tenofovir is used for periods up to 48 weeks, a growing number of case series suggest that some patients manifest tubular injury that may resolve over a period of months to years[25]; others have described partial recovery or progression to CKD.[24,26] This apparent incongruity may be explained by the use of tenofovir in clinical practice in patients with other renal injury risk factors and by its frequent long-term use. Risk factors for tenofovir-induced renal toxicity include low CD4 count, prior renal impairment, and possibly combined therapy with didanosine and protease inhibitors (lopinavir and ritonavir). Five gene products may mediate tenofovir handling by the proximal tubular cells: *SLC22A6* (organic anion transporter 1 [OAT1]) and to a lesser extent *SLC22A8* (OAT3) are responsible for tubular cell uptake of tenofovir from the tubular fluid; and *ABCC2* (encoding MRP2 [multidrug resistance protein 2]), *ABCC4* (encoding MRP4), and *ABCC10* (encoding MRP10) may contribute to tenofovir efflux on the apical side. Mutations in *ABCC4* are associated with increased plasma tenofovir concentrations,[27] and mutations in *ABCC10* are associated with increased risk of phosphate wasting.[28]

Other protease inhibitors are also associated with variable risk for nephrotoxicity (Table 58-2). Nucleotide and nucleoside reverse transcriptase inhibitors (NRTIs) may have variable effects on tubular function. In addition to tenofovir, the most common renal toxicities are seen with indinavir, which is associated with crystalluria, nephrolithiasis, and AKI (see Table 58-2). Most other case reports involving protease inhibitors have been associated with multiple

Renal Toxicity of Antiviral Therapy

Antiretroviral Class	Antiretroviral Therapy	Renal Effect	Clinical Recommendations
Protease inhibitors	Indinavir	Nephrolithiasis, crystalluria, dysuria, papillary necrosis, acute kidney injury, interstitial nephritis Ritonavir and lopinavir may increase toxicity of indinavir	Daily fluid intake of >2 l/day
	Ritonavir	Reversible AKI (usually in combination with nephrotoxic drugs)	
	Saquinavir, nelfinavir	Renal calculi (rare)	Increased fluid intake
Reverse transcriptase inhibitors	Tenofovir, abacavir	Renal tubular damage: proximal tubular dysfunction, Fanconi syndrome, nephrogenic diabetes insipidus, acute tubular necrosis, AKI	Patients taking tenofovir should be monitored for signs of tubular dysfunction (elevated serum creatinine, hypophosphatemia, low serum uric acid, acidosis glycosuria, proteinuria)
	Didanosine, lamivudine, stavudine	Isolated case reports of tubular dysfunction	
Other	Cidofovir, adefovir	Renal tubular damage, proximal tubular dysfunction (cidofovir)	

Table 58-2 Renal toxicity of antiviral therapy. The toxicity of these agents has been the subject of a recent review. *AKI,* Acute kidney injury. *(From reference 23.)*

confounding factors (sepsis, concomitant nephrotoxic agents), and most of these factors are reversible.[23] Lopinavir and ritonavir may increase plasma concentrations of tenofovir by 30%. NRTIs have a good renal safety profile.[23] Non-nucleoside reverse transcriptase inhibitors (NNRTIs) also have a good safety profile, with an isolated case report of AKI from interstitial nephritis caused by a hypersensitivity reaction to efavirenz. The fusion inhibitor enfuvirtide has been associated with an isolated case report of MPGN in a diabetic patient.

CHRONIC KIDNEY DISEASE AND END-STAGE RENAL DISEASE IN HUMAN IMMUNODEFICIENCY VIRUS–INFECTED PATIENTS

Epidemiology

The Developed World

With the advent of ART, the range of common renal diagnoses has expanded from HIV-associated CG in individuals of African descent and ICGN associated with either IgA or all immunoglobulins to include diseases such as FSGS, diabetic nephropathy, and arteriosclerosis. In patients with hepatitis, MN associated with hepatitis B and MPGN associated with hepatitis C should be considered. Uncommon but important diagnoses include MN (presumably idiopathic, but possibly related to the polyclonal B cell expansion typical of HIV disease) and amyloid. Chronic tubular injury, especially associated with tenofovir therapy but possibly associated with other ART, is not uncommon; but when early diagnosis leads to cessation of the offending medication, CKD is usually averted. Despite the plethora of diagnoses, HIV-associated CG remains the leading cause of ESRD in patients with HIV disease.

There are few data on the worldwide prevalence of CKD in HIV infection. In a cross-sectional study from 31 European countries, Israel, and Argentina, CKD stages 3 to 5 was present in 4.7% of HIV-infected patients by use of the Modification of Diet in Renal Disease (MDRD) formula. A study from Hong Kong showed CKD (defined as estimated glomerular filtration rate [eGFR] ≤60 ml/min/1.73 m^2 or proteinuria for more than 3 months) in 18% of HIV-infected Chinese patients, but this study excluded those with ESRD.

The United States Renal Data System (USRDS) reports that for the period 2006 to 2010, there were 3834 cases of AIDS nephropathy (0.7% of total ESRD); the racial breakdown was 86% African American and 15% Caucasian.[29] The Department of Health and Human Services reported that in 2009 there were an estimated 787,701 Americans living with HIV disease, of whom 43% were African American and 35% were Caucasian.[30] Thus the unadjusted relative risk for ESRD was 4.7 for those of Black race. This relative risk is less than previously estimated for HIV-associated CG and supports the idea that the distribution of kidney diseases associated with HIV infection is shifting.

The Developing World

More than two thirds (69%) of the total HIV-infected population in the world live in sub-Saharan Africa, and the majority infected are women (58%). Transmission of HIV infection is largely by heterosexual contact in most of the region. Of HIV-infected individuals in sub-Saharan Africa, 56% have access to ART.[1] Access to renal replacement therapy (RRT), however, is frequently limited. Reported prevalence of CKD has been assessed by the presence of proteinuria or eGFR (based on serum creatinine measurements) and ranges widely from 6% to 48.5% in Africa.[31] This wide variation may be partly ascribed to differences in study design, populations studied, and definitions used for CKD based on dipstick proteinuria and quantitative measure of proteinuria or serum creatinine. Isolated screening studies with relatively small numbers using persistent proteinuria as a marker of CKD have been done in various countries with the following prevalence rates: 1% to 6% in Brazil, 27% in India, and 20% in Iran.

Human immunodeficiency virus–associated CG is the dominant disease documented in up to 80% of kidney biopsy specimens, which is consistent with findings in the United States. As in developed countries, other renal causes are also observed, including ICGN from postinfectious and other causes, MN, and interstitial nephritis. There are nonspecific histologic changes, such as mesangial hyperplasia and chronic active interstitial nephritis, that do not necessarily fulfill the diagnostic criteria for HIV-associated CG but show regression on ART, which suggests that the histologic criteria for HIV-associated CKD may need to be revised.[32-34]

A significant response of HIV-associated CKD to ART has been shown, with the median eGFR improving by 21% after 2 years on

ART.[35] A recent study of 221 HIV-positive patients in South Africa with renal histology reported that both HIV-associated CG and ICGN showed response to ART.[36] The presence of kidney dysfunction, in the setting of HIV infection, acts as an independent predictor of poor outcome, with an increased mortality after 90 days.[37]

Dosage of Antiretroviral Therapy in Chronic Kidney Disease

Many antiretroviral medications are partially or completely eliminated by the kidney and require dosage adjustment in CKD (Table 58-3). Certain drug classes, such as the protease inhibitors and the NNRTIs, are extensively metabolized by the liver and do not require dosage adjustment.[38] Most of the NRTIs are excreted unchanged in the urine and require dosage adjustment, with the exception of zidovudine and abacavir, which both have substantial extrarenal biotransformation that requires less or no dosage adjustment. In uremia, drug dosages may be affected by altered gastric pH and variable volumes of distribution.[39] Factors that influence dialyzability of antiretroviral medications relate to the properties of the dialysis membrane and molecular weight, degree of protein binding, molecular charge, and water solubility of the drug. If removal of the drug occurs during hemodialysis (HD), it should be taken after dialysis. If the drug is removed in peritoneal dialysis (PD) effluent, the dose may have to be supplemented.[39] Dosage recommendations in both HD and PD are limited by the lack of reliable data. Fixed drug combinations should not be used in patients with eGFR below 30 to 50 ml/min.[38]

Dose Adjustments for ART in CKD and ESRD

Name	CKD (Adjusted According to Creatinine Clearance [CrCl] by eGFR)		Dialysis
Nucleoside or nucleotide analogues			
Abacavir	No adjustment		No adjustment HD: dosing independent of dialysis sessions
Azidothymidine (AZT), zidovudine*	CrCl ≥15 ml/min: no adjustment CrCl <15 ml/min: 100 mg PO q6-8h		HD:100 mg PO q6-8h* or 300 mg PO qd PD: no data
Didanosine (ddi)	Weight >60 kg CrCl 30-59 ml/min: 200 mg PO qd CrCl 10-29 ml/min: 150 mg PO qd CrCl <10 ml/min: 125 mg PO qd	Weight <60 kg 150 mg PO qd 100 mg PO qd 75 mg PO qd	Dosage for CrCl <10 ml/min† HD, PD: same dose
Emtricitabine‡	CrCl >50 ml/min: no adjustment CrCl 30-49 ml/min: 200 mg PO q48h CrCl 15-29 ml/min: 200 mg PO q72h CrCl <15 ml/min: 200 mg PO q96h		HD: 200 mg PO q96h† PD: no data
Lamivudine* (3TC)	CrCl >50 ml/min: no adjustment CrCl 30-49 ml/min: 150 mg PO qd CrCl 15-29 ml/min: 150 mg first dose, then 100 mg PO qd CrCl 5-14 ml/min: 150 mg first dose, then 50 mg PO qd CrCl <5 ml/min: 50 mg first dose, then 25 mg PO qd		HD: 50 mg first dose, then 25 mg PO qd†
Stavudine (d4T)	CrCl >50 ml/min: no adjustment CrCl 26-50 ml/min: 15-20 mg PO bid CrCl ≤25 ml/min: 15-20 mg PO qd		20 mg PO qd† PD: has been used safely
Tenofovir‡	CrCl >50 ml/min: no adjustment CrCl 30-49 ml/min: 300 mg q48h CrCl 10-29 ml/min: 300 mg q72h		300 mg PO every 7 days†
Zalcitabine	CrCl ≥40 ml/min: no adjustment CrCl 10-40 ml/min: 0.75 mg q12h CrCl <10 ml/min: 0.75 mg q24h		HD: dosage for CrCl <10 ml/min† PD: no data
Non-nucleoside reverse transcriptase inhibitors§	No adjustment		
Protease inhibitors§	No adjustment		No adjustment
Entry or fusion inhibitor Enfuvirtide	CrCl ≥35 ml/min: no adjustment CrCl <35 ml/min: unknown, use with caution		Unknown, use with caution
CCR5 antagonist Maraviroc	No dosage recommendations Patients with CrCl <50 ml/min should receive maraviroc and CYP3A inhibitor only if potential benefit outweighs the risk		No data
Integrase inhibitor§ Raltegravir	No adjustment		No adjustment

Table 58-3 Dose adjustments for ART in CKD and ESRD. U.S. Food and Drug Administration (FDA) recommendations are based on CrCl or eGFR calculated as ml/min, but are likely valid for these expressed as ml/min/1.73 m^2. Atripla (efavirenz, tenofovir, and emtricitabine) is not recommended for CrCl < 5 ml/min. *ART,* Antiretroviral therapy; *CCR5,* cysteine-cysteine chemokine receptor 5; *CKD,* chronic kidney disease; *CrCl,* creatinine clearance; *eGFR,* estimated glomerular filtration rate; *ESRD,* end-stage renal disease; *HD,* hemodialysis; *PD,* peritoneal dialysis. *Combination AZT/lamivudine tablets (300 mg/150 mg) should be administered separately when eGFR < 50 ml/min. †Defer daily dose(s) until after hemodialysis (removal of drug occurs on dialysis). ‡Combination emtricitabine-tenofovir tablets (200 mg/300 mg): if CrCl = 30-49 ml/min, 1 tablet PO q48h; if CrCl <30 ml/min, the combination tablet should not be prescribed. §No dose adjustment necessary for any drug from this class in patients with renal dysfunction, hemodialysis, or peritoneal dialysis.

RENAL REPLACEMENT THERAPY IN THE PATIENT WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

With the increasing survival of HIV-infected patients with treatment and the declining cost of ART, the magnitude of HIV-associated ESRD will likely increase worldwide, as it has in developed countries.[40] Life expectancy in HIV infection with ART has increased by 10 to 20 years in developed countries, and many of these patients are now dying of the complications of ESRD rather than of HIV infection. Currently, HIV-infected patients requiring either HD or PD, who are stable on ART, are achieving survival rates comparable to those of dialysis patients without HIV infection, and choice of dialysis modality does not have an impact on survival.

Immunization schedules are the same as for non–HIV-infected dialysis patients and should include vaccinations against *Streptococcus pneumoniae,* influenza virus, hepatitis A virus, and hepatitis B virus.[21] In both CKD and HIV infection, the presence of anemia is independently associated with shorter survival. The response to recombinant erythropoietin (EPO) in HIV-infected patients with ESRD is similar to that in HIV-negative patients.[41] Measurements of iron indices are complicated in HIV-infected patients, resembling those of the anemia of chronic disease, especially because levels of ferritin (an acute phase reactant) are often elevated in patients with HIV infection.

Elevated soluble transferrin receptor concentrations are more reliable than serum ferritin to distinguish iron deficiency in inflammatory disease states.[42]

Hemodialysis

Strict use of universal precautions is the best form of prevention of HIV transmission in dialysis units. Although HIV-infected patients do not have to be isolated from other patients or dialyzed on separate machines, concerns of staff and patients result in these patients being dialyzed in separate facilities in some institutions. Reprocessing of dialyzers from HIV-positive patients should not place staff members at increased risk for infection if necessary sterile precautions are undertaken. The risk of HIV seroconversion after a needlestick injury from an infected patient is estimated to be approximately 0.2% to 0.5% lower than that of HBV and HCV (5% to 40% and 3% to 10%, respectively). ART may reduce the risk of transmission after a needle stick injury, and postexposure prophylaxis with a combination of two reverse transcriptase inhibitors and one protease inhibitor is recommended.

Native arteriovenous fistulas are the preferred types of access because of better patency rates once established and lower complication rates compared with those associated with other access options.

Peritoneal Dialysis

Human immunodeficiency virus has been shown to survive in peritoneal effluents at room temperature for up to 7 days and in PD exchange tubing for up to 48 hours. Dialysate should therefore be handled as a contaminated body fluid.[43] Sodium hypochlorite (50% solution) and household bleach (10% solution), each further diluted 1:512, are effective at killing HIV in dialysate. PD patients should be instructed to pour dialysate into the home toilet and to dispose of dialysate bags and lines by tying them in plastic bags and disposing of the plastic bags in conventional home garbage.[21,43,44]

Kidney Transplantation

Kidney transplantation has been performed with success in HIV-infected patients. Preliminary short-term data in liver, kidney, and heart transplant recipients suggest that patient survival rates are similar to those of HIV-uninfected transplant recipients, and there has been no increase in the prevalence of opportunistic infection.[45] The largest series to date of 150 kidney transplants in the United States has reported patient and graft survival of 88% and 74%, respectively, at 3 years. In spite of high rates of acute graft rejection, survival appears to be similar to that of HIV-uninfected recipients, falling between that of older kidney transplant recipients and all kidney transplant recipients.[46] In areas with high endemic rates of HIV infection, it has been proposed that HIV-infected cadaveric donor organs may be transplanted into HIV-infected recipients with ESRD.[47] Four such transplantations have been reported with good graft and recipient survival.[48] With the series currently at 20 kidney transplants from HIV-positive deceased donors, 1- and 4-year graft survival rates have been 88% and 83%, respectively, and patient survival rates have been 94% and 89% (E. Muller, personal communication).

SCREENING FOR CHRONIC KIDNEY DISEASE

As noted previously, treatment of HIV-associated CG, and possibly HIV-associated ICGN, may slow progression of renal functional decline. Studies suggest that creatinine clearance and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine eGFR equation provide suitable estimates of true GFR as assessed by iothalamate GFR.[45]

Patients with HIV disease are at increased risk for CKD and should receive regular screening. A committee of the Infectious Diseases Society of America has laid out a proposal for screening.[21] Annual screening should include assessment of blood pressure, assessment of serum creatinine and/or cystatin C, and a quantitative measure of urine protein. In a resource-limited setting, this might be a urine protein-creatinine measurement. In other settings, adding the urine albumin-creatinine ratio (ACR) provides additional information about cardiovascular risk and also the source of proteinuria, as the ACR gives an indication of glomerular versus tubular disease.[50] Support for screening has come from published data confirming that CKD in HIV infection is common, can occur at any stage of HIV infection (even before seroconversion), and can progress rapidly to ESRD if it is untreated.

The role of microalbuminuria in the natural history of HIV-associated CKD and screening is an area of active investigation. Microalbuminuria may indicate early glomerular disease, including in diabetes, arterionephrosclerosis, HIV-associated glomerular disease, tubular disease (drug toxicity), metabolic syndrome, or systemic inflammation.[51] Its role in diagnosis and screening in the setting of HIV infection remains to be determined. Microalbuminuria is associated with an increased risk of cardiovascular disease and mortality in patients with diabetes and hypertension, and also in the general population.[52] Han and colleagues[32] found that six of seven South African patients with persistent microalbuminuria had HIV-associated CG; these findings tell us that HIV-associated CG can present insidiously, at a stage when therapy may slow its progression. Nevertheless, these patients were ART naive, and this HIV-infected population may lack the high prevalence of diabetes, hypertension, and drug-induced renal toxicity that characterizes patients with HIV disease in developed countries. Szczech and colleagues[53] found microalbuminuria in 11% of patients with HIV disease compared

with 2% of controls; the presence of microalbuminuria was associated with insulin resistance, systolic hypertension, and advanced HIV disease characterized by a low CD4 count. Whether this association predicts increased risk of cardiovascular disease and mortality in HIV disease needs to be investigated. Hadigan and colleagues reported recently that the period of prevalence of persistent microalbuminuria, defined as the mean of three samples over 6 to 9 months, was 14% in an HIV population from which those with diabetes, chronic viral infection, and cancer had been excluded; furthermore, a single urine ACR result had a 98% negative predictive value but only a 74% positive predictive value to identify those with persistent microalbuminuria.[47]

Screening, early detection, and treatment of HIV-associated CKD are strongly recommended (Fig. 58-3). In the algorithm, management of leukocyturia, in addition to proteinuria, has been included because it occurs commonly and the presence of sterile pyuria may

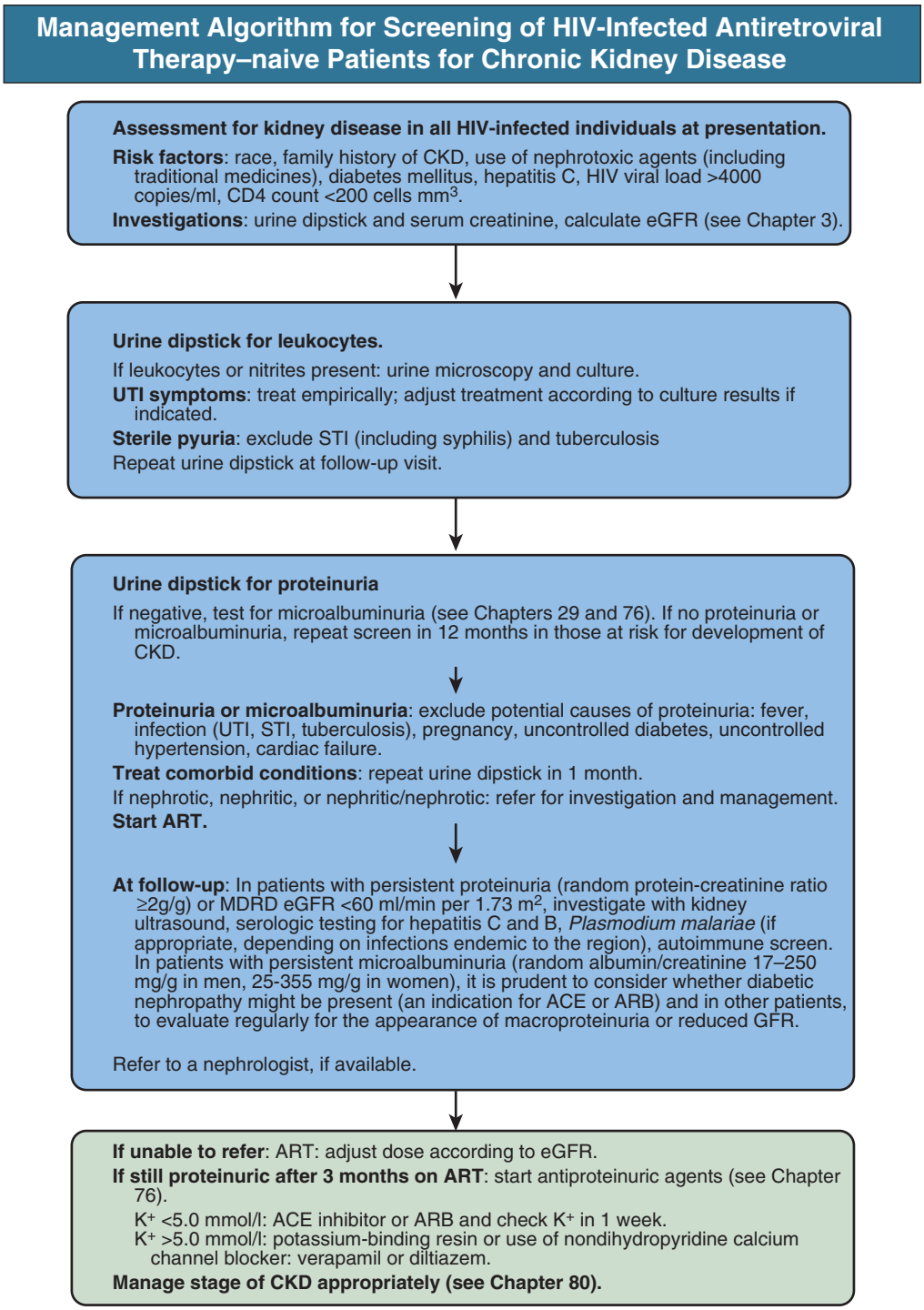

Figure 58-3 Management algorithm for screening of human immunodeficiency virus (HIV)–infected antiretroviral therapy–naive patients for chronic kidney disease. Tuberculosis may be pulmonary or extrapulmonary. Antiproteinuric agents may be used in normotensive individuals with gradual uptitration of dose, depending on tolerance and severity of proteinuria. *ACE,* Angiotensin-converting enzyme; *ARB,* angiotensin II receptor blocker; *ART,* antiretroviral therapy; *CKD,* chronic kidney disease; *eGFR,* estimated glomerular filtration rate, calculated by the Cockcroft-Gault formula or the modified Modification of Diet in Renal Disease (MDRD) formula; *STI,* sexually transmitted infection; *UTI,* urinary tract infection.

be associated with comorbid disease. Urinary screening is inexpensive and easy to perform and to interpret, provided guidelines are given to staff at the primary health care level to initiate treatment, to investigate, and, if necessary, to refer. Effective screening programs are more realistic in resource-limited developing countries when the alternative is considered, which is that access to RRT is extremely limited and progression of CKD to ESRD is ultimately fatal for most patients.

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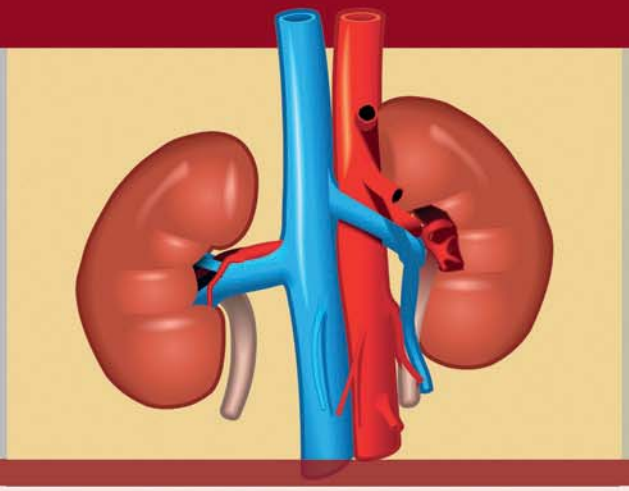

SECTION X

Urologic Disorders

CHAPTER 59

Nephrolithiasis and Nephrocalcinosis

David A. Bushinsky and Rebeca D. Monk

Kidney stones are common and are associated with significant morbidity. *Nephrolithiasis* refers to stone formation within the renal tubules or collecting system, although calculi are often found within the ureters or in the bladder.[1-3] Most renal calculi are calcium oxalate, calcium phosphate, struvite, uric acid, and cystine. Clinical presentation varies from asymptomatic small stones to large, obstructing staghorn calculi that impair renal function and cause chronic kidney disease (CKD). The severity of stone disease depends on the pathogenesis as well as stone type, size, and location. *Nephrolithiasis* classically presents as ureteral colic, but may also commonly present with hematuria or urinary tract infection (UTI). Diffuse renal parenchymal calcification is termed *nephrocalcinosis.* These calcifications are usually calcium phosphate or calcium oxalate and may deposit in the renal cortex or medulla, depending on the cause.

NEPHROLITHIASIS

Epidemiology

Kidney stones are common in industrialized nations, with an annual incidence of over 1/1000 persons and a lifetime risk of forming stones of approximately 5% in women and approximately 13% in men.[1,3,4] In the United States the prevalence of nephrolithiasis increased from 3.2% in the late 1970s to 5.2% in the 1990s[5] and further to 8.8% in the 2000s, in parallel with the rising incidence of obesity, insulin resistance, and type 2 diabetes mellitus.[6-8] Incidence peaks in the third and fourth decades and prevalence increases with age until approximately 70 years in men and 60 years in women.[5] Factors that determine renal stone prevalence include age, sex, race, and geographic distribution. In the United States, Caucasians are more likely to develop renal stones than African Americans, Hispanics, or Asian Americans, but the prevalence is rising in non-Caucasians as well.[8] Men are more prone to stone formation than women.[8] In the United States the tendency for the development of stones also depends on geographic location, with an increasing prevalence from north to south and, to a lesser degree, from west to east. Increased environmental temperatures have been associated with increased stone formation rates.[9] The increase in nephrolithiasis rates may be a result of the greater sunlight exposure leading to an increase in insensible losses through sweating, and more concentrated urine.[4,10] The higher urine calcium excretion in a smaller urine volume will increase the risk for supersaturation for calcium-containing crystals, thereby promoting stone formation.

Stone type varies with worldwide geography and genetic predisposition. In the Mediterranean and Middle East, 75% of stones are composed of uric acid, whereas in the United States the majority of stones are calcium oxalate or calcium phosphate (>70%), with less than 10% being pure uric acid stones. Magnesium ammonium phosphate (struvite) stones account for 10% to 25% of stones formed (with a higher incidence in the United Kingdom), and cystine stones constitute 2% of all stones formed (Fig. 59-1).[11]

Outbreaks of kidney stones can also occur as a result of dietary supplements or medications. A large number of Chinese infants and toddlers developed kidney stones, and in some, renal failure, because of obstruction caused by stones. This outbreak was associated with melamine contamination in infant formulas and powdered milk as a means of raising the apparent concentration of protein in the products.[12]

Pathogenesis

Stones occur in urine that is supersaturated with respect to the ionic constituents of the specific type of stone. Supersaturation is dependent on the product of the free ion activities of stone components rather than on their molar concentrations. Whereas an increasing concentration of crystal components increases their free ion activity, other factors diminish it. When calcium and oxalate are dissolved in pure water, for example, the solution becomes saturated when the addition of any more calcium or oxalate does not result in further dissolution. However, urine, unlike pure water, contains numerous ions and molecules that can form soluble complexes with the ionic components of the stone. The interactions with these other solutes (e.g., citrate) may result in a decrease in free ion activity, which allows the stone constituents to increase in total concentration to levels that would normally cause stone formation in water. Urinary pH also influences free ion activity. The level of chemical free ion activity in which stones will neither grow nor dissolve is referred to as the *equilibrium solubility product,* or the upper limit of metastability. Above this level, the urine will be supersaturated and any stone present will grow in size.

When the solution becomes supersaturated with respect to a solid phase, ions can join together to form the more stable, solid phase, a process termed *nucleation.* Homogeneous nucleation refers to the joining of similar ions into crystals. The more common and thermodynamically favored heterogeneous nucleation results when crystals grow adjacent to crystals or other substances in the urine such as sloughed epithelial cells. Calcium oxalate crystals, for example, can nucleate with uric acid crystals. These small crystals may then aggregate to form larger stones, which would pass into the urine, causing crystalluria, if they did not anchor to the urothelium.

Calcium oxalate crystals anchor on areas of calcium phosphate deposits termed *Randall plaques*, which are located in the renal papillae and are composed of apatite (a complex of mostly calcium and phosphate) crystals. The apatite appears to originate around the thin loop of Henle, in the tubular basement membrane, and extends into the interstitium without filling the tubular lumen or damaging the tubular cells. Calcium oxalate crystals attach to Randall plaques, allowing significant stone growth.[13-15] Clinically apparent stone

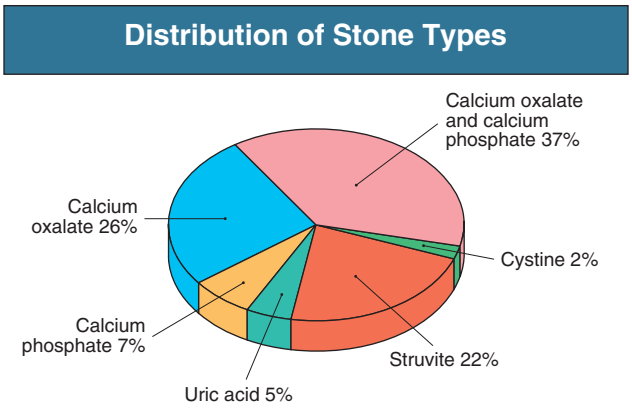

Figure 59-1 **Proportion of stone types in a typical U.S. population.**

Figure 59-2 **Ureteral calculus.** A 1-cm-wide calcium oxalate stone that provoked ureteral colic and required surgical removal.

Clinical Presentations of Nephrolithiasis

Presentation	Characteristics
Pain	Ureteral colic, loin pain, dysuria
Hematuria	—
Urinary tract infection	Recurrent, chronic infection, pyelonephritis
Asymptomatic urine abnormality	Microhematuria, proteinuria, sterile pyuria
Interruption of urinary stream	—
Calculus anuria	—

Table 59-1 **Clinical presentations of nephrolithiasis.**

Causes of Hematuria

- Nephrolithiasis
- Infection: cystitis, prostatitis, urethritis, acute pyelonephritis, tuberculosis, schistosomiasis
- Malignancy: renal cell carcinoma, transitional cell carcinoma, prostatic carcinoma, Wilms tumor
- Trauma
- Glomerular disease
- Interstitial nephritis
- Polycystic kidney disease
- Papillary necrosis
- Medullary sponge kidney
- Coagulopathy: bleeding disorders, anticoagulation therapy
- Miscellaneous: loin pain–hematuria syndrome, arteriovenous malformation, chemical cystitis, caruncle, factitious

Box 59-1 **Causes of hematuria.**

disease occurs when the calcium oxalate crystals break off from the Randall plaques and cause injury or obstruction.

Clinical Manifestations

The two most characteristic symptoms of nephrolithiasis are pain and hematuria. Other presentations include UTIs and acute kidney injury (AKI) caused by obstructive uropathy if stones cause bilateral renal tract obstruction or unilateral obstruction in a single functioning kidney (Table 59-1).

Pain

The classic presentation of pain in patients with nephrolithiasis is ureteral colic. Pain is of abrupt onset and intensifies over time into an excruciating, severe flank pain that resolves only with stone passage or removal. The pain may migrate anteriorly along the abdomen and inferiorly to the groin, testicles, or labia majora as the stone moves toward the ureterovesical junction. Gross hematuria, urinary urgency, frequency, nausea, and vomiting may occur. Stones smaller than 5 mm usually pass spontaneously with hydration, whereas larger stones often require urologic intervention (Fig. 59-2).[14,16] Ureteral colic may also occur with the passage of clots from hematuria of any cause ("clot colic"), or with papillary necrosis. As well as colic, nephrolithiasis may provoke less-specific loin pain that poorly localizes to the kidney and therefore has a wide differential diagnosis, particularly if not associated with other urinary symptoms. The finding of a stone on radiologic examination does not preclude a coincidental cause of pain from another source.

Hematuria

Stone disease is a common cause of hematuria. Macrohematuria occurs more commonly with large calculi and during UTI and colic. Although typically associated with loin pain or ureteral colic, the hematuria of nephrolithiasis may also be painless. The clinical differential diagnosis of hematuria is therefore wide (Box 59-1). Painless microhematuria in children may occur with hypercalciuria in the absence of demonstrable stones.

Loin Pain–Hematuria Syndrome

Loin pain–hematuria syndrome is a poorly understood condition that must always be considered in the differential diagnosis of nephrolithiasis. It is diagnosed by exclusion when patients (most typically young and middle-aged women) present with loin pain and persistent microhematuria or intermittent macrohematuria.[17,18] Careful evaluation is required to exclude small stones, tumor, UTI, and glomerular disease. Angiographic abnormalities implying intrarenal vasospasm or occlusion have been reported, as have renal biopsy abnormalities typified by deposition of complement C3 in arteriolar walls. However, these findings are not consistent, nor do they provide a coherent framework to explain the pathogenesis of this condition.

In one study, 43 consecutive patients with clinical manifestations of loin pain–hematuria syndrome were evaluated by renal biopsy

after other causes of their symptoms had been excluded with at least two imaging studies.[17] Thirty-four patients were considered to have idiopathic loin pain–hematuria syndrome after nine with histologic evidence of IgA nephropathy were excluded. Of these, 66% had glomerular basement membranes that were either unusually thick or thin on electron microscopy, and 47% had a history of kidney stones, though none had obstructing stones at the time of assessment. Evidence of glomerular hematuria was more common in biopsies of patients with loin pain–hematuria syndrome compared with those of healthy living kidney donors who also underwent renal biopsy. The investigators postulated that the structurally abnormal glomerular basements in the majority of these patients may lead to rupture of the glomerular capillary walls, with consequent hemorrhage into the renal tubules. Tubular obstruction by red blood cells or potentially by microcrystals ensues. Local and global renal parenchymal edema follow, ultimately resulting in stretching of the renal capsule and in severe flank pain.

Loin pain–hematuria syndrome is a chronic condition requiring reassurance, careful management of analgesia, and ongoing psychological support. The condition usually remits after several years. Denervation of the kidney by autotransplantation is rarely successful.[18] The extreme measure of nephrectomy has been used, but pain often recurs promptly in the contralateral kidney. Bilateral nephrectomy and renal replacement therapy has been reported as an approach of very last resort. Referral to a pain clinic can assist in providing psychiatric counseling, analgesia, and exclusion of other disorders. In one retrospective study, patients who eventually came to accept a nonsurgical approach along with pain-coping strategies that did not involve narcotic analgesics had the most successful outcomes.[19]

Asymptomatic Stone Disease

Even large staghorn calculi may be asymptomatic and discovered only during the investigation of unrelated abdominal or musculoskeletal symptoms. Obstructive uropathy caused by calculi may also be painless; therefore, nephrolithiasis should always be considered in the differential diagnosis of unexplained renal failure.

In the outbreak of melamine-associated nephrolithiasis in Chinese infants, the majority of patients brought to a screening clinic had no symptoms or signs of stones, and the diagnosis of nephrolithiasis was made only by ultrasound in at-risk infants and toddlers.[12]

Clinical Evaluation of Stone Formers

All patients with recurrent nephrolithiasis merit metabolic evaluation to determine the cause of their kidney stones. Complete evaluation of patients who have formed only a single stone is controversial because of the undetermined cost-benefit ratio. A National Institutes of Health Consensus Development Conference on the Prevention and Treatment of Kidney Stones determined that all patients, even those with a single stone, should undergo a basic evaluation, which need not include a 24-hour urine collection. Those with metabolically active stones (stones growing in size or number within 1 year), all children, noncalcium stone formers, and patients in demographic groups not typically prone to stone formation warrant a more complete evaluation, which includes a 24-hour urine collection made with the patient taking his or her typical diet.[20]

Basic Evaluation

The clinic evaluation of stone formers includes a general history and physical examination and requires specific data gathering on stone formation, diet, and specific laboratory studies, as shown in Box 59-2.

The Basic Evaluation of Nephrolithiasis

- Stone history
  - Number of stones formed
  - Frequency of stone formation
  - Age at first onset
  - Size of stones passed or still present
  - Kidney involved (left, right, or both)
  - Stone type, if known
  - Need for urologic intervention: ESWL, percutaneous nephrolithotomy, and so on
  - Response to surgical procedure
  - Are stones associated with urinary tract infections?
- Medical history
- Medications
- Family history
- Occupation and lifestyle
- Fluid intake and diet
- Physical examination
  - Evidence of systemic causes of stones (e.g., tophi)
- Laboratory data
  - Urinalysis
  - Urine culture
  - Stone analysis
- Blood chemistry
  - Sodium, potassium, chloride, bicarbonate
  - Creatinine, calcium, phosphorus, uric acid
  - Intact parathyroid hormone level if calcium elevated
- Radiologic evaluation
  - Abdominal radiograph (no contrast)
  - Noncontrast CT
  - IVU
  - Ultrasound

Box 59-2 The basic evaluation of nephrolithiasis. *CT,* Computed tomography; *ESWL,* extracorporeal shock wave lithotripsy; *IVU,* intravenous urography.

History The history serves to uncover a systemic cause for nephrolithiasis. Any disease that can lead to hypercalcemia (including malignancy, hyperparathyroidism, and sarcoidosis) can result in hypercalciuria and increase the risk for calcium stone formation. A number of malabsorptive gastrointestinal disorders (including Crohn disease and sprue [celiac disease]) can result in calcium oxalate stone formation as a result of volume depletion and hyperoxaluria. Uric acid stones often occur in patients with a history of gout and, increasingly, in patients with insulin resistance.[11]

The stone history (see Box 59-2) includes the number and frequency of stones formed, patient age at incidence of first stone, size of stones, stone type (if known), and whether the patient required surgical removal of the calculi. This information indicates the severity of the stone disease and provides clues to the cause of the stone formation. For example, large staghorn calculi that do not pass spontaneously and recur despite frequent surgical intervention are more consistent with struvite than calcium oxalate stones. Stones that develop at a young age may be caused by cystinuria or primary hyperoxaluria. Stone response to intervention is also significant; cystine stones, for example, do not fragment well with lithotripsy. If stones recur frequently in a single kidney, a congenital abnormality in that kidney, such as megacalyx or medullary sponge kidney, should be explored.

Family history is important because a number of stone types have a genetic basis. Idiopathic hypercalciuria is most likely a polygenic disorder. Mutations in the claudins, which regulate calcium reabsorption in the thick ascending limb of the loop of Henle, cause familial hypercalciuria and nephrocalcinosis. A genome-wide association study in kidney stone patients identified sequence variants in the gene encoding claudin 14 that were associated with hypercalciuria.[21]

Cystinuria is usually autosomal recessive, and hyperuricosuria has been associated with rare inherited metabolic disorders. Nephrolithiasis and nephrocalcinosis can also result from a variety of monogenic disorders, such as Dent disease (X-linked recessive nephrolithiasis), McCune-Albright syndrome, osteogenesis imperfecta type 1, and congenital lactate deficiency. The various genetic disorders can lead to hypercalciuria by increasing bone resorption, affecting intestinal absorption, or decreasing renal tubular reabsorption transport, or through other, as yet unknown mechanisms.[4,14,15,22,23]

A number of medications are known to potentiate calcium stone formation (e.g., loop diuretics are calciuric) or may predispose to uric acid lithiasis (salicylates, probenecid) (Box 59-3). Certain drugs can precipitate into stones themselves, such as rapidly infused intravenous acyclovir, high-dose sulfadiazine, triamterene, and the antiretroviral agents indinavir and nelfinavir.[24] In addition, some medications, such as acetazolamide and topiramate (a medication used for seizures and migraine headaches), promote nephrolithiasis by inhibiting carbonic anhydrase activity. In this setting the metabolic acidosis that ensues, along with lower urine citrate, higher urine pH, and increased urinary calcium excretion, predisposes to calcium phosphate stone formation.[25]

The social history should include details regarding occupation and lifestyle. Cardiothoracic surgeons and real-estate agents, for example, may minimize fluid intake to avoid bathroom breaks during the workday. Those who engage in vigorous physical activities, such as running, may not rehydrate adequately to keep up with insensible losses, producing excessively concentrated urine and precipitation of stone crystals in those prone to nephrolithiasis.

A dietary history and review of fluid intake are essential in determining potential causes or contributors to stone formation. The patient should be asked about commonly consumed foods, with attention paid to sodium-containing foods, as well as quantities of calcium, animal protein, purine, and oxalate (Box 59-4). Dietary calcium intake should be reviewed, because many patients with nephrolithiasis are erroneously instructed to eliminate all calcium from their diet, a suggestion that can result not only in bone demineralization, particularly in women and children, but also in an *increase* in stone formation.[1-3,26-28] Sugar-sweetened soda appears to be associated with a greater risk of stone formation, whereas consumption of coffee, tea, beer, wine, and orange juice appears to be associated with a lower risk.[29] The exact mechanism of nephrolithiasis from soda is not known but is likely related to the high fructose content of soda which may alter urinary composition and pH.[30]

Physical Examination Most patients with idiopathic hypercalciuria are healthy and have normal physical examination findings. Patients with hyperuricosuria and uric acid stone formation may display tophi. Central obesity is associated with a predisposition to metabolic syndrome and uric acid stones. Paraplegic patients with a chronic indwelling bladder catheter may be predisposed to chronic UTI and struvite stones.

Laboratory Findings Urine pH is generally high in patients with struvite and calcium phosphate stones but low in patients with

Medications Associated with Nephrolithiasis and Nephrocalcinosis

Calcium Stone Formation
Loop diuretics
Vitamin D
Corticosteroids
Calcium supplements
Antacids (calcium and noncalcium antacids)
Theophylline
Acetazolamide*
Amphotericin*
Topiramate

Uric Acid Stone Formation
Salicylates
Probenecid
Allopurinol (usually associated with xanthine stones)
Melamine (in contaminated infant formula and milk products)

Medications that May Precipitate into Stones
Triamterene
Acyclovir (if infused rapidly intravenously)
Indinavir
Nelfinavir

Box 59-3 Medications associated with nephrolithiasis and nephrocalcinosis. *Associated with nephrocalcinosis.

Foods High in Oxalate and Purine

High-Oxalate Foods (Avoid in Setting of Hyperoxaluria)
Green beans
Beets
Celery
Green onions
Leeks
Leafy greens: collard greens, dandelion greens, Swiss chard, spinach, escarole, mustard greens, sorrel, kale, rhubarb
Cocoa
Chocolate
Black tea
Berries: blackberries, blueberries, strawberries, raspberries, currants, gooseberries
Orange peel
Lemon peel
Dried figs
Summer squash
Nuts, peanut butter
Tofu (bean curd)

High-Purine Foods (Avoid in Setting of Hyperuricosuria)
Organ meats: sweetbreads, liver, kidney, brains, heart
Shellfish
Meat: beef, pork, lamb, poultry
Fish: anchovies, sardines (canned), herring, mackerel, cod, halibut, tuna, carp
Meat extracts: bouillon, broth, consommé, stock
Gravies
Certain vegetables: asparagus, cauliflower, peas, spinach, mushrooms, lima and kidney beans, lentils

Box 59-4 Some foods high in oxalate and purine.

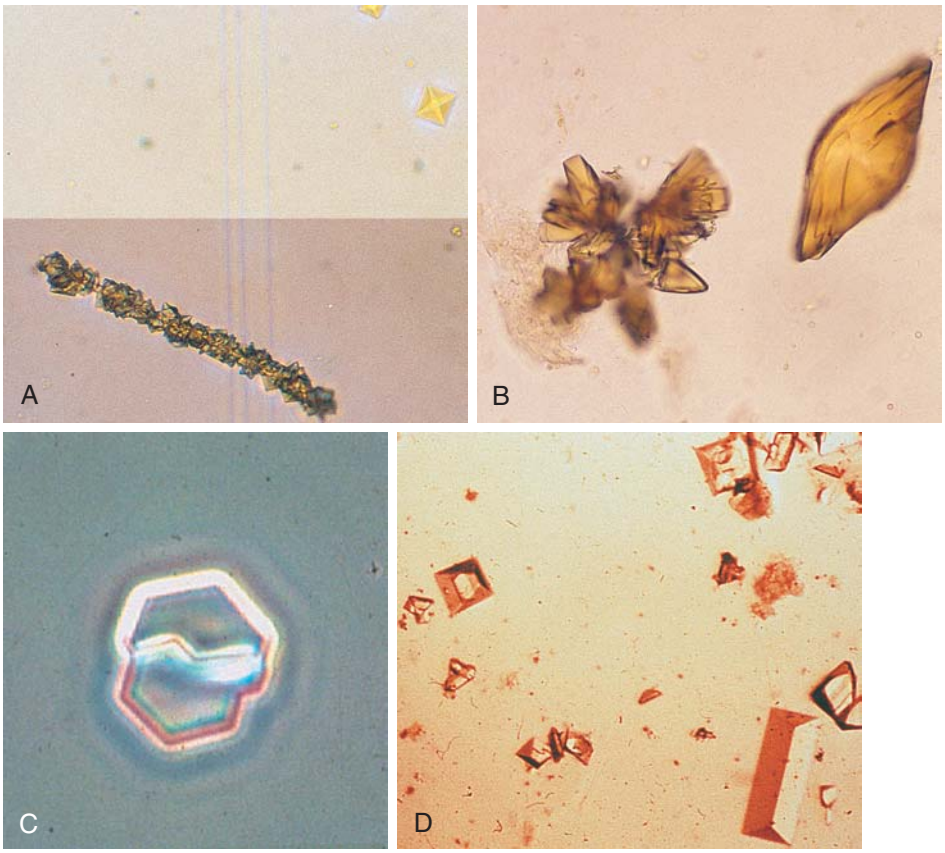

Figure 59-3 Urine crystals. A, Oxalate crystals: a pseudocast of calcium oxalate crystals accompanied by crystals of calcium oxalate dihydrate. **B,** Uric acid crystals: complex crystals suggestive of acute uric acid nephropathy or uric acid nephrolithiasis. **C,** A typical hexagonal cystine crystal; a single crystal provides a definitive diagnosis of cystinuria. **D,** Coffin lid crystals of magnesium ammonium phosphate (struvite). *(Courtesy Dr. Patrick Fleet, University of Washington, Seattle.)*

uric acid and calcium oxalate stones. The specific gravity, if high, will confirm inadequate fluid intake in many patients. Hematuria may imply active stone disease with crystal or stone passage. Examination of the urine may reveal red blood cells along with characteristic crystals (Fig. 59-3). Bacteriuria with urine pH of 6 to 6.5 suggests struvite stones. Urine should be cultured, and because many bacteria produce urease even when urine bacterial colony counts are low, the microbiology laboratory should be instructed to type the organism even if there are fewer than 100,000 colony-forming units/ml.

Blood tests required in the basic evaluation are serum electrolytes (sodium, potassium, chloride, and bicarbonate), creatinine, calcium, phosphorus, and uric acid. If the serum calcium is elevated or at the upper limit of normal, especially if the serum phosphorus is low, a serum parathyroid hormone level should be measured. A low potassium or bicarbonate level may indicate a cause for hypocitraturia, such as distal renal tubular acidosis.

Stone Analysis Patients should be encouraged to retrieve any stone they excrete for chemical analysis, which may help define the underlying metabolic abnormality and guide therapy.

Imaging Patients should have a plain film of the abdomen performed with views of the kidneys, ureters, and bladder (KUB). This may reveal opacifications in the areas of the kidneys and ureters that could be a result of calcium, cystine, or struvite stones (Fig. 59-4). Uric acid and xanthine calculi are radiolucent and will not be visible on plain films. The unenhanced helical computed tomography (CT) scan, also known as spiral CT, or CT urography, has replaced contrast intravenous urography (IVU) as the diagnostic test of choice for acute ureteral colic; it has a higher sensitivity and specificity than IVU for detecting ureteral stones and ureteral obstruction[16] and avoids the need for contrast. CT scanning is more likely to reveal causes of colic other than stones. It is more rapid, with results being available in minutes rather than hours, an advantage in the emergency room setting. However, an experienced radiologist, required for optimal interpretation of the images, may not be available at all times in urgent care facilities. Disadvantages of CT imaging include a radiation dose approximately three times that of a conventional IVU, and higher cost. Both tests should be avoided or limited in patients at risk for radiation exposure such as children and pregnant women.[31,32] The role of CT urography is also discussed in Chapter 5.

Contrast should generally be avoided in patients with renal impairment or other contraindications to the use of contrast. The IVU generally demonstrates urinary tract obstruction caused by calculi and can identify abnormalities of the genitourinary tract that may predispose to stone formation, such as medullary sponge kidney (see Chapter 47) or calyceal anomalies (see Chapter 52) (Fig. 59-5). During acute colic, the radiographic contrast used in the IVU, by creating a strong osmotic diuresis, may assist in moving the stone along the ureter. If stones are radiopaque, a KUB can be obtained if a patient develops symptoms suggestive of recurrent stone disease.

Renal ultrasound provides great specificity in the evaluation of stones, but is not a sensitive screening test. Both radiolucent and radiopaque stones within the kidneys should be detectable on ultrasound, but ureteral stones are often missed. Nonetheless, this is the test of choice for those patients who must avoid radiation exposure.

Periodic monitoring, if deemed necessary, should be obtained with a KUB and/or ultrasound scan rather than CT, whenever possible, to minimize radiation exposure. The combination of ultrasound and KUB has been found to be more sensitive in detecting stones than either test alone, while minimizing radiation compared with CT.[33] Many stone patients have recurrent disease and are therefore at risk for repeated exposure to radiation. Especially when

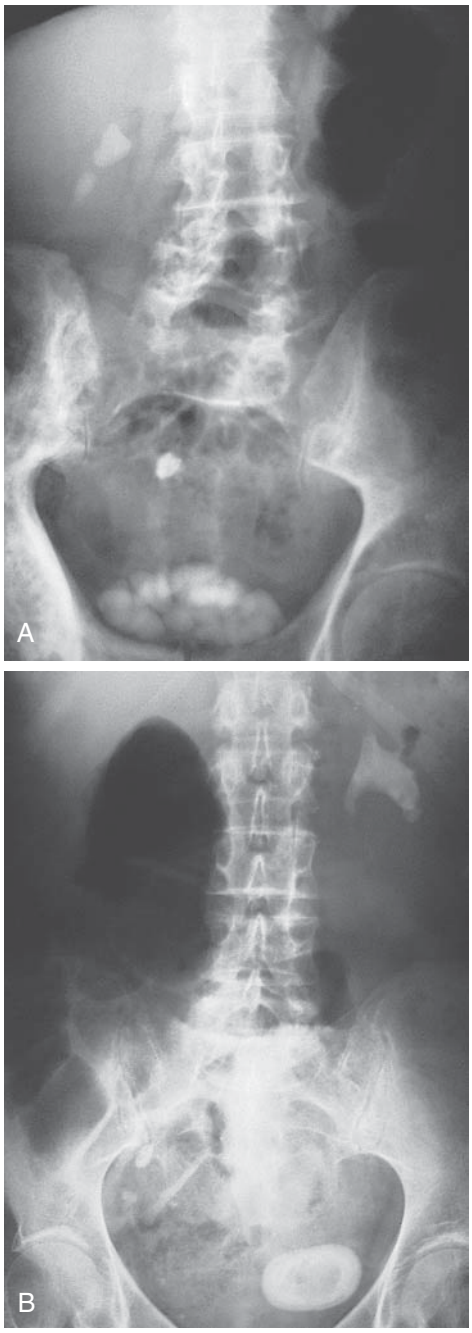

Figure 59-4 Radiopaque renal calculi. A, X-ray film showing multiple cystine stones in the right kidney, right ureter, and bladder. **B,** Struvite stones: left staghorn calculus and a single bladder stone.

caring for patients who may father or subsequently carry offspring, every effort should be made to limit radiation exposure. In general, we do not order routine follow-up x-ray examinations and do not order x-ray examinations unless the results will alter subsequent care. If x-ray films are ordered, every effort should be made to limit radiation exposure—for example, by not routinely ordering both a noncontrast and a contrast study. Often the results of the noncontrast study alone are sufficient to guide therapy.

Complete Evaluation

A complete evaluation should be undertaken in patients with multiple or metabolically active stones (i.e., stones that grow in size or increase in number within a year), in all children, in patients from

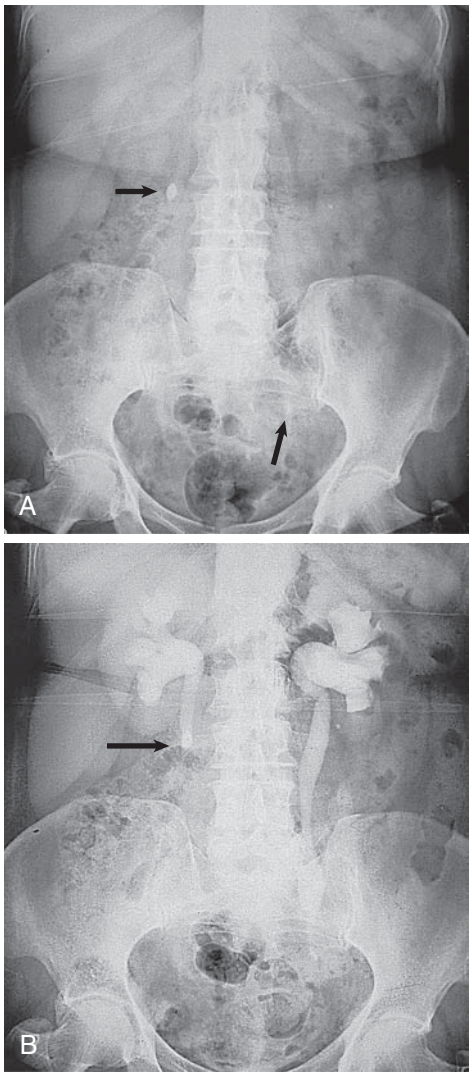

Figure 59-5 Obstructive uropathy resulting from nephrolithiasis in a patient with acute renal impairment. A, X-ray film showing a stone in the right upper ureter and a very small stone in the lower left ureter *(arrows).* **B,** Intravenous urogram at the same time showing bilateral hydronephrosis caused by ureteral obstruction.

demographic groups not typically prone to stone formation, and in those with stones other than those containing calcium.

The complete evaluation should include a measure of urine volume and the quantity of calcium, oxalate, phosphorus, uric acid, sodium, citrate, and creatinine excreted in a 24-hour urine collection (Table 59-2). Urine creatinine is useful in assessing adequacy of the collection; men should excrete more than 15 mg/kg (132.6 µmol/kg) and women should excrete more than 10 mg/kg (88.4 µmol/kg) daily. Patients should be encouraged to perform the urine collection on a typical day while eating a typical diet, although many patients prefer to collect the urine on weekends when their diet and habits may differ from those during usual workdays. Specialized testing, such as the use of high- or low-calcium diets, is not recommended.[20] Careful instructions should be given to avoid overcollection or undercollection. Patients should be instructed to flush the first morning urine and collect all urine for the next 24 hours including the second morning urine.

A disadvantage of the standard 24-hour urine collection is that laboratories vary in the preservatives required to process the various constituents. Many require more than one collection to measure all

Optimal 24-Hour Urine Values in Recurrent Nephrolithiasis	
24-Hour Urine Values	
Volume	>2 to 2.5 l
Calcium	<4 mg/kg (0.1 mmol/kg), ~300 mg (7.5 mmol) in men, ~250 mg (6.3 mmol) in women
Oxalate	<40 mg (0.36 mmol)
Uric acid	<750 mg (4.5 mmol) in women and <800 mg (4.7 mmol) in men (can be pH dependent)
Citrate	>320 mg (17 mmol)
Sodium	<3000 mg (<130 mmol)
Phosphorus	<1100 mg (35 mmol)
Creatinine	>10 mg/kg (88 µmol/kg) in women and >15 mg/kg (132 µmol/kg) in men, if specimen is a complete collection
Urine Supersaturation Values	
Calcium oxalate supersaturation	<5
Calcium phosphate supersaturation	0.5-2
Uric acid supersaturation	0-1

Table 59-2 Evaluation of nephrolithiasis: optimal 24-hour urine values.

the urinary constituents, reducing compliance and therefore the accuracy of the results.

A better approach available in some laboratories is to undertake a 24-hour urine collection for quantification of supersaturation for the common solid phases of calcium oxalate, brushite (calcium phosphate), and uric acid (see Table 59-2). Urine for supersaturation analysis has been shown to correlate well with stone composition.[34] Determination of supersaturation is far more informative than evaluation of the individual urinary constituents.

Patients can bring their specimens to a local laboratory or may directly mail them to specialized laboratories that measure calcium, oxalate, citrate, uric acid, creatinine, sodium, potassium, magnesium, sulfate, phosphorus, chloride, urine urea nitrogen, and pH. Supersaturation is calculated with a computer program such as EQUIL2.[35] Calculation of supersaturation from a 24-hour urine specimen will provide values lower than the peak postprandial supersaturation and peak nighttime supersaturation, either of which may initiate stone formation. Patients should stop taking any vitamin C or multivitamins containing more than 100 mg of vitamin C for at least 5 days before the urine collection because the antioxidants in the vitamin may interfere with the assay. Only undersaturated urine ensures that stones will not recur; the risk of stone formation rises with increasing supersaturation.

JESS (Joint Expert Speciation System) is another program that measures the concentration of the various complexes in solution under many different conditions. It may prove to be more accurate than supersaturation analysis but is currently used for research purposes only.[36,37]

General Treatment

Intervention for stone removal may be required when pain, obstruction, and/or infection resulting from nephrolithiasis do not respond to conservative management. Surgical management of stones includes extracorporeal shock wave lithotripsy and both endoscopic and percutaneous surgical removal of stones (see Chapter 60). The risk for developing renal impairment varies with the type of stone, and this must be considered in planning management.[38]

Medical Management

Patients who are seen by stone "specialists" often have a decrease in stone recurrence even without pharmacologic intervention.[39] This phenomenon, termed the "stone clinic effect," is likely a result of modifications in diet and fluid intake. These nonpharmacologic measures include an increase in fluid intake, which increases urine volume; restriction of dietary sodium, which leads to a reduction of urine calcium excretion; restriction of animal protein, which also leads to a reduction of urine calcium excretion and an increase in excretion of the calcification inhibitor citrate; and ingestion of an age- and gender-appropriate amount of dietary calcium. Although dietary calcium restriction continues to be prescribed by many physicians, increasing evidence indicates that this is not beneficial and can actually increase the rate of stone formation (see the later discussion of calcium stones).[3,26]

Fluid Intake An increase in urine volume to more than 2 to 2.5 L daily has been proven to reduce the incidence of stones.[39-41] Large urine volumes will reduce calcium oxalate supersaturation, as well as precipitation of other crystals. Increased fluid intake to augment urine volume is also a mainstay of therapy for patients with uric acid and cystine stones. The period of maximum risk for stone formation is at night, when urine concentration is physiologically increased. Patients should be encouraged to drink enough fluid in the evening to provoke nocturia and then drink further fluid before returning to bed.

Salt Intake Urine sodium excretion directly correlates with urine calcium excretion[1,2]; thus, dietary salt restriction is associated with decreased urine calcium excretion. Patients should be instructed to limit daily sodium intake to 2 g (87 mmol sodium).

Dietary Protein Animal protein ingestion increases the frequency of renal stone formation by a number of mechanisms. Metabolism of certain amino acids leads to generation of sulfate ions, which render urinary calcium ions less soluble.[42,43] The metabolic acidosis that results from protein ingestion causes calcium release from bone and a consequent increase in the filtered load of calcium.[42,43] Acidosis also decreases tubular calcium reabsorption, resulting in hypercalciuria. Urinary citrate excretion is also pH dependent, with acidosis leading to a decrease in citrate excretion. The result of increased animal protein intake is an increase in urinary calcium excretion that is rendered less soluble because of concomitant sulfate excretion and hypocitraturia. Low urine pH, coupled with increased uric acid excretion from the metabolism of animal protein, can result in uric acid lithiasis. For these reasons stone formers should consume only a moderate-protein diet (0.8 to 1.0 g/kg daily).[1] Dietary fructose may also increase uric acid lithiasis.[30]

Dietary Calcium Despite conventional wisdom, several studies have demonstrated a decrease in stone incidence when people consume diets adequate in calcium.[41,44-46] This beneficial effect has been attributed to intestinal binding of ingested oxalate (which is highly lithogenic) by dietary calcium. Although women have reduced stone formation while ingesting an age-appropriate amount of dietary calcium, this benefit may not extend to those taking calcium in the form of calcium supplements.[47] The data are inconsistent as to whether calcium supplements increase the risk of nephrolithiasis.[48,49] Some have postulated that any increased risk may be a result of timing the supplemental calcium ingestion apart from meals, which would enhance calcium absorption without reducing oxalate

absorption. In addition, the calcium supplements may dissociate rapidly, leading to rapid absorption, increased filtered calcium load, and transitory hypercalciuria, leading to increased supersaturation. We advise patients that it is best to obtain calcium from dairy products rather than supplements.

Some, but not all, recent studies have demonstrated that women ingesting calcium supplements have a great risk of cardiovascular disease and death.[51-52] In one long-term study of more than 60,000 Swedish women, those with a dietary calcium intake exceeding 1400 mg/day had an increased risk of cardiovascular mortality with a hazard ratio of 1.49 (1.09-2.02, 95% confidence interval [CI]). The risk for all-cause mortality rose to 2.57 (1.19-5.55, 95% CI) when any calcium tablet supplements were added to this high dietary intake.[50] Bolland and colleagues reviewed cardiovascular mortality in over 15 studies involving calcium supplementation versus placebo. They noted an increased risk of myocardial infarction in those randomized to calcium supplements with a hazard ratio of 1.31 (1.02-1.67, 95% CI) that rose to 1.85 (1.28-2.67, 95% CI) in patients already taking more than 805 mg of dietary calcium daily.[51] The Institute of Medicine recently adjusted their recommended allowance of calcium to 1000 mg daily for adults older than 19 years and to 1200 mg for women over age 50 years.[53] As noted earlier, we generally recommend that women take the appropriate amount of calcium in the form of food with limited supplement intake, except in cases of severe osteoporosis with insufficient dietary intake.

Previously, hypercalciuric patients were divided into a number of groups including those with excessive renal calcium excretion ("renal leak") and those who absorbed excessive amounts of calcium via the gastrointestinal tract ("absorptive hypercalciuria"). However, it is apparent that hypercalciuric patients generally do not have a transport defect limited to a single site; they appear to have a systemic dysregulation of calcium transport at the major calcium transporting sites, the intestine, kidney, and bone. In both hypercalciuric rats and in humans placed on a low-calcium diet, there is a continuous, wide spectrum of calcium excretion. Hypercalciuric patients may appear to have renal leak on one examination and absorptive hypercalciuria on another.[1,2] Some patients excrete more calcium than they consume, indicating a negative total body calcium balance. This calcium must be derived from the mineral phases of bone, which contain by far the largest repository of calcium in the body.[27] Support for the use of an age- and gender-appropriate amount of dietary calcium was recently provided by a randomized prospective study comparing the rate of stone formation in men assigned a low-calcium diet with those assigned a normal-calcium, low-sodium, and low–animal protein diet.[26] The men assigned the low-calcium diet were twice as likely to have recurrent stones over 5 years compared with those on the normal-calcium, low-sodium, and low–animal protein diet. Urinary calcium oxalate supersaturation also diminished more rapidly in those on the higher-calcium diet and remained lower than that of men on the low-calcium diet for most of the 5-year study. This reduction in supersaturation was the result of a greater fall in urinary oxalate in the men eating the normal-calcium, low-sodium, and low–animal protein diet.[26,54]

Patients prescribed a low-calcium diet can avoid excessive hyperoxaluria when adequately instructed to also consume a low-oxalate diet.[55] Some contend that this approach may benefit patients with excessive intestinal absorption of calcium associated with severe hypercalciuria by allowing calcium restriction without the risk of significant osteopenia. We recommend, however, an age- and gender-appropriate calcium intake, best derived from a diet containing an adequate amount of dairy products. Because stone formation can be reduced with normal calcium intake and there is a risk of bone demineralization with calcium restriction, we consider the low-calcium diet to be obsolete.[26,27,54] Dietary calcium intake exceeding the age and gender recommendations and calcium supplements should be avoided in patients with calcium nephrolithiasis.

Vitamin D Given the great degree of vitamin D deficiency and insufficiency in Northern latitudes, vitamin D supplementation is very common.[56] Patients and physicians often express concern that this might exacerbate nephrolithiasis, given the role of vitamin D in mineral metabolism. In fact, studies have shown no association between vitamin D supplementation or serum 25-hydroxyvitamin D levels and calcium excretion, nor an increased rate of stone formation in hypercalciuric patients on vitamin D supplementation. It is reasonable to treat vitamin D deficiency (25-hydroxyvitamin D levels below 20 ng/ml) with either cholecalciferol or ergocalciferol with no fear of worsening hypercalciuria or increasing stone formation.[57]

SPECIFIC TYPES OF STONES

Calcium Stones

Calcium-containing kidney stones constitute approximately 70% of all stones formed. Most calcium stones are composed of calcium oxalate, either alone or in combination with calcium phosphate or uric acid. A small percentage of stones are composed entirely of calcium phosphate.[1] Most calcium stones do not exceed 1 to 2 cm in width, although surgical intervention is often required for stones greater than 5 mm.

Calcium-based stones most often develop as a result of excessive excretion of calcium (hypercalciuria). Other causes of calcium stones are excessive excretion of oxalate (hyperoxaluria) and uric acid (hyperuricosuria), insufficient citrate excretion (hypocitraturia), renal tubular acidosis, certain medications, and congenital abnormalities of the genitourinary tract (Fig. 59-6). Specific therapy for patients with calcium stones depends on the underlying metabolic abnormalities detected on evaluation. Nonspecific or general therapy as outlined earlier should always be instituted; however, more definitive treatment is often required to significantly decrease the rate of recurrent stone formation.

Hypercalciuria

Etiology Hypercalciuria for which a causative metabolic abnormality cannot be determined is called *idiopathic hypercalciuria.* Affected patients typically have excessive intestinal calcium absorption and may also have decreased renal tubular calcium reabsorption and increased bone resorption. The cause of this systemic disorder in calcium transport has, in hypercalciuric stone–forming rats and in humans, been linked to an excessive number of receptors for vitamin D.[58-60] Metabolic disorders leading to an elevation in serum calcium, parathyroid hormone, or $1,25(OH)_2D$ (1,25-dihydroxyvitamin D) also may result in hypercalciuria.

Treatment For hypercalciuria the usual first-line therapy is a thiazide diuretic, which acts to reduce urinary calcium. In the United States, chlorthalidone 25 to 50 mg is the drug of choice, as it requires only once daily administration. Indapamide 1.25 to 2.5 mg daily does not tend to raise serum lipids as much as other thiazides and may be preferred for patients with cardiac risk factors or elevated serum lipids. On commencing these medications, patients should be instructed to increase their dietary potassium intake, and a serum potassium level should be checked 7 to 10 days later. If the level of potassium is low, oral potassium supplementation should be initiated. Potassium citrate is preferred over potassium chloride because citrate forms complexes with urinary calcium, further lowering supersaturation. However, most patients find potassium citrate

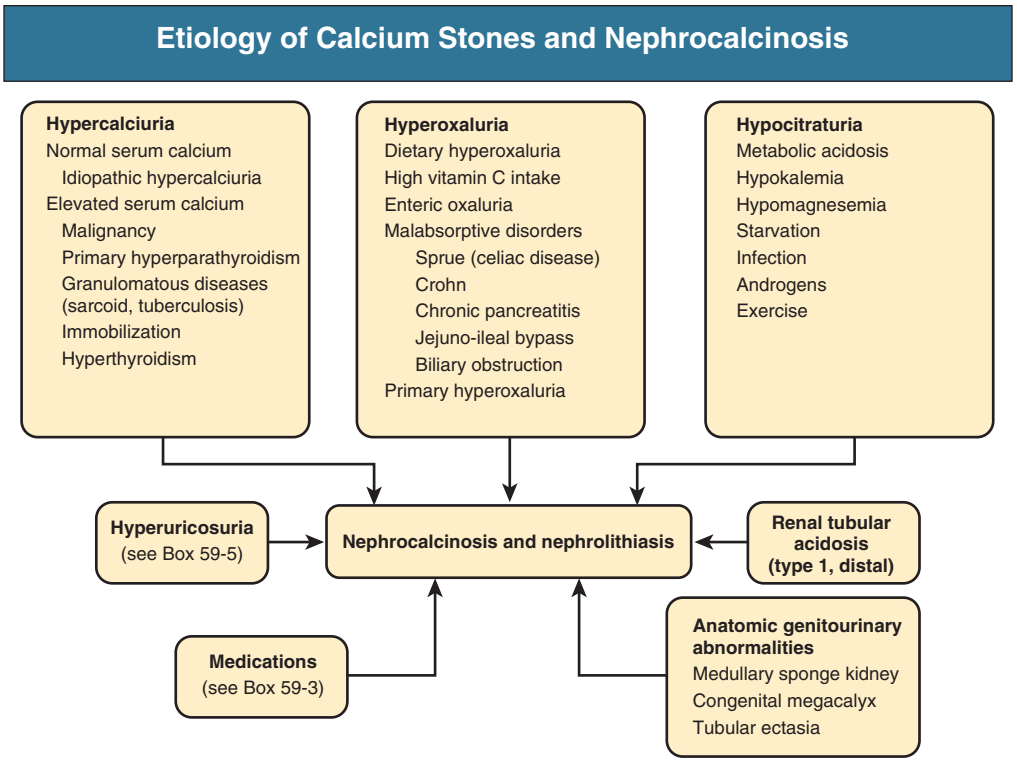

Figure 59-6 **Etiology of calcium stones and nephrocalcinosis.**

liquid preparations unpalatable. A wax matrix tablet of potassium citrate is well tolerated and is available in some countries. In general, patients are able to maintain a normal serum potassium level with potassium citrate 20 to 40 mmol daily. The serum potassium and bicarbonate levels should be rechecked 7 to 10 days later for further dosage adjustment. Because citrate is a base, potassium citrate may excessively raise the serum bicarbonate level or urinary pH, and a change to potassium chloride may be required.

The 24-hour urine calcium, sodium, and citrate should be rechecked after several weeks. If the calcium excretion remains elevated, the thiazide dose should be increased. However, if the sodium excretion also remains high, patients should be encouraged to limit their sodium intake further because they will not have an adequate response to the diuretic on a high-sodium diet. If the serum potassium remains low despite supplementation or the calcium excretion remains high despite increased thiazide dosing, addition of a potassium-sparing diuretic may be required to increase serum potassium. Triamterene should not be used for treatment of hypokalemia because it can precipitate into stones. Amiloride (starting dose 5 mg daily) is a better option to treat thiazide-induced hypokalemia.[1,2]

Dietary Recommendations See the discussion of general treatment.

Hyperoxaluria

Etiology Elevated urinary oxalate results from excessive dietary intake (dietary oxaluria), gastrointestinal disorders that can lead to malabsorption (enteric oxaluria), or an inherited enzyme deficiency that results in excessive metabolism of oxalate (primary hyperoxaluria) (see Fig. 59-6).[61]

Dietary excess of oxalate generally does not raise urinary oxalate above 60 mg/24 h (0.54 mmol/24 h). Enteric oxaluria may occur when malabsorption results in excessive colonic absorption of oxalate, as a result of sprue (celiac disease), Crohn disease, chronic pancreatitis, or short bowel syndrome or after bariatric surgery. The anion exchange transporter Slc26a6 appears responsible for intestinal oxalate secretion, and mice with targeted inactivation of this transporter have hyperoxaluria.[62] It is not yet known whether patients with enteric hyperoxaluria have mutations in Slc26a6. Urinary oxalate is generally more than 60 and can exceed 100 mg/24 h (0.54 and 0.9 mmol/24 h).[63] In primary hyperoxaluria, the tremendous oxalate production results in widespread calcium oxalate deposition throughout the body at an early age. This infiltration of calcium oxalate into organs can result in cardiomyopathy, bone marrow suppression, and renal failure. Urinary oxalate values may range from 80 to 300 mg/24 h (0.72 to 2.70 mmol/24 h).

There are three types of primary hyperoxaluria with unique enzymatic defects in the liver glyoxylate pathway.[64] In type 1, the defective enzyme is alanine–glyoxylate aminotransferase, encoded by the gene *AGXT* on chromosome 2; this accounts for approximately 80% of cases. Type 2 tends to be a milder disorder and is caused by mutations in the *GRHPR* gene on chromosome 9, which results in failure of glyoxylate reduction to glycolate; this accounts for approximately 10% of the cases. Type 3 is a result of mutations in the gene that encodes the mitochondrial 4-hydroxy-2-oxoglutarate aldolase enzyme, which catalyzes the cleavage of 4-hydroxy-2-oxoglutarate to pyruvate and glyoxylate and accounts for about half of the remaining cases.[65]

Treatment of Dietary and Enteric Hyperoxaluria Treatment of dietary oxaluria consists of dietary oxalate restriction. Patients should be given a list of foods that have high oxalate content to avoid or eat in moderation (see Box 59-4). Calcium carbonate 1 to 1.5 g may be added at each meal and snack to bind intestinal oxalate and prevent its absorption.

Specific therapy for the malabsorptive disorder, such as a gluten-free diet for patients with sprue, is the first line of treatment for enteric hyperoxaluria. More generalized therapy for steatorrhea, such as a low-fat diet, cholestyramine, and administration of medium-chain triglycerides, may reduce fat malabsorption as well

as oxalate absorption and subsequent excretion. The low-oxalate diet and mealtime calcium carbonate prescribed for patients with dietary oxaluria is also helpful for these patients. The diarrhea associated with these disorders may result in low urine volumes, hypokalemia, hypocitraturia, and hypomagnesuria. Patients should therefore be advised to increase their fluid intake and to take potassium citrate (in this case, the liquid, although unpalatable, is better absorbed than the tablets) as well as a magnesium supplement. Magnesium also serves as a urinary stone inhibitor and can be given as magnesium gluconate 0.5 to 1 g every 8 hours or as magnesium oxide 400 mg every 12 hours.

Treatment of Primary Hyperoxaluria Primary hyperoxaluria type 1 (PH1) is a severe disorder that can be cured only with liver transplantation to replace the defective hepatic enzyme. Pyridoxine (vitamin B_6 in doses ranging from 2.5 to 15 mg/kg/24 h) may reduce oxalate production in patients with PH1. Efforts should be made to render the calcium and oxalate more soluble in the urine by raising the urinary pH (to at least 6.5) and giving supplemental citrate and magnesium. Potassium citrate and magnesium supplementation can be prescribed as noted earlier. Orthophosphate is also an effective inhibitor of urinary calcium oxalate precipitation and can be safely administered in patients with a glomerular filtration rate (GFR) exceeding 50 ml/min. Because oxalate is poorly excreted in CKD and is not removed well by dialysis, renal transplantation serves not only to improve renal function, but also to improve oxalate excretion and diminish systemic oxalosis.[14,66]

Oxalobacter formigenes primarily uses oxalate for cellular metabolism.[67,68] Calcium oxalate stone formers who are colonized with *O. formigenes* have lower urine oxalate levels than those who are not colonized.[67] A small human therapeutic trial involving administration of *O. formigenes* resulted in a modest decrease in urinary oxalate in some patients.[68] Further studies with larger numbers of patients and an end point of reduction of recurrent stone formation will be necessary before this novel approach becomes accepted therapy.

Hypocitraturia

Citrate inhibits stone formation. A number of conditions reduce urinary citrate excretion, predisposing to stone formation. Excessive protein intake, hypokalemia, metabolic acidosis, exercise, hypomagnesemia, infections, androgens, starvation, and acetazolamide have all been implicated in decreased urinary citrate excretion. Therapy involves treatment of the underlying condition and potassium citrate supplementation. The potassium salt is preferred to sodium citrate because sodium promotes renal calcium excretion. Potassium citrate 15 to 25 mmol two or three times daily is required, and tablets are considered by most patients to be more palatable than the liquid preparation. In patients with renal impairment, serum potassium should be monitored carefully, and dose reduction may be needed if hyperkalemia develops.[14,69]

Distal Renal Tubular Acidosis

Patients with distal (type 1) renal tubular acidosis have impaired distal tubular excretion of hydrogen ions with a non–anion gap metabolic acidosis and alkaline urine (see Chapter 12). The acidosis causes calcium and phosphate to be released from bone with an ensuing increase in renal excretion of these ions. The acidosis also leads to an increase in citrate reabsorption by the proximal tubule. The end result is a high urinary pH, hypocitraturia (urinary citrate generally <100 mg/24 h [0.53 mmol/24 h]), and increased renal excretion of calcium and phosphate, all of which increase the propensity for calcium phosphate precipitation. Nephrocalcinosis in this setting is not uncommon because of calcium precipitating in the alkaline tubule fluid. The metabolic acidosis and hypocitraturia should be treated with a combination of sodium citrate (or bicarbonate) and potassium citrate (or bicarbonate). Often large amounts, 1 to 2 mmol/kg daily in two or three divided doses, are required to neutralize the acidosis.[1] Citrate is generally preferred to bicarbonate by patients because it does not produce carbon dioxide on contact with stomach acid with resultant gastrointestinal bloating. However, citrate is generally more expensive than bicarbonate.

Hyperuricosuria

Calcium oxalate crystals often nucleate around other crystal types such as uric acid. Hyperuricosuria contributes to nephrolithiasis in 10% to 15% of calcium stones. Patients with hyperuricosuric calcium oxalate nephrolithiasis have hyperuricosuria with normal urinary calcium and oxalate, but often a higher urinary pH (>5.5) than patients with pure uric acid stones. Therapy for hyperuricosuria consists of increased fluid intake and reduced dietary purine intake. If uric acid excretion remains elevated, allopurinol should be initiated at 100 to 300 mg daily.[1]

Uric Acid Stones

Epidemiology

The prevalence of uric acid stones depends greatly on geographic location. In the United States, uric acid stones constitute 5% to 10% of all stones formed, whereas in Mediterranean and Middle Eastern countries uric acid stones may constitute as much as 75% of stones. The stones are radiolucent and therefore poorly visible on plain radiographs. They are detectable on ultrasound and CT, and as filling defects on IVU (Fig. 59-7).

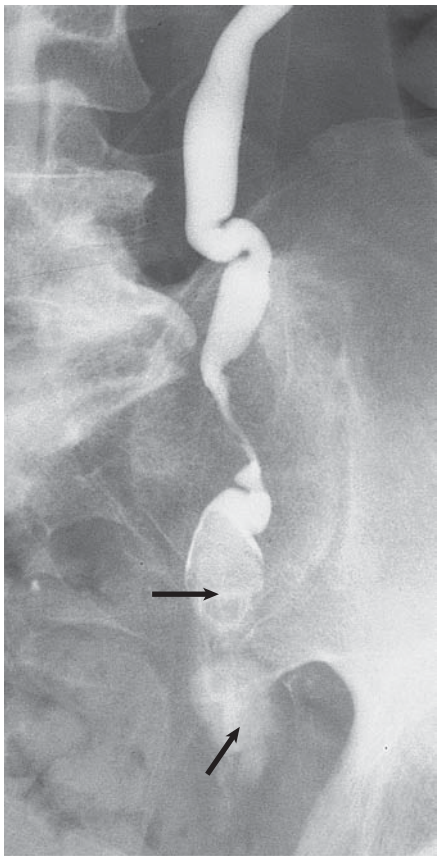

Figure 59-7 Radiolucent urate calculi. Antegrade pyelogram showing multiple radiolucent uric acid stones *(arrows)* obstructing the lower ureter.

Etiology and Pathogenesis

Causes of hyperuricosuria include excessive dietary purine or protein intake, disorders associated with cellular breakdown (tumor lysis syndrome, myeloproliferative disorders, hemolytic anemia), gout, uricosuric medications, certain inborn errors of metabolism, and possibly excessive fructose intake.

Three major factors influence uric acid stone formation: low urine pH, low urine volume, and elevated urinary uric acid levels (Box 59-5). Of the three, low urine pH is the principal metabolic disorder found in patients with uric acid nephrolithiasis. Uric acid is poorly soluble at pH below 5.5. Solubility increases with urine alkalinity such that at urine pH 6.5, urine can contain over six times the quantity of uric acid present at pH 5.3, without exceeding supersaturation. The rising incidence of obesity and insulin resistance in the United States has led to a parallel increase in uric acid lithiasis. The urinary acidosis is likely a result of impaired ammoniagenesis, which results in excessive excretion of unbuffered acid and a very low urine pH.[7,11,70,71]

Treatment

Treatment of uric acid stones involves increasing urine pH and volume as well as decreasing uric acid excretion. Alkaline urine not only can prevent uric acid stone formation, but may also result in stone dissolution. To raise urine pH, potassium citrate is recommended. While sodium bicarbonate alkalinizes the urine and enhances uric acid solubility, the added sodium increases sodium urate formation, which serves as a nidus for calcium oxalate precipitation. Potassium citrate 40 to 50 mmol/day in divided doses is given, increasing the dose as necessary to achieve a urine pH of 6.5 to 7. Patients should monitor pH with urine dipsticks at various times of the day and adjust the dosage accordingly. If urine pH remains low despite potassium citrate exceeding 100 mmol daily, or if that dose results in hyperkalemia, acetazolamide may be added. This carbonic anhydrase inhibitor produces an alkaline urine similar to that seen in renal tubular acidosis. Patients should be cautioned not to exceed urine pH 7 because this may result in calcium phosphate precipitation.

A low-purine and low–animal protein diet is also useful in raising urinary pH and decreasing uric acid excretion (see Box 59-4). If uric acid excretion remains high despite dietary intervention, as in patients with disorders of cellular catabolism, allopurinol should be prescribed, 100 mg increasing to 300 mg daily as needed to keep urinary uric acid excretion below 750 mg/24 h (4.5 mmol/24 h). See Box 59-4 for high-purine foods to avoid.[72]

Factors Associated with Uric Acid Stone Formation

Low Urine pH (≤5.5)
- High–animal protein diet
- Diarrhea
- Insulin resistance (high body mass index, metabolic syndrome, type 2 diabetes)

Low Urine Volume
- Inadequate fluid intake
- Excessive extrarenal fluid losses
  - Diarrhea
  - Insensible losses (e.g., perspiration)

Hyperuricosuria
- Excessive dietary purine intake
- Hyperuricemia
  - Gout
  - Intracellular-to-extracellular uric acid shift
    - Myeloproliferative disorders
    - Tumor lysis syndrome
- Inborn errors of metabolism
  - Lesch-Nyhan syndrome
  - Glucose-6-phosphatase deficiency

Medications
- See Box 59-3.

Box 59-5 Factors associated with uric acid stone formation.

Struvite Stones

Struvite stones are also referred to as "infection stones" or "triple phosphate stones." The stones grow rapidly to a large size, can reduce renal function in the affected kidney, and are difficult to eradicate. Because of the significant morbidity in patients with struvite stones, they have also been termed "stone cancer." Most staghorn calculi, large stones that penetrate more than one renal calyx, are composed of struvite. Their formation requires the presence of urease-producing bacteria in the urine (Box 59-6).[73]

Etiology and Pathogenesis

Struvite stones are composed of magnesium ammonium phosphate and calcium carbonate apatite. They form when urease production by certain urinary bacteria breaks down urea to ammonium (NH_4^+) and a carboxyl (OH^-) group. The urine becomes quite alkaline; urinary phosphate becomes insoluble and forms a solid phase with magnesium, calcium, and the ammonium. Women are more prone to struvite nephrolithiasis than men because of an increased propensity for UTI. Others predisposed to developing struvite stones through infections or urinary stasis include patients with indwelling urinary catheters, neurogenic bladders, genitourinary tract anomalies, and spinal cord lesions. An alkaline urine (pH 7), urine culture of urease-producing bacteria, and large stones suggest the diagnosis of struvite nephrolithiasis.[73]

A number of gram-negative and gram-positive bacteria have been implicated in urease production and consequent struvite formation, with the most common being *Proteus* species (see Box 59-6). *Escherichia coli,* which is frequently present in urine cultures, is not a urease producer. If there is a strong suspicion for struvite stones but no organism is detected in the urine, a specific culture request for

Factors Associated with Struvite Stone Formation

- Urease-producing bacteria
  - *Proteus*
  - *Haemophilus*
  - *Yersinia species*
  - *Staphylococcus epidermidis*
  - *Pseudomonas*
  - *Klebsiella*
  - *Serratia*
  - *Citrobacter*
  - *Ureaplasma*
- Elevated urinary pH

Box 59-6 Factors associated with struvite stone formation. *Escherichia coli* is not a urease producer.

Ureaplasma urealyticum should be considered, because it does not grow on routine culture media.

Treatment

Struvite stones require aggressive medical and surgical management. Antibiotic therapy is important to reduce further stone growth and for stone prevention. Bacteria will remain in the stone interstices, however, and stones will continue to grow unless chronic antibiotic suppression is maintained or the calculi are completely eradicated. Given the need for complete stone removal to effect a cure, early urologic intervention is advised. Stones smaller than 2 cm may respond well to extracorporeal shock-wave lithotripsy (ESWL); however, larger stones will likely require percutaneous nephrolithotomy (PCNL), often in combination with ESWL (see Chapter 61). Any stone fragments retrieved should be cultured, and culture-specific antibiotics continued. Once the urine is sterile, usually approximately 2 weeks after initiation of therapy, the dose is halved. Monthly urine cultures should be performed, and if they remain sterile for 3 consecutive months, antibiotics may be discontinued, although surveillance urine cultures should continue monthly for a full year.[74]

Adjunct medical therapies include urease inhibitors and chemolysis. The most commonly used urease inhibitor is acetohydroxamic acid. By inhibiting urease, these agents retard stone growth and prevent new stone formation. Unfortunately, they have numerous side effects that limit their use, although adverse effects resolve on discontinuation of the drug. In addition, they require adequate renal clearance to be effective and therefore are not useful in patients with CKD (estimated GFR <60 ml/min).[73] Chemolysis involves irrigation of the kidney via a nephrostomy tube or the ureter with a solution designed to dissolve the stones. The most common solution is 10% hemiacidrin, which contains carbonic acid, citric acid, D-gluconic acid, and magnesium at pH 3.9. Lavage chemolysis is controversial because it has previously been associated with a high mortality rate, but it is now considered safe with appropriate monitoring for UTI, assessment of obstruction to flow by intrapelvic pressure measurement, and serum magnesium levels. Although not a treatment of choice for large stones, it may be useful when surgical techniques have been effective but have left residual stone fragments.

Cystine Stones

Cystinuria is an autosomal disorder in which there is a tubular defect in dibasic amino acid transport, resulting in increased cystine, ornithine, lysine, and arginine excretion (see Chapter 50). The pattern of inheritance may be autosomal recessive or autosomal dominant with incomplete penetrance. The stone disease is usually clinically manifest by the second and third decades of life. Because of the high sulfur content of the cystine molecule, the stones are apparent on plain radiographs (see Fig. 59-4, *A*) and will often present as staghorn calculi or multiple bilateral stones.

Cystine is poorly soluble, only approximately 300 mg/l (1.25 mmol/l) at a neutral pH. Normal cystine excretion of approximately 30 to 50 mg (0.12 to 0.21 mmol) per day is readily soluble in the usual daily urine output of approximately 1 l. However, homozygote cystinurics often excrete 250 to 1000 mg (1.04 to 4.20 mmol) of cystine per day, with heterozygotes excreting an intermediate amount. Treatment is directed at decreasing the urinary cystine concentration below the limits of solubility. Because the dietary precursor of cystine, methionine, is an essential amino acid, it is impractical to significantly reduce intake. Increasing urine volume so that cystine remains below the limits of solubility sometimes requires 4 l of urine per day. A low-sodium diet has been reported to reduce urine cystine excretion, although the mechanism by which this occurs is not clear.[75] Increasing urine pH above 7.5 will increase cystine solubility, but this is difficult to achieve on a long-term basis. D-Penicillamine (starting dose 250 mg daily, maximum dose 2 g daily) or tiopronin (800 mg/day in three divided doses) will both bind cystine and reduce urinary supersaturation; however, side effects may limit their use. The angiotensin-converting enzyme inhibitor captopril may be effective by forming a thiol-cysteine disulfide bond that is more soluble than cystine.[76]

Stones Associated with Melamine Exposure

By late 2008, more than 50,000 Chinese children younger than 3 years had been reported to have kidney stones associated with contaminated milk products. Powdered milk and infant formulas were noted to contain melamine, a nitrogenous substance synthesized from urea that increases the apparent protein content of the product.[12] Risk factors for nephrolithiasis after melamine exposure may include volume depletion, small body size, uricosuria, and low urine pH.

Although affected children often were presented with dysuria and hematuria, many children who were subsequently screened were asymptomatic despite kidney stones identified on ultrasound.[12] On urinalysis some children exhibited fan-shaped crystals. The kidney stones formed were radiolucent and fragile. Many were composed of a combination of uric acid with melamine and were amenable to dissolution by hydration and alkalinization. In animal studies of melamine exposure, the distal tubular crystal deposition may lead to tubulointerstitial inflammation and fibrosis. Whether a similar process may occur in humans is unknown.[12]

NEPHROCALCINOSIS

Nephrocalcinosis refers to augmented calcium content within the kidney.[15,77] This disorder may be symmetric or, in anatomic disorders such as medullary sponge kidney, may involve only a single kidney.

Etiology and Pathogenesis

Medullary Nephrocalcinosis

Medullary nephrocalcinosis in which the calcification tends to occur in the area of the renal pyramids accounts for the majority of cases of nephrocalcinosis. It is typically associated with elevated urinary calcium, phosphate, and oxalate, or it can occur with alkaline urine (Box 59-7). Any disorder that can lead to hypercalcemia and/or hypercalciuria may be implicated. Instead of stone formation, smaller parenchymal calcifications deposit in the medulla, which are usually bilateral and relatively symmetric (Fig. 59-8). Some metabolic disorders, particularly oxalosis caused by primary hyperoxaluria, can result in both medullary and cortical nephrocalcinosis[77] (Fig. 59-9).

In adults, the most common causes of medullary nephrocalcinosis are primary hyperparathyroidism, distal renal tubular acidosis, and medullary sponge kidney (see Chapter 47), as well as medications including acetazolamide, amphotericin, and triamterene (see Box 59-3).

Whereas a similar range of disorders can be seen in children, the most common associations are with furosemide therapy and the hereditary disorders associated with hypercalciuria.[15,22] Furosemide, when used in premature neonates and older infants with congestive heart failure, can result in nephrocalcinosis with or without hypercalciuria. The lesions often resolve with discontinuation of therapy. A normal calcium-creatinine ratio at the time of diagnosis of nephrocalcinosis (approximately 0.40 [mg/mg] in premature infants) appears to be a good predictor of resolution.

Causes of Nephrocalcinosis

Medullary

Disturbed Calcium Metabolism

- Hyperparathyroidism
- Sarcoidosis
- Milk-alkali syndrome
- Rapidly progressive osteoporosis
- Idiopathic hypercalciuria

Other Tubular Disease

- Distal (type 1) renal tubular acidosis
- Oxalosis*
- Dent disease (X-linked hypercalciuric nephrolithiasis)
- X-linked hypophosphatemic rickets
- Bartter syndrome
- Hypomagnesemia-hypercalciuria syndrome

Anatomic Disease

- Medullary sponge kidney
- Papillary necrosis

Medications

- Acetazolamide
- Amphotericin
- Triamterene

Cortical

- Cortical necrosis
- Transplant rejection
- Chronic glomerulonephritis
- Trauma
- Tuberculosis
- Oxalosis*

Box 59-7 Causes of nephrocalcinosis. *Oxalosis typically causes both cortical and medullary nephrocalcinosis.

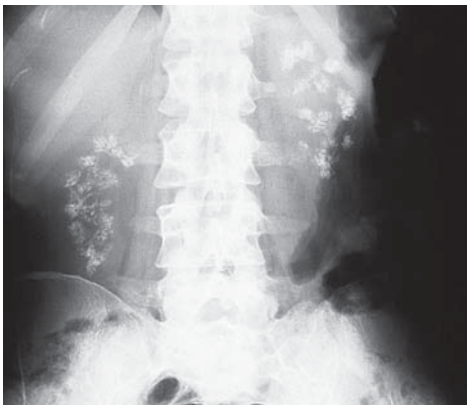

Figure 59-8 Medullary nephrocalcinosis. Plain radiograph showing bilateral metastatic medullary nephrocalcinosis in a patient with distal renal tubular acidosis.

Figure 59-9 Nephrocalcinosis. Dense cortical and medullary calcification in the shrunken kidneys of a patient with oxalosis and longstanding renal failure.

There are many uncommon hereditary disorders associated with nephrocalcinosis including X-linked hypercalciuric nephrolithiasis, X-linked hypophosphatemic rickets, hypomagnesemia-hypercalciuria syndrome, and Bartter syndrome.

X-linked hypercalciuric nephrolithiasis is also termed Dent disease in the United Kingdom, low-molecular-weight proteinuria with hypercalciuria and nephrocalcinosis in Japan, and X-linked recessive hypophosphatemic rickets in Italy.[78] A number of mutations affecting the CLCN5 gene on the X chromosome have been identified that lead to inactivation of CLC-5 voltage-gated chloride channels. The result is a clinical syndrome typically affecting young boys and usually including hypercalciuria, nephrocalcinosis, nephrolithiasis, and hematuria, as well as low-molecular-weight proteinuria, glycosuria, aminoaciduria, hypophosphatemia, renal failure, and rickets.[78]

In X-linked hypophosphatemic rickets, the recommended treatment, with phosphate repletion and vitamin D, may itself result in hypercalcemia, hypercalciuria, and nephrocalcinosis. Thus only enough phosphate and vitamin D should be prescribed to allow bone growth and prevent symptomatic hypophosphatemia.

Another cause of medullary nephrocalcinosis in children is primary hypomagnesemia-hypercalciuria syndrome.[14,15,79] This rare autosomal recessive condition results from defective production of the cellular tight-junction protein paracellin-1. This claudin family protein is necessary for adequate calcium and magnesium reabsorption in the thick ascending limb (TAL) of the loop of Henle. Children typically present with symptoms of UTI (often with nephrolithiasis), polyuria, tetanic seizures (caused by hypomagnesemia), and muscle cramps and weakness. Hypercalciuria, hypermagnesuria, and a urinary concentrating defect also occur. Patients often have renal impairment and may require renal replacement therapy by the third decade of life. Sensorineural hearing disorders and ocular impairment may accompany the renal manifestations in a subset of patients. These inherited tubular disorders are discussed further in Chapter 50.

Cortical Nephrocalcinosis

Cortical nephrocalcinosis is usually the result of dystrophic calcification, which follows parenchymal tissue destruction rather than the precipitation of excessive urinary constituents. It is secondary to infarction, neoplasm, and infection. It is typically asymmetric and is usually localized to the renal cortex (Fig. 59-10). Causes of cortical nephrocalcinosis include transplant rejection, cortical necrosis, tuberculosis, ethylene glycol toxicity, and chronic glomerulonephritis.

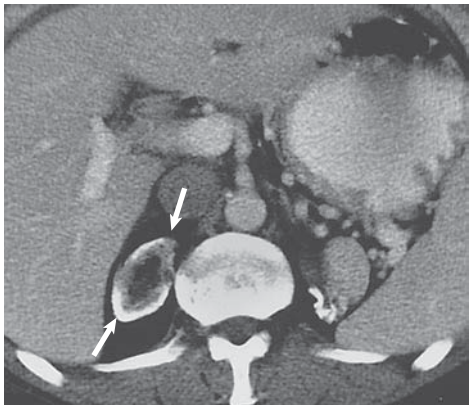

Figure 59-10 Cortical nephrocalcinosis. Noncontrast computed tomography (CT) showing cortical nephrocalcinosis *(arrows)* in the right kidney after cortical necrosis.

Clinical Manifestations

Patients who do not have nephrolithiasis associated with nephrocalcinosis are often asymptomatic. Ultrasound and CT scanning are sensitive diagnostic tests for both cortical and medullary nephrocalcinosis, demonstrating the parenchymal calcifications before they can be visualized on plain radiographs. The extent of calcification correlates poorly with renal function.

Treatment

Similarly to nephrolithiasis, treatment of nephrocalcinosis relies on therapy for the underlying disease, as well as measures to reduce hypercalcemia, hyperphosphatemia, and oxalosis, if possible. The goal of treatment is usually to prevent further deposits, because therapy cannot eradicate existing calcium deposits.

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CHAPTER 60

Urinary Tract Obstruction

Jeremy Hughes

DEFINITIONS

Obstructive uropathy refers to the structural or functional changes in the urinary tract that impede normal urine flow. *Obstructive nephropathy* refers to the renal disease caused by impaired flow of urine or tubular fluid. *Hydronephrosis* refers to dilation of the urinary tract. *Hydronephrosis* is not synonymous with *obstructive uropathy* because the former can occur without functional obstruction to the urinary tract and can be absent in established obstruction. Obstructive uropathy and nephropathy frequently coexist, and their management requires close collaboration between nephrologists and urologists. Some surgical aspects of obstruction to the urinary tract are discussed in Chapter 61.

Obstructive uropathy is classified according to the site, degree, and duration of the obstruction. Acute or chronic obstruction can occur anywhere in the urinary tract and includes intrarenal causes (casts, crystals) and extrarenal causes. Acute or chronic obstruction is further subdivided into upper urinary tract obstruction (usually unilateral obstruction occurring above the vesicoureteral junction) and lower urinary tract obstruction (usually bilateral obstruction located below the vesicoureteral junction). Complete obstruction of the urinary tract is termed *high grade,* whereas partial or incomplete obstruction is termed *low grade.*

Unilateral obstruction in a patient with two normal kidneys will not result in significant renal impairment because the contralateral kidney compensates. However, bilateral obstruction or the obstruction of a single functioning kidney will result in renal failure. In acute urinary tract obstruction, changes are mainly functional, whereas structural damage to the kidney results from more chronic obstruction. The kidney with acute functional changes may recover after the effective release of the obstruction, but structural changes may be permanent and lead to chronic renal impairment. Urinary tract obstruction remains a major cause of renal impairment worldwide in children and adults.

ETIOLOGY AND PATHOGENESIS

The causes of obstructive uropathy affecting the upper and lower urinary tracts are summarized in Table 60-1 and Box 60-1.

Congenital Urinary Tract Obstruction

Congenital urinary tract obstruction occurs most frequently in males, most commonly as a result of either posterior urethral valves or pelviureteral junction (PUJ) obstruction. If obstruction occurs early during development, the kidney fails to develop and becomes dysplastic. If the obstruction is bilateral, there is a high mortality rate as a result of severe renal failure. If the obstruction occurs later in gestation and is low grade or unilateral, hydronephrosis and nephron loss will still occur, but renal function may be sufficient to allow survival, and such patients may not present until later in childhood. Pelviureteral junction obstruction, if it is mild, may not present until adulthood and in some patients may be an incidental finding (Fig. 60-1). However, with increased use and improved sensitivity of antenatal scanning, congenital abnormalities of the urinary tract are now frequently identified early, allowing prompt postnatal (and in some cases antenatal) intervention to relieve the obstruction and hence to preserve renal function. Congenital causes of obstruction are discussed further in Chapter 52.

Acquired Urinary Tract Obstruction

Acquired urinary tract obstruction may affect either the upper or lower urinary tract and can result from either intrinsic or extrinsic causes. Intrinsic causes of obstruction may be intraluminal or intramural.

Intrinsic Obstruction

Intraluminal Obstruction Intraluminal obstruction may result from tubular intrarenal obstruction, such as the deposition of uric acid crystals in the tubular lumen after treatment for hematologic malignancies (tumor lysis syndrome). It may also occur with the precipitation of Bence Jones protein in myeloma and with the precipitation or crystal formation of a number of drugs, including sulfonamides, acyclovir, methotrexate, and indinavir. Uncommonly, patients with an underlying glomerulonephritis such as IgA nephropathy may develop severe glomerular hematuria with tubular obstruction from erythrocytes and acute renal dysfunction that typically resolves with time.

Extrarenal intraluminal obstruction in young adults is most commonly caused by renal calculi (see Chapter 59). Calcium oxalate stones are the most common and typically cause intermittent acute unilateral urinary tract obstruction but rarely result in marked chronic renal impairment. Less common causes of urinary lithiasis, such as struvite stones, uric acid stones, and cystinuria are often bilateral and hence more likely to cause long-term renal impairment. Renal calculi lodge more commonly in the calyx, PUJ, or vesicoureteral junction and at the level of the pelvic brim. Surgical management of stones is discussed in Chapter 61. Intraluminal obstruction can also result from a sloughed papilla after papillary necrosis, or blood clots after macroscopic hematuria (clot colic). Papillary necrosis may occur in diabetes mellitus, sickle cell trait or disease, analgesic nephropathy, renal amyloidosis, and acute pyelonephritis. Clot colic can occur with bleeding from renal tumors or arteriovenous malformations, after renal trauma, and in patients with polycystic kidney disease.

Intramural Obstruction Intramural obstruction can result from either functional or anatomic changes. Functional disorders include adynamic ureteral segments (usually at the junction of the ureter with the pelvis or bladder) and neurologic disorders. The latter may result in a contracted (hypertonic) bladder or a flaccid (atonic)

Causes of Upper Urinary Tract Obstruction

Intrinsic Causes	Extrinsic Causes
Intraluminal Intratubular deposition of crystals (uric acid, drugs) *Stones* Papillary tissue Blood clots Fungal ball	**Reproductive system** Cervix: *carcinoma* Uterus: *pregnancy, tumors,* prolapse, endometriosis, pelvic inflammatory disease Ovary: tumor, cysts Prostate: *carcinoma*
Intramural Functional: pelviureteral or vesicoureteral junction dysfunction Anatomic: tumors (benign or malignant) Infections, granulomas, strictures	**Vascular system** Aneurysms: aorta, iliac vessels Aberrant arteries: pelviureteral junction Venous: ovarian veins, retrocaval ureter **Gastrointestinal tract** Crohn disease Pancreatitis Appendicitis Diverticulitis Tumors **Retroperitoneal space** Lymph nodes Fibrosis: idiopathic, drugs, inflammatory or IgG4-related disease Tumors: primary or metastatic Hematomas Radiation therapy Surgical disruption or ureteral ligation

Table 60-1 Causes of upper urinary tract obstruction. The most common causes are in italics.

Causes of Lower Urinary Tract Obstruction

Urethral anatomic causes

Urethral strictures: trauma, *postinstrumentation*, infections such as gonococcal urethritis, nongonococcal urethritis, tuberculosis

Posterior urethral valves

Stones

Blood clots

Periurethral abscess

Phimosis

Paraphimosis

Meatal stenosis

Urethral functional causes

Anticholinergic drugs, antidepressants, levodopa

Prostate

Benign prostatic hypertrophy

Prostatic carcinoma

Bladder anatomic causes

Bladder cancer

Schistosomiasis (*Schistosoma haematobium* infection)

Bladder calculi

Bladder trauma, pelvic fracture

Bladder functional causes

Neurogenic bladder: spinal cord defects or trauma, diabetes, multiple sclerosis, Parkinson disease, cerebrovascular accidents

Box 60-1 Causes of lower urinary tract obstruction. The most common causes are in italics.

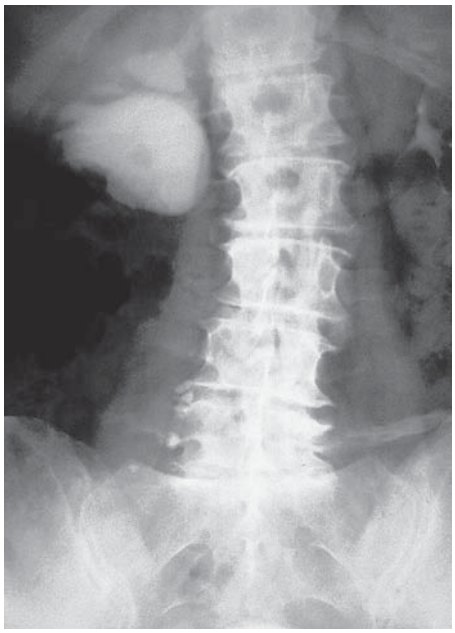

Figure 60-1 Intravenous urogram demonstrating pelviureteral junction obstruction. The study was performed in a previously asymptomatic adult to investigate nonspecific right loin pain. There is unilateral (right side) dilation of the pelvicalyceal system. The ureter has not been visualized.

bladder, depending on whether the lesion affects upper or lower motor neurons, and may lead to impaired bladder emptying with vesicoureteral reflux. Bladder dysfunction is very common in patients with multiple sclerosis and after spinal cord injury and is also seen in diabetes mellitus, in Parkinson disease, and after cerebrovascular accidents. Some drugs (anticholinergics, levodopa) can alter neuromuscular activity of the bladder and result in functional obstruction, especially if there is preexisting bladder outflow obstruction (e.g., prostatic hypertrophy).

Anatomic causes of intramural obstruction of the upper urinary tract include transitional cell carcinoma of the renal pelvis and ureter and ureteral strictures secondary to radiotherapy or retroperitoneal surgery. Rarely, obstruction may result from ureteral valve malfunction, polyps, or strictures after therapy for tuberculosis. Intramural obstruction of the lower urinary tract can result from urethral strictures, which are usually secondary to chronic instrumentation or previous urethritis, or malignant and benign tumors of the bladder. Infection with *Schistosoma haematobium* when the ova lodge in the distal ureter and bladder is a common cause of obstructive uropathy worldwide; up to 50% of chronically infected patients develop ureteral strictures and fibrosis, with contraction of the bladder.

Extrinsic Obstruction

The most common cause of extrinsic compression in women is pressure from a gravid uterus on the pelvic rim; the right ureter is more commonly affected. It is usually asymptomatic, and the changes resolve rapidly after delivery. Rarely, bilateral obstruction and acute kidney injury (AKI) may occur. Ureteral dilation may frequently be seen in pregnancy as a result of hormonal effects (especially progesterone) on smooth muscle, but this does not indicate functional obstruction (see Chapter 43, Fig. 43-1). Carcinoma of the cervix may also cause extrinsic obstruction secondary to direct extension of the tumor to involve the urinary tract. Other pelvic pathologic processes that can cause ureteral compression include benign and malignant uterine and ovarian masses, abscesses, endometriosis, and pelvic inflammatory disease. Compression of the ureters outside the bladder may also occur with uterine prolapse. Rarely, inadvertent

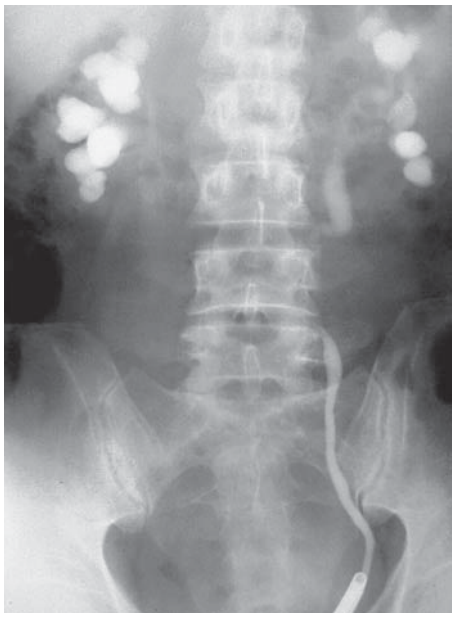

Figure 60-2 Retrograde pyelogram showing idiopathic retroperitoneal fibrosis. Dilation of the pelvicalyceal system is clearly demonstrated. The ureters, however, are not dilated, and the left ureter can be seen displaced medially as a result of being encased in thick fibrous tissue.

ureteric ligation may occur during surgical procedures, particularly those related to obstetrics and gynecology. Unilateral ligation may go undetected, but AKI will result from bilateral ligation.

In men, the most common cause of extrinsic obstruction of the lower urinary tract is benign prostatic hypertrophy. Carcinoma of the prostate can also result in obstruction either from direct tumor extension to the bladder outlet or ureters or from metastatic spread.

Retroperitoneal pathology may also result in extrinsic obstruction of the ureters, as can metastases or extension of tumors from the cervix, prostate, bladder, colon, ovary, and uterus. Primary tumors of the retroperitoneum, such as lymphomas and sarcomas, can commonly cause obstruction. Obstruction can also result from inflammatory conditions affecting the retroperitoneum, such as Crohn disease and large bowel diverticulitis. In Crohn disease the obstruction is usually right sided as a result of ileocecal disease. Less common pathologic processes include retroperitoneal fibrosis, in which thick fibrous tissue extends out from the aorta to encase the ureters and draw them medially (Fig. 60-2). Retroperitoneal fibrosis may be idiopathic but can result from inflammatory aortic aneurysms, certain drugs (e.g., β-blockers, bromocriptine, and methysergide), previous irradiation, trauma or surgery, and granulomatous disease (e.g., tuberculosis, sarcoidosis). Retroperitoneal fibrosis is also associated with IgG4-related disease, which typically presents with autoimmune pancreatitis, and elevated serum IgG4 levels suggests this diagnosis.[1] IgG4-related disease is also suggested in retroperitoneal biopsy material by an IgG4 positive plasma cell infiltrate, fibrosis with a whorled cartwheel pattern, and an obliterative venous phlebitis.[2] Ureteral compression may also be a result of vascular abnormalities, including aneurysmal dilation of the aorta or iliac vessels, aberrant vessels, and anatomic variations in the location of the ureter (retrocaval ureter).

PATHOPHYSIOLOGY

Obstruction of the renal tract causes profound functional and structural changes of the kidney. Initially, changes are predominantly functional and potentially reversible, but with time, chronic and irreversible structural changes occur. Our understanding of the consequences of urinary tract obstruction stems mainly from the study of animal models.[3] Although many studies have focused on the effects of complete ureteral obstruction in rodents, investigators have also examined models of chronic complete, partial, or reversible obstruction in adult and neonatal animals.[3] Available experimental data show little species-to-species variation in the response to acute obstruction, suggesting that similar changes are likely to occur in humans. The complex effects of urinary tract obstruction on the kidney affect both glomerular hemodynamics and tubular function.

Changes in Glomerular Function

Glomerular filtration rate (GFR) declines progressively after the onset of complete ureteral obstruction.[4] Glomerular filtration is determined by the mean hydraulic pressure gradient between the glomerular capillary lumen and Bowman space, the renal plasma flow, the ultrafiltration coefficient of the glomerular capillary wall, and the mean oncotic pressure difference across the glomerular wall. Obstruction can affect all of these, and the effects vary with the duration of the obstruction, the hydration state, and presence or absence of a contralateral functioning kidney.

After complete ureteral obstruction, there is an initial rise in proximal tubular pressure. At the same time, afferent arteriolar dilation occurs as a result of the generation of vasodilatory prostaglandins. Glomerular capillary hydraulic pressure increases, but this does not offset the rise in tubular pressure, and there is a net decrease in the hydraulic pressure gradient across glomerular capillaries, resulting in an 80% decline in GFR.[4]

About 2 to 5 hours after obstruction, renal blood flow begins to decline, whereas intratubular pressure continues to increase. Within 5 hours, proximal tubular pressure begins to decline toward control values. From this time, the main determinant of the decrease in GFR is the fall in intraglomerular capillary pressure as a result of an increase in resistance of afferent arterioles. This results in a progressive fall in renal plasma flow, which reaches 30% to 50% of control values by 24 hours. Preferential constriction of the preglomerular blood vessels lowers both plasma flow and glomerular capillary pressure, resulting in a greater decrement in GFR than in plasma flow and a fall in filtration fraction. A falling filtration fraction also results from diversion of blood to nonfiltering areas of the kidney or a reduction in the ultrafiltration coefficient.[4] The relative changes in ureteral pressure, renal plasma flow, and GFR are summarized in Figure 60-3.

The intrarenal vasoconstriction results from the generation of angiotensin II and thromboxane A_2, the release of vasopressin (antidiuretic hormone), and decreased nitric oxide production. Intrarenal angiotensin II generation occurs secondary to an increase in renin release either through reduced delivery of sodium and chloride to the distal nephron (macula densa mechanism) or through a reduction in transmural pressure at the baroreceptor as a consequence of the prostaglandin-dependent dilation of the afferent arteriole. Generation of thromboxane A_2 occurs in both glomeruli and infiltrating interstitial cells. Angiotensin II and thromboxane A_2 may also reduce the ultrafiltration coefficient. The central role of these two vasoconstrictors has been demonstrated by studies in rats, in which pretreatment with angiotensin-converting enzyme inhibitors and thromboxane synthase inhibitors virtually normalized renal function after the relief of short-term ureteral obstruction.[5]

An interstitial leukocyte infiltrate, predominantly macrophages, develops in response to chemoattractants such as monocyte chemoattractant protein 1 and osteopontin expressed by tubular cells.

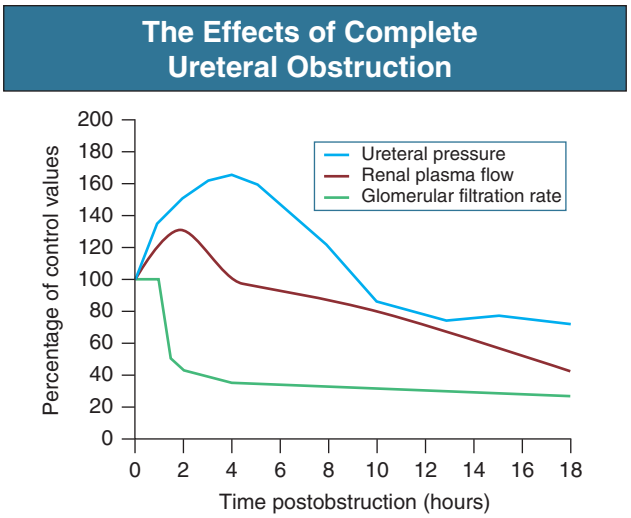

Figure 60-3 The effects of complete ureteral obstruction. The relative changes in ureteral pressure, renal plasma flow, and glomerular filtration rate are shown using data from experimental studies of unilateral ureteral obstruction in rats.

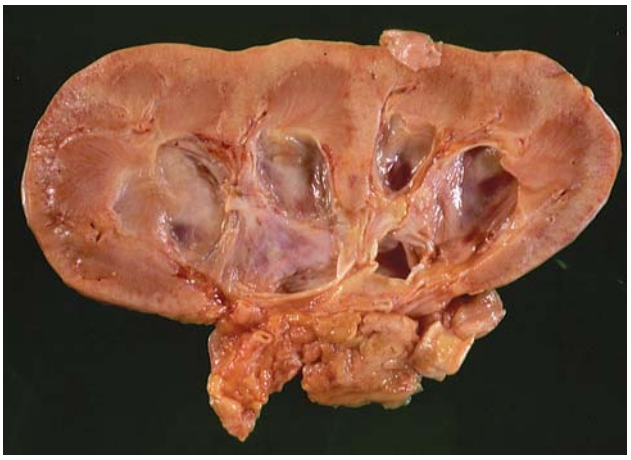

Figure 60-4 Autopsy specimen of a kidney showing the early effects of ureteral obstruction. The kidney is enlarged and edematous with pelvicalyceal dilation. There is good preservation of the renal parenchyma.

This infiltrate plays a key role in the acute functional changes after ureteral obstruction[6] and the pathogenesis of the late structural changes that occur after obstruction as macrophage depletion limits experimental interstitial fibrosis.[7]

The extent to which glomerular function recovers after the release of ureteral obstruction depends on the duration of the obstruction. Whole kidney GFR may return to normal after short-term obstruction (days), whereas recovery may be incomplete after prolonged obstruction. Evidence from studies in rats suggests that even with shorter periods of obstruction (72 hours), there may be a permanent loss of nephrons, and whole kidney GFR returns to normal only at the expense of hyperfiltration (increase in single nephron GFR) in the remaining functional nephrons.[8]

Changes in Tubular Function

Abnormalities in tubular function are common in urinary tract obstruction and manifest as altered renal handling of electrolytes and changes in the regulation of water excretion.[9] The degree and nature of the tubular defects after obstruction depend in part on whether the obstruction is bilateral or unilateral. These differences could result from the dissimilar hemodynamic responses, different intrinsic changes within the nephron, differences in extrinsic factors (e.g., volume expansion and accumulation of natriuretic substances in bilateral obstruction) between the two states, or a combination of all three.

After ureteral obstruction, the ability to concentrate the urine is markedly impaired, with maximum values of 350 to 400 mOsm/kg reported in the rat. Causative factors include a loss of medullary tonicity, an overall decrease in GFR in deep nephrons, and a reduced expression of sodium transporters.[10] Also, the collecting duct is unresponsive to vasopressin because of a reduction in the expression of renal aquaporins that results from both cyclooxygenase-2 activity[11] and angiotensin II.[12]

Rats exhibit reduced expression of multiple acid-base transporters after ureteral obstruction,[13] and patients with urinary tract obstruction often exhibit urinary acidification defects. These defects may be detected only by exogenous acid loading, but hyperchloremic acidosis caused by impaired distal acid secretion, hyporeninemic hypoaldosteronism (type IV renal tubular acidosis), and a combination of these findings have been described. This acidifying defect results from a marked increase in bicarbonate excretion or from a distal acidification defect, possibly as a result of abnormalities of the H^+-ATPase activity of intercalated cells of the collecting duct after ureteral obstruction.

Obstruction alters renal potassium handling. In the presence of a normal functioning contralateral kidney, potassium excretion is reduced after relief of obstruction, either in proportion to or perhaps even exceeding the fall in GFR (i.e., fractional excretion of potassium is unaltered or slightly reduced). There is a defect in the distal potassium secretory mechanism after unilateral obstruction that may be secondary to reduced responsiveness of that nephron segment to aldosterone. By contrast, after release of bilateral ureteral obstruction, there is a marked increase in both net and fractional potassium excretion. The major mechanism by which potassium losses occur in this setting is an increased delivery of sodium to the distal tubule, resulting in an accelerated sodium-potassium exchange.

Recovery of tubular function after release of obstruction is slow and may remain abnormal even after whole-kidney GFR has returned to normal. In rats, acidification and potassium-handling abnormalities persist for at least 14 days and urinary concentrating ability is abnormal for up to 60 days after the release of 24 hours of unilateral ureteral obstruction. These observations are consistent with persistent alterations in distal tubular and collecting duct function or a loss in functioning juxtaglomerular nephrons after the release of the obstruction.

Histopathologic Changes

The morphologic alterations in renal architecture are similar irrespective of the cause of the obstruction. Initially, renal enlargement and edema occur with pelvicalyceal dilation (Fig. 60-4). Tubular dilation that predominantly affects the collecting duct and distal tubular segments develops microscopically, although cellular flattening and atrophy of proximal tubular cells can also occur. Glomerular structures are usually preserved initially, although Bowman space may be dilated and some periglomerular fibrosis may ultimately develop.

Inadequately treated obstruction eventually causes irreversible structural changes to the renal tract. The renal pelvis becomes widely dilated, with the renal papillae either flattened or hollowed out. The cortex and medulla become grossly thinned, such that the kidney

becomes a thin rim of renal tissue surrounding a large saccular pelvis (Fig. 60-5). Histologic examination demonstrates tubulointerstitial fibrosis and obliteration of nephrons. Tubular proliferation and apoptosis, interstitial myofibroblast accumulation, increased extracellular matrix deposition, and tubular atrophy occur. Ischemia as a result of the decreased renal blood flow contributes to the parenchymal damage after obstruction. In both genetic and interventional studies, an important pathologic role for angiotensin II and transforming growth factor β (TGF-β) has been established.[14,15]

Figure 60-5 Chronic ureteral obstruction. Surgical specimen of a kidney showing gross dilation of the pelvicalyceal system and the reduction of the renal cortex to a thin fibrotic rim of tissue. There would have been no prospect for any significant functional recovery in this kidney after the relief of the obstruction.

Infiltrating macrophages play a pivotal role in the chronic tissue injury and fibrosis that result from prolonged ureteral obstruction (Fig. 60-6).[7,16] Interstitial macrophages release profibrogenic factors such as TGF-β and galectin-3 that promote progressive fibrosis. Local angiotensin II generation may also stimulate tubular cell production of TGF-β. Treatments shown to ameliorate chronic interstitial damage in experimental obstructive uropathy include angiotensin receptor blockers, pentoxifylline, simvastatin, and growth factors (such as bone morphogenetic protein 7, hepatocyte growth factor, and epidermal growth factor); beneficial effects include a reduction in tubulointerstitial inflammation and fibrosis and tubular cell apoptosis.[3] However, it is pertinent that differences have been noted in the responses of adult and neonatal rodents to experimental therapeutic interventions and it is unclear whether such differences might occur in humans.

EPIDEMIOLOGY

Obstructive uropathy is a common entity and can occur at all ages. The prevalence of hydronephrosis at autopsy is 3.5% to 3.8%, with about equal distribution between males and females, although this underestimates the true incidence because these figures exclude transient obstruction. The frequency and cause of obstruction vary

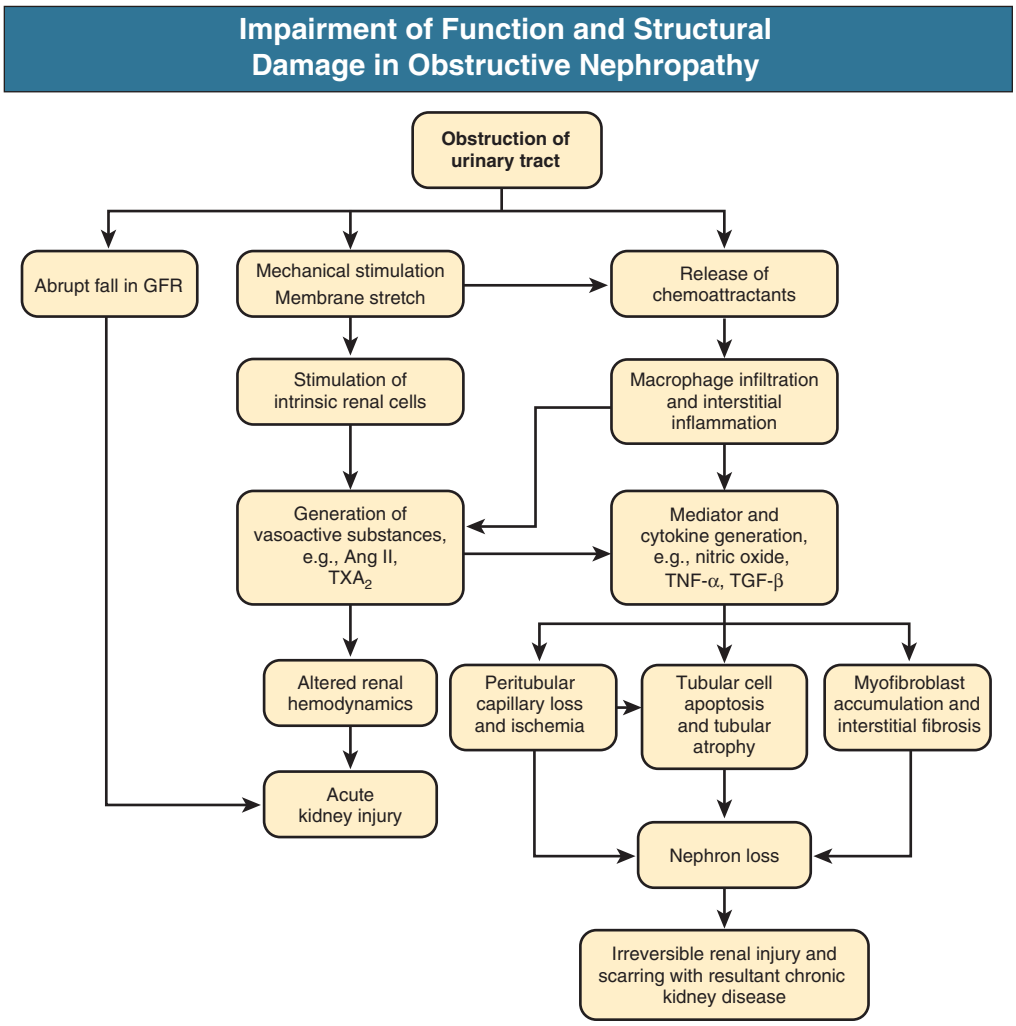

Figure 60-6 Events leading to acute impairment of renal function and chronic structural damage in obstructive nephropathy. *Ang II,* Angiotensin II; *GFR,* glomerular filtration rate; *TGF-β,* transforming growth factor β; *TNF-α,* tumor necrosis factor α; *TXA_2,* thromboxane A_2.

in both sexes with age. Antenatal ultrasound has significantly increased the detection rate of lower urinary tract obstruction in the fetus.[17] In children younger than 10 years, obstruction is more common in boys; congenital urinary tract anomalies, such as urethral valves and pelviureteral obstruction, account for most cases. In North America, obstructive uropathy remains the most common cause of end-stage renal disease (ESRD) in pediatric patients registered for renal transplantation, accounting for 16% of cases. In addition, congenital obstructive uropathy accounts for 0.7% of all patients (median age, 31 years) maintained with renal replacement therapy, demonstrating the continued impact of this disease into adult life.[18] In young adults (younger than 20 years), the frequency of urinary tract obstruction is similar in males and females. Beyond 20 years of age, obstruction becomes more common in females, mainly as a result of pregnancy and gynecologic malignant neoplasms. The peak incidence of renal calculi occurs in the second and third decades of life with a threefold increased incidence in men. After the age of 60 years, obstructive uropathy occurs more frequently in men secondary to benign prostatic hypertrophy and prostatic carcinoma. About 80% of men older than 60 years have some symptoms of bladder outflow obstruction, and up to 10% have hydronephrosis. In Europe, acquired urinary tract obstruction accounts for 3% to 5% of the cases of ESRD in patients older than 65 years, with most resulting from prostatic disease.[19] In the United States, the number of patients receiving renal replacement therapy as a result of acquired obstruction continues to increase, accounting for 1.4% of prevalent patients, although the rise is not as rapid as with other causes of ESRD.[18]

CLINICAL MANIFESTATIONS

Obstruction of the urinary tract can present with a wide range of clinical symptoms, depending on the site, degree, and duration of obstruction. The clinical manifestations of upper and lower urinary tract obstruction differ. Symptoms can be caused by mechanical obstruction of the urinary tract (usually pain) or can result from the complex alterations in glomerular and tubular function that may occur in obstructive nephropathy. The latter commonly present as alterations in urine volume and as renal failure, which can be acute or chronic. For example, patients with complete obstruction present with anuria and AKI, whereas those with partial obstruction may present with polyuria and polydipsia as a result of acquired vasopressin resistance. Alternatively, there may be a fluctuating urine output, alternating from oliguria to polyuria. However, obstructive uropathy and hence obstructive nephropathy can occur without symptoms and with minimal clinical manifestations; therefore obstruction of the urinary tract must be considered in the differential diagnosis of any patient with renal impairment.

Pain

Pain is a frequent complaint in patients with obstructive uropathy, particularly in those with ureteral calculi. The pain is believed to result from stretching of the collecting system or the renal capsule. Its severity correlates with the degree of distention and not with the degree of dilation of the urinary tract. On occasion the location of the pain helps determine the site of obstruction. With upper ureteral or pelvic obstruction, flank pain and tenderness typically occur, whereas lower ureteral obstruction causes pain that radiates to the groin, the ipsilateral testicle, or the labia. Acute high-grade ureteral obstruction may be accompanied by a steady and severe crescendo flank pain radiating to the labia, the testicles, or the groin ("classic" renal colic). The acute attack may last less than half an hour or as long as a day. By comparison, patients with chronic slowly progressive obstruction may have no pain or minimal pain during the course of their disease. In such patients, any pain that does occur is rarely colicky in nature. In PUJ obstruction, pain may occur only after fluid loading to promote a high urine flow rate.

Lower Urinary Tract Symptoms

Obstructive lesions of the bladder neck or bladder disease may cause a decrease in the force or caliber of the urine stream, intermittency, postmicturition dribbling, hesitancy, or nocturia. Urgency, frequency, and urinary incontinence can result from incomplete bladder emptying. Such symptoms commonly result from prostatic hypertrophy and are frequently referred to as *prostatism,* but they are not pathognomonic for this condition.

Urinary Tract Infections

Urinary stasis resulting from obstruction predisposes to urinary tract infections, and patients may develop cystitis with dysuria and frequency or pyelonephritis with loin pain and systemic symptoms. Infection occurs more often in patients with lower urinary tract obstruction than in those with upper urinary tract obstruction.

Urinary tract infection in men or young children of either sex, recurrent or persistent infections in women, infections with unusual organisms such as *Pseudomonas* species, and a single attack of acute pyelonephritis require further investigation to exclude obstruction. Also, the presence of obstruction makes effective eradication of the infection difficult. Infections of the urinary tract with a urease-producing organism such as *Proteus mirabilis* predispose to stone formation. These organisms generate ammonia, which results in urine alkalinization and favors the development of magnesium ammonium phosphate (struvite) stones. Struvite calculi can fill the entire renal pelvis to form a staghorn calculus that eventually leads to loss of the kidney if it is untreated. Thus, stone formation and papillary necrosis can also be consequences of urinary tract obstruction as well as causes of obstruction.

Hematuria

Calculi may cause trauma to the urinary tract uroepithelium and result in either macroscopic or microscopic hematuria. Any neoplastic lesion that obstructs the urinary tract, especially uroepithelial malignancies, may bleed, resulting in macroscopic hematuria. Urinary tract bleeding may also result in obstruction, giving rise to clot colic when it is in the ureter or clot retention when it is in the bladder.

Changes in Urine Output

Complete bilateral obstruction or unilateral obstruction of a single functioning kidney such as a renal transplant will result in anuria. However, when the lesion results in partial obstruction, urine output may be normal or increased (polyuria). A pattern of alternating oliguria and polyuria or the presence of anuria strongly suggests obstructive uropathy.

Abnormal Physical Findings

Physical examination findings can be completely normal. Some patients with upper urinary tract obstruction may have flank tenderness. Longstanding obstructive uropathy may result in an enlarged palpable kidney in children. Lower urinary tract obstruction causes

a distended, palpable, and occasionally painful bladder. A rectal examination and, in women, a pelvic examination should be performed because they may reveal a local malignant neoplasm or prostatic enlargement.

Acute or chronic hydronephrosis, either unilateral or bilateral, may cause hypertension as a result of impaired sodium excretion with expansion of extracellular fluid volume or from the abnormal release of renin. On occasion, in patients with partial urinary tract obstruction, hypotension occurs as a result of polyuria and volume depletion.

Abnormal Laboratory Findings

Urinalysis may show hematuria, bacteriuria, pyuria, crystalluria, and low-grade proteinuria, depending on the cause of obstruction. However, urinalysis findings may be completely negative despite advanced obstructive nephropathy. In the acute phase of obstruction, urinary electrolyte values are similar to those seen in a "pre-renal" state, with a low urinary sodium (<20 mmol/l), a low fractional excretion of sodium (<1%), and a high urinary osmolality (>500 mOsm/kg). However, with more prolonged obstruction, a decreased ability to concentrate the urine and an inability to reabsorb sodium and other solutes occur. These changes are particularly marked after the release of chronic obstruction and give rise to the syndrome commonly referred to as *postobstructive diuresis*.

Increases in serum urea and creatinine are the most significant laboratory abnormalities in patients with obstructive uropathy. Electrolyte abnormalities may also occur, including a hyperchloremic hyperkalemic (type 4) metabolic acidosis or hypernatremia as a result of acquired nephrogenic diabetes insipidus. The development of obstruction in patients with underlying chronic kidney disease may accelerate the rate of progression. ESRD may occasionally be caused by chronic obstructive uropathy that had been asymptomatic.

Obstruction in Neonates or Infants

With the advent of routine antenatal scanning, the diagnosis of hydronephrosis and genitourinary abnormalities is now frequently made antenatally; however, unsuspected obstructive uropathy may present in the postnatal period with failure to thrive, voiding difficulties, fever, hematuria, or symptoms of renal failure. Oligohydramnios at the time of delivery should raise the suspicion of obstructive uropathy, as should the presence of congenital anomalies of the external genitalia. Nonurologic anomalies such as ear deformities, a single umbilical artery, imperforate anus, or a rectourethral or rectovaginal fistula should prompt investigation for urinary tract obstruction. Any infant with neurologic abnormalities may have a neurogenic bladder with associated obstructive uropathy.

DIAGNOSIS

Prompt diagnosis of urinary tract obstruction is essential to allow treatment to limit any long-term adverse consequences. Symptoms such as "renal colic" may suggest the diagnosis and prompt appropriate investigation. However, urinary tract obstruction should be actively considered in any patient with unexplained acute or chronic kidney impairment. The diagnostic approach has to be tailored to the clinical presentation (Fig. 60-7), but a careful history and thorough physical examination are mandatory in all patients.

Urinalysis may provide valuable diagnostic information. Hematuria suggests that the obstructing lesion is a calculus, sloughed papilla, or tumor. Bacteriuria suggests urinary stasis, especially in men or in pregnant women, but it may also be a complication of chronic obstruction. The presence of crystals in the urine sediment (cystine or uric acid) may be an indication of the type of stone causing the ureteral obstruction or the intrarenal obstruction resulting in AKI. Laboratory studies should include an assessment of renal function (serum creatinine and urea) and the measurement of serum electrolytes.

Imaging

Because the sites, causes, and consequences of obstruction to the renal tract are so variable, no single imaging investigation can diagnose renal tract obstruction with certainty. No single imaging investigation should be relied on to definitively exclude obstruction, especially if the clinical suspicion of obstruction is high. Therefore, the approach to the patient with suspected obstruction may require the complementary use of a number of different imaging techniques.

Ultrasound is the most widely used imaging modality, with computed tomography (CT) scanning and magnetic resonance (MR) urography becoming increasingly useful in accurately diagnosing both the site and cause of obstruction. Although less commonly used, older imaging techniques, such as intravenous urography (IVU), can be used effectively to evaluate patients with obstructive uropathy. The role of imaging techniques is shown in Figure 60-7. Imaging is also discussed in Chapter 5.

Ultrasound

Ultrasound can define renal size and demonstrate calyceal dilation[20] but depends on the expertise of the operator (Fig. 60-8). Although it is sensitive for detection of hydronephrosis, ultrasound will often not detect its cause. Pathologic change within the ureter is difficult to demonstrate, and tiny stones will not generate acoustic shadows. However, unilateral hydronephrosis suggests obstruction of the upper urinary tract by stones, blood clots, or tumors. Bilateral hydronephrosis is more likely to result from a pelvic problem obstructing both ureters or obstruction of the bladder outlet, in which case the bladder will also be enlarged. Ultrasound may be combined with radiographic examination of the kidneys, ureters, and bladder (often known as KUB) to ensure that ureteral stones or small renal stones are not overlooked.

Ultrasound produces false-negative results in cases of nondilated obstructive uropathy.[20] Immediately after acute obstruction (within 24 hours), the relatively noncompliant collecting system may not have dilated, so ultrasound examination findings may be normal. Furthermore, if urine flow is low, as in severe dehydration or renal failure, there may be little dilation of the urinary tract. Dilation may also be absent in slowly progressive obstruction when the ureters are encased by fibrous tissue (as in retroperitoneal fibrosis) or by tumor, and in some renal transplants in which there is dense surrounding scar tissue. The acoustic shadow of a staghorn calculus can also mask dilation of the upper urinary tract. The sensitivity of ultrasound for diagnosis of obstruction can be improved by measuring the resistive index with color Doppler sonography. A resistive index above 0.7 reflects the increased vascular resistance present in obstruction and effectively discriminates between obstructed and nonobstructed kidneys.[20] Such ultrasound techniques are particularly useful when it is especially important to minimize radiation exposure, for example, in pregnant women and children, and in the follow-up of patients requiring repeated imaging, such as after extracorporeal shock wave lithotripsy.

Even in experienced hands, ultrasound may have a significant false-positive rate, especially if minimal criteria are adopted to

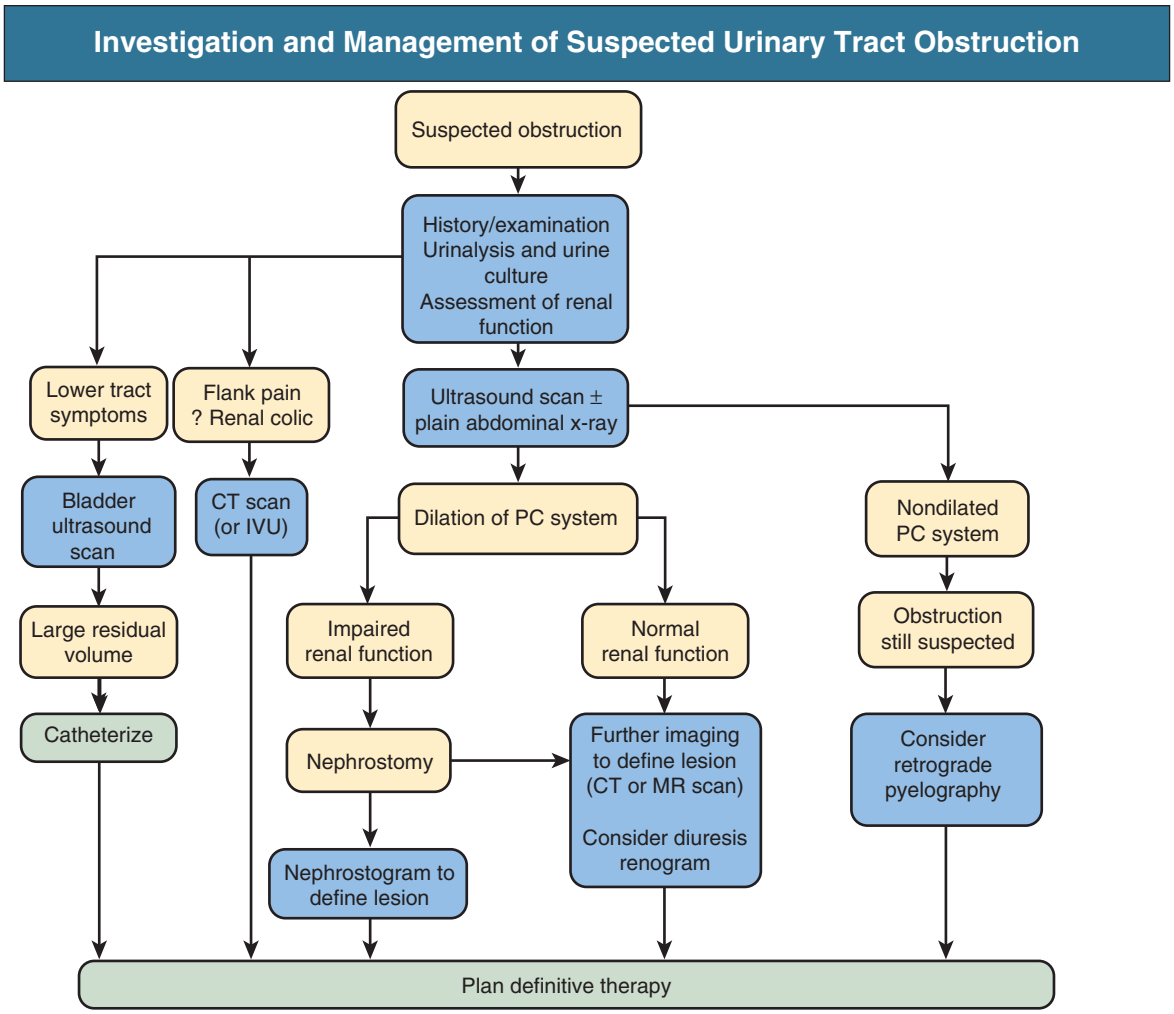

Figure 60-7 Investigation and management of suspected urinary tract obstruction. A full history should be taken and a thorough examination performed, together with urinalysis, urine microscopy and culture, and measurement of renal function and serum electrolytes. Ultrasound is a useful first-line investigation for any patient with suspected urinary tract obstruction. Computed tomography *(CT)* is now the preferred imaging technique when renal calculi are suspected. Either CT or magnetic resonance *(MR)* urography can accurately diagnose both the site and cause of obstruction in most cases. If there is renal impairment, a nephrostomy allows the effective relief of the obstruction and time for renal function to recover while definitive therapy is planned. *IVU,* Intravenous urography; *PC,* pelvicalyceal.

diagnose obstruction. In addition, the echogenicity produced by multiple renal cysts may be mistaken for hydronephrosis.

Ultrasound scanning can be used to assess bladder emptying and should be undertaken in patients with lower urinary tract symptoms. A large postmicturition residual volume suggests bladder outflow obstruction, which should prompt further urologic investigation and treatment.

The investigation of neonates with hydronephrosis diagnosed antenatally depends on the grade of hydronephrosis identified. Neonates with grade 1 or 2 hydronephrosis (no calyceal dilation) undergo ultrasound scanning; neonates with grade 3 or 4 hydronephrosis (indicating increasingly severe pelvicalyceal dilation) require both ultrasound scanning and voiding cystourethrography.[21] This combination can distinguish megaureter resulting from obstruction or reflux and enable the diagnosis of posterior urethral valves and ureteropelvic junction obstruction.

Plain Abdominal Radiography

A plain abdominal radiograph (or KUB) allows an assessment of kidney size and contour and frequently demonstrates renal calculi because about 90% of calculi are radiopaque.

Intravenous Urography

IVU was formerly the first-choice investigation for suspected upper urinary tract obstruction. In patients with normal renal function, it can usually define both the site and the cause of the obstruction. However, the excretion of contrast material may be poor or delayed in patients with low GFR because of a decreased filtered load of the contrast agent, which is potentially nephrotoxic. IVU is no longer a first-line investigation to diagnose urinary tract obstruction, especially in patients with impaired renal function.

Computed Tomography

Non–contrast-enhanced spiral CT scanning is used increasingly as the primary imaging modality for the evaluation of patients with acute flank pain.[22] Stones are easily detected because of their high density, and CT can provide an accurate and rapid diagnosis of an obstructing ureteral calculus with a stone being found more commonly in men.[23] In addition, it provides useful information about the site and nature of the obstructing lesion, especially when this is extrinsic to the urinary tract (Fig. 60-9; see also Chapter 61, Fig. 61-1). CT demonstrates retroperitoneal disease, such as para-aortic and paracaval lymphadenopathy; retroperitoneal fibrosis is evident

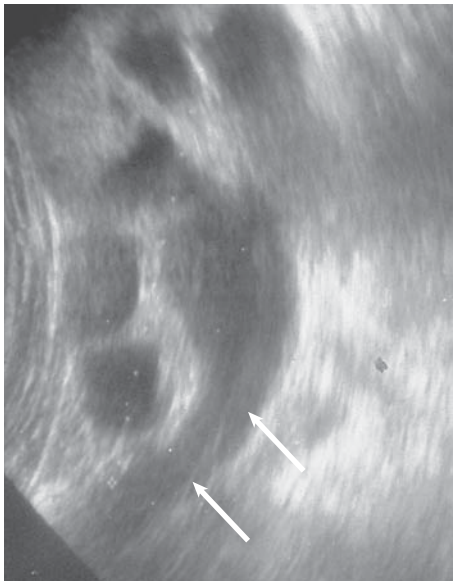

Figure 60-8 Renal ultrasound scan of a patient with obstruction of the urinary tract causing hydronephrosis. The kidney is hydronephrotic with dilation of the pelvicalyceal system; dilation of the upper ureter is also clearly seen *(arrows)*.

Figure 60-9 Computed tomography scan of the abdomen showing a grossly hydronephrotic kidney on the left (*arrows* mark dilated renal pelvis). Dilated loops of small bowel are seen in the right hypochondrium. Sequential sections demonstrated that the ureter was dilated along its length and that there was a pelvic mass, which was responsible for both bowel and left ureteral obstruction. The mass was subsequently shown to be arising from a carcinoma of the colon.

as increased attenuation within the retroperitoneal fat, with encasement of one or both ureters. Hematomas, primary ureteral tumors, and polyps are also detectable. The diagnostic potential of CT is enhanced by the administration of contrast material, but this may limit its use in patients with renal impairment. In addition, it involves considerable exposure to ionizing radiation.

Magnetic Resonance Urography

Magnetic resonance urography (combined with KUB) can enable the diagnosis of ureteral obstruction caused by renal calculi with accuracy similar to that of spiral CT scanning but without exposure to contrast medium or ionizing radiation. The technique has less observer variability and is more accurate than CT in detecting indirect evidence of obstruction, such as perirenal fluid. MR urography can rapidly and accurately depict the morphologic features of dilated urinary tracts and provide information about the degree and level of obstruction (Fig. 60-10).[24] MR urography is a particularly attractive imaging modality for the evaluation of hydronephrosis in children because it provides both anatomic and functional data and can indicate whether the hydronephrosis is compensated (symmetric changes of signal intensity of the nephrogram) or decompensated.[25] Signs of decompensation (acute on chronic obstruction) include edema of the renal parenchyma, a delayed and increasingly dense nephrogram, a delayed calyceal transit time, and a more than 4% difference in the calculated differential renal function. MR urography is likely to be increasingly used in the future.

Figure 60-10 Magnetic resonance urography showing obstructive uropathy. T2-weighted MR image showing a proximal right-sided ureteral obstruction with an associated mild hydronephrosis *(arrow)*. The obstruction was secondary to a ureteric calculus.

Retrograde Pyelography

Retrograde pyelography (Fig. 60-11; see also Fig. 60-2) may be particularly useful to identify both the site and the cause of the obstruction. It is also helpful when nondilated urinary tract obstruction is suspected or when there is a history of allergic reactions to contrast material. Urinary tract infection that may become overwhelming if obstruction is present is a contraindication to retrograde pyelography.

Diuresis Renography

A diuresis renogram using technetium Tc 99m mercaptoacetyltriglycine (^{99m}Tc-MAG3), combined with intravenous furosemide administered 20 to 30 minutes after injection of the isotope (diuretic isotopic renography), can be used to distinguish between simple dilation of the collecting system and true obstruction.[26] Normally there is a rapid washout of the isotope from the kidney, and persistence of the isotope suggests a degree of obstruction (Fig. 60-12). Poor renal function significantly limits the usefulness of renography

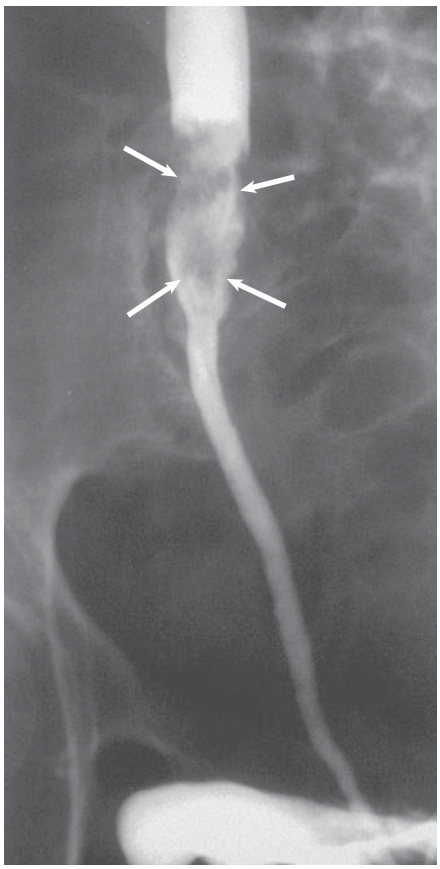

Figure 60-11 Ureteral obstruction by a tumor. A retrograde pyelogram shows the tumor is within and obstructing the ureter *(arrows)*. Above the tumor there is dilation of the ureter, but below it the ureter is of a normal caliber.

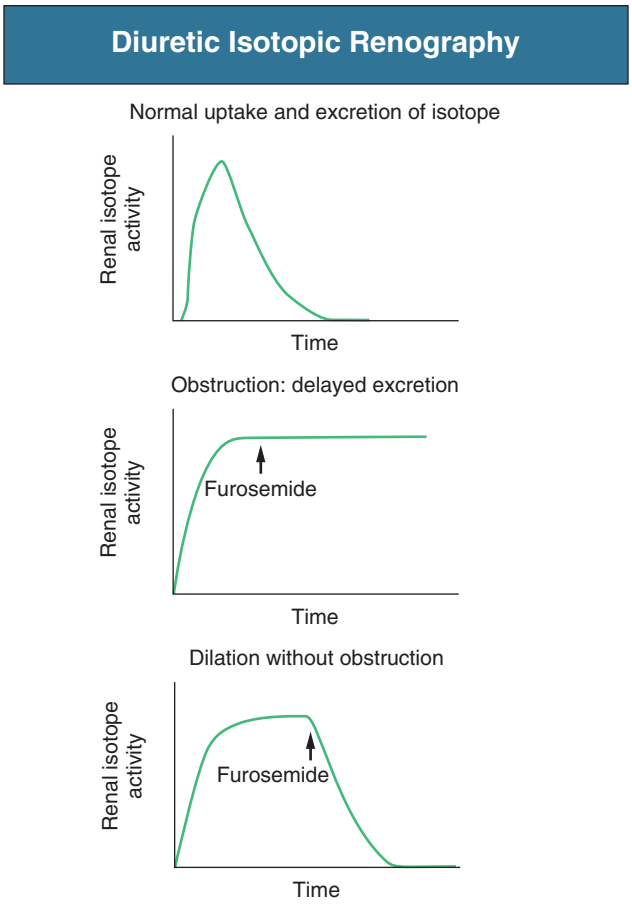

Figure 60-12 Diuretic isotopic renography. Idealized tracings for normal, obstructed, and dilated kidneys without obstruction of the upper urinary tract. In obstruction, there is delayed excretion of ^{99m}Tc-MAG3 despite administration of furosemide. When there is dilation of the upper urinary tract without obstruction, the isotope is retained but is rapidly excreted after the administration of furosemide.

because the diuretic response to furosemide may be absent. Diuresis renography may also be used for follow-up of patients who have undergone surgical procedures to relieve obstruction, such as a pyeloplasty.

Pressure-Flow Studies

A pressure-flow study (Whitaker test) involves puncture of the collecting system with a fine-gauge needle to perfuse fluid (at 10 ml/min) with concurrent measurement of the differential pressure between the bladder and the collecting system: a pressure greater than 20 cm H_2O indicates obstruction. Although this test is rarely required, it can be informative.[27]

Other Evaluations

Lower urinary tract obstruction may be evaluated by cystoscopy, which allows a visual inspection of the entire urethra and the bladder. Urodynamic studies (see Chapter 52, Fig. 52-15) can assess bladder outlet obstruction, measure the residual urine volume after voiding, and detect functional bladder abnormalities.

DIFFERENTIAL DIAGNOSIS

Diagnostic uncertainty arises with nonobstructive dilation of the upper urinary tract, which may be seen with vesicoureteral reflux, diuretic administration, diabetes insipidus, congenital megacalyces, chronic pyelonephritis, and postobstructive atrophy. Diuresis renography or retrograde pyelography may be required to exclude obstruction.

NATURAL HISTORY

Obstructive uropathy is potentially curable but will result in progressive irreversible loss of nephrons and renal scarring if it is left untreated (Fig. 60-13). ESRD will result if both kidneys are affected or if there is only a solitary kidney. Outcome data for obstructive uropathy are limited, but the exact prognosis will depend on the pathologic process responsible for the obstruction, the duration of the obstruction, and the presence or absence of urosepsis. Relief of short-term obstruction (<1 to 2 weeks) usually results in an adequate return of renal function. With chronic progressive obstruction (>12 weeks), there is often irreversible and severe renal damage, and renal functional recovery may be limited even after relief of the obstruction. A single-center study identified 104 patients who presented with obstructive nephropathy.[28] The mean GFR at presentation and at 3, 12, and 36 months was 9 ml/min, 28, 29, and 30 ml/min (patients on dialysis excluded), demonstrating significant but nonprogressive renal impairment after relief of obstruction. It is likely that the prognosis for renal functional recovery is better the earlier the obstruction is diagnosed and relieved.

TREATMENT

General Considerations

Treatment is dictated by the location of the obstruction, the underlying cause, and the degree of any renal impairment. If renal impairment is present, the treatment of obstruction requires close collaboration between nephrologists and urologists to reduce the risks associated with the metabolic and electrolyte consequences of renal failure and to optimize the chances for long-term recovery of renal function. For example, complete bilateral ureteral obstruction presenting as AKI is a medical emergency and requires rapid intervention to salvage renal function. Prompt intervention to relieve the obstruction should result in a rapid improvement in renal function. Dialysis should rarely be required in patients with AKI secondary to obstruction except to make the patient fit for intervention, for example, by improving life-threatening hyperkalemia or severe fluid overload. The rapid relief of obstruction will limit permanent renal damage, but renal function may not recover immediately if acute tubular necrosis has resulted from obstruction or any accompanying sepsis.

Some surgical aspects of the management of obstructive uropathy are discussed in Chapter 61. The site of obstruction frequently determines the approach. If the obstruction is distal to the bladder, a urethral catheter or, if this cannot be passed, a suprapubic cystostomy will effectively decompress the kidneys. Placement of nephrostomy tubes or cystoscopy and passage of a retrograde ureteral catheter will relieve upper urinary tract obstruction. Percutaneous nephrostomy (PCN) is generally the appropriate emergency treatment for upper urinary tract obstruction, especially in the setting of AKI. PCN can be achieved with local anesthetic and should allow rapid recovery of renal function in most patients (>70%), avoiding the need for dialysis. After relief of the obstruction by a nephrostomy, the exact site and nature of the obstructing lesion can be determined by an antegrade study infusing radiographic contrast material into the nephrostomy tube (nephrostogram), and time can be taken to plan definitive therapy (Fig. 60-14). Major complications of nephrostomy insertion (abscess, infection, and hematoma) occur in less than 5% of patients. If both kidneys are obstructed, the nephrostomy should initially be placed in the kidney with the most preserved renal parenchyma, although bilateral nephrostomies may be required to maximize the potential for the recovery of renal function. If infection occurs above a ureteral obstruction (pyonephrosis), drainage of the kidney by PCN can play an important therapeutic role together with appropriate antibiotics.

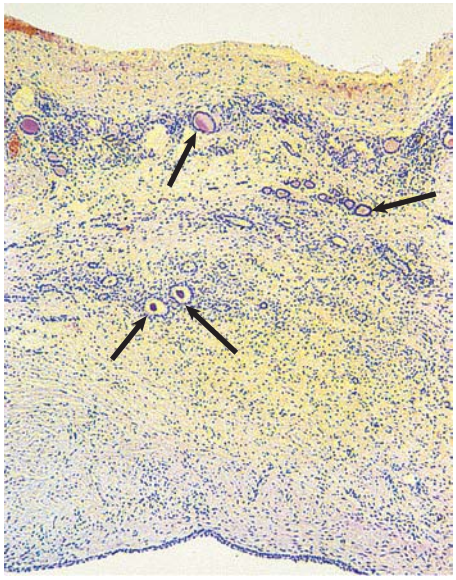

Figure 60-13 Pathology of chronic ureteral obstruction. This is a section of the rim of renal tissue from the kidney shown in Figure 60-5. The renal capsule is at the top, the urinary space at the bottom. The cortex is considerably thinned, and only a few atrophic tubules remain *(arrows)* within an interstitium comprising dense fibrous tissue and a mononuclear cell infiltrate *(blue-staining nuclei)*. No glomeruli can be seen. This demonstrates why there would be no prospect for any significant functional recovery in this kidney even after the relief of the obstruction.

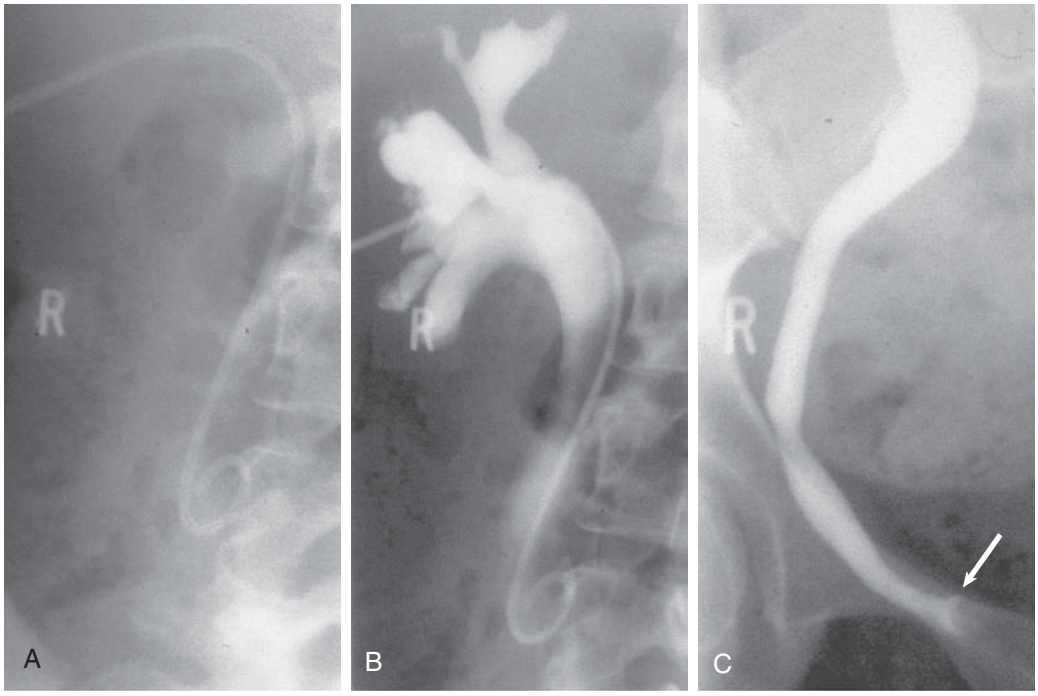

Figure 60-14 Nephrostogram. A nephrostomy has been placed percutaneously into the dilated collecting system of the kidney under ultrasound control **(A).** After infusion of contrast material down the nephrostomy, the dilated pelvicalyceal system and upper ureter **(B)** and the lower ureter **(C)** are outlined. The ureter is dilated along its length but tapers abruptly at the vesicoureteral junction *(arrow)*. In this patient the obstruction was caused by a radiolucent stone.

A nephrostomy can be used to gauge the potential for functional recovery in patients with chronic obstruction. Failure of renal recovery after several weeks of nephrostomy drainage strongly suggests irreversible structural damage and therefore no likely benefit from undertaking a more definitive surgical correction of the obstructing lesion. Long-term nephrostomy is increasingly used as a definitive therapy for patients who are unsuitable for major surgical intervention and those with incurable malignant disease (see Chapter 59 for further discussion).

Ureteral obstruction requiring intervention occurs in up to 3% of renal transplant recipients.[29] It can be treated by nephrostomy and ureteral stenting, percutaneous incision or balloon dilation of the stricture, or open surgical repair (see Chapter 103).

Specific Therapies

Calculi are the most common cause of ureteral obstruction, and their treatment includes relief of pain, elimination of obstruction, and treatment of infection (see Chapters 59 and 61). Ureteral obstruction by papillary tissue, blood clots, or a fungus ball is treated by procedures similar to those used for calculi. When obstruction is caused by neoplastic, inflammatory, or neurologic disease, there is unlikely to be spontaneous remission of the obstruction, and some form of urinary diversion, such as an ileal conduit, should be considered. Some obstructing neoplastic lesions, such as lymphadenopathy from lymphoma, may respond to chemotherapy. Management of malignant urinary tract obstruction is discussed further in Chapter 61.

In idiopathic retroperitoneal fibrosis, ureterolysis (in which the ureters are surgically freed from their fibrous encasement) may be beneficial, especially if combined with corticosteroid therapy to prevent recurrence. A recent retrospective study demonstrated the effectiveness of ureteric stent insertion and corticosteroids in idiopathic retroperitoneal fibrosis[30]; retroperitoneal fibrosis complicating IgG4 disease may also respond to corticosteroid treatment.[2]

Functionally significant PUJ obstruction should be corrected surgically by either an open (Anderson-Hynes) pyeloplasty or a laparoscopic approach. The laparoscopic approach results in significantly less morbidity and has good long-term outcomes that are comparable to those of the open procedure.[31] Balloon dilation of the abnormal segment of the ureter is also possible, but the recurrence rate is high. Studies have suggested the usefulness of urine proteomics to identify neonates with ureteropelvic junction obstruction who require surgical intervention,[32] although a subsequent small study indicated that this approach was less specific and sensitive in older children.[33]

Benign prostatic hypertrophy is the most common cause of lower urinary tract obstruction in men and may be mild and nonprogressive. A patient with minimal symptoms, no infection, and a normal upper urinary tract can continue with assessment until he and his physician agree that further treatment is desirable. Medical therapy with either α-adrenergic blockers (e.g., tamsulosin) or 5α-reductase inhibitors (e.g., finasteride) may be used in patients with moderate symptoms.[34] α-Blockers relax the smooth muscle of the bladder neck and prostate and decrease urethral pressure and outflow obstruction. 5α-Reductase inhibitors inhibit the conversion of testosterone to the active metabolite dihydrotestosterone and reduce prostatic hypertrophy. Combination therapy with these agents may be synergistic. Surgical intervention with transurethral resection of the prostate is generally required for failed medical treatment, debilitating symptoms, urinary retention, recurrent infection, or evidence of renal parenchymal damage. Holmium laser enucleation of the prostate is a less invasive alternative to transurethral resection of the prostate with good short-term and long-term outcomes.[35]

Urethral strictures in men can be treated by dilation or direct-vision internal urethrotomy. The incidence of bladder neck and urethral obstruction in women is low and treatment rarely required. Suprapubic cystostomy may be necessary for bladder drainage in patients unable to void after injury to the urethra or in those who have an impassable urethral stricture.

When obstruction results from neuropathic bladder function, urodynamic studies (see Chapter 52, Fig. 52-15) are essential to determine therapy. The goals of therapy are to establish the bladder as a urine storage organ without causing renal parenchymal injury and to provide a mechanism for bladder emptying that is acceptable to the patient. Patients may have either a flaccid atonic or an unstable hypertonic bladder. Ureteral reflux and parenchymal damage may develop in both cases, although it is more common in patients with a hypertonic bladder. Asking the patient to void at regular intervals may achieve satisfactory emptying of the bladder. Patients with an atonic bladder and significant residual urine retention associated with recurrent urosepsis need to undertake clean intermittent self-catheterization. The aim should be to catheterize four or five times per day to ensure that the amount of urine drained from the bladder on each occasion is less than 400 ml. External sphincterotomy has also been used in men with an atonic bladder and may relieve outlet obstruction and promote bladder emptying, but it may cause urinary incontinence and the need to wear an external collection device. In patients with a hypertonic bladder, improvement in the storage function of the bladder may be obtained with anticholinergic agents. Occasionally, chronic clean intermittent self-catheterization is necessary.

Whenever possible, chronic indwelling catheters should be avoided in patients with a neurogenic bladder because they may lead to the formation of bladder stones, urosepsis, and urethral erosion, and they predispose to squamous cell carcinoma of the bladder. Patients who have had chronic indwelling catheters for more than 5 years should have annual cystoscopic examinations. If deterioration in renal function occurs despite conservative measures or there is intractable incontinence or a small contracted bladder, an upper urinary tract diversion procedure such as an ileal conduit may be required.

Management of Postobstructive Diuresis

Marked polyuria (postobstructive diuresis) is frequently seen after the release of bilateral obstruction or obstruction of a single functioning kidney. Indeed, a diuresis of greater than 7 liters per day is associated with a good functional outcome.[36] Release of unilateral obstruction rarely results in a postobstructive diuresis[37] despite the presence of tubular dysfunction and a concentrating defect. This is because of intrinsic differences in the tubular response to unilateral and bilateral obstruction and, more important, the salt and water retention and renal impairment that occurred in bilateral obstruction (not evident in unilateral obstruction because of the contralateral normal kidney). The resultant increase in natriuretic factors (including atrial natriuretic peptide) and substances able to promote an osmotic diuresis such as urea[38] promote an appropriate postobstructive diuresis to excrete water and electrolytes that were retained during the period of obstruction. However, the postobstructive diuresis may also be inappropriate as a result of tubular dysfunction, and, if not managed correctly, this may result in severe volume depletion and electrolyte imbalance with continued renal dysfunction. Intravenous and oral fluid replacement is usually required, with careful and regular assessment of the fluid balance and serum

electrolytes to tailor the fluid replacement regimen appropriately. Once the patient is deemed euvolemic, urine losses plus an allowance for insensible losses should be replaced. Urine volume should be measured regularly (hourly) to facilitate fluid administration, and serum electrolytes should be measured at least daily and as frequently as every 6 hours when there is a massive diuresis. Daily weighing of the patient is also helpful. Replacement fluid regimens should include sodium chloride, a source of bicarbonate and potassium. Calcium, phosphate, and magnesium replacement may also be necessary.

If fluid administration is overzealous, the kidney will not recover its concentrating ability, and a continued "driven" diuresis will result. It may then be necessary to decrease fluid replacement to levels below those of the urine output and observe the patient carefully for signs of volume depletion.

Future Prospects

Understanding the pathophysiologic changes that follow ureteral obstruction has allowed the development of rational interventional therapies to hasten the recovery of renal function and limit permanent renal damage. Although the best treatment option in humans remains the prompt and effective relief of the obstruction, the development and implementation of improved imaging modalities that provide more sophisticated anatomic and functional information (including intrarenal oxygen content[39]) as well as future advances in urine proteomics will undoubtedly refine patient management and increase the data available for making key clinical decisions such as whether and when surgical intervention is required.

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CHAPTER 61

Urologic Issues for the Nephrologist

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Close interaction between nephrologists and urologists is crucial to the optimal management of a number of common clinical problems. A proper understanding of urologic strategies helps the nephrologist ensure that patients with these problems are given clear information and are optimally managed. Areas in which such coordinated work is most important are discussed in this chapter. They include the management of stone disease, the surgical approach to urinary tract obstruction, the investigation of hematuria, and the management of urinary tract malignant neoplasms.

SURGICAL MANAGEMENT OF STONE DISEASE

The management of urinary tract stones has been irrevocably changed by the introduction of extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL), and ureteroscopy.

Such advances have rendered open stone surgery an increasingly rare management option that is now second- or third-line treatment when indicated. Table 61-1 details the use of different treatment modalities over time since the introduction of newer techniques.[1] As familiarity with available techniques and technology develops, standardized treatment strategies will undoubtedly evolve. At present, however, there remains controversy over the optimal treatment for a variety of stone patients, the specifics of which are beyond the scope of this text.

Advances in Imaging for Urinary Tract Stones

In recent years, unenhanced computed tomography (CT) scanning of the abdomen and pelvis has replaced intravenous urography (IVU) as the standard imaging modality for stone diagnosis (Fig. 61-1). CT offers increased sensitivity compared with IVU (99% vs. 70%) without the need for the intravenous administration of contrast material. An additional advantage is the ability of CT to demonstrate radiolucent stones (mainly uric acid and xanthine stones) and to detect concomitant lesions and/or alternative diagnoses. CT does require an increased radiation dose, but this is lessening with modern machines. Comparative doses are 0.42 mSv for plain radiography of the kidneys, ureters, and bladder (KUB); 2.5 mSv for IVU; and 4 mSv for non–contrast-enhanced CT.

Treatment of Urinary Tract Stones

Spontaneous stone passage can be expected in up to 80% of patients with a stone size smaller than 4 mm. Conversely, for stones with a diameter of more than 7 mm, the chance of spontaneous stone passage is very low. The location is also important; up to 70% of distal ureteral stones pass spontaneously, in contrast to only 45% of midureteral and 25% of proximal ureteral stones. Intervention is strongly recommended when there is persistent pain (for more than 72 hours) despite adequate analgesia, persistent obstruction with risk of impaired renal function (e.g., with preexisting renal impairment or in a single kidney), bilateral obstruction, or associated urinary tract sepsis.

In the absence of an acute indication for surgical management, medical expulsive therapy (tamsulosin 400 μg once daily, nifedipine 30 mg once daily), which relaxes the distal ureter and increases the likelihood of stone passage, is now commonplace in many centers. There is a growing body of evidence to support the use of medical expulsive therapy in ureteral stone disease. However, there is inconsistency in reported studies (with respect to stone size and location), and as yet outcomes of well-conducted randomized controlled trials (RCTs) are still awaited.

Another conservative treatment option is chemolysis, as several stone types are in principle amenable to dissolution by oral medications or by direct instillation of chemical solutions. However, in most patients this form of treatment is either impractical or clinically ineffective. The major exception is patients with uric acid stones, which can readily be dissolved by alkalization of the urine, usually with oral potassium citrate. (Commercially available preparations typically include potassium citrate 30% and citric acid monohydrate 5% to be diluted in water for a dose of 10 ml three times daily.)

Acute Surgical Intervention

The main goal of acute surgical intervention is to relieve obstruction. If the patient is considered well enough for general anesthesia, ureteroscopic stone destruction can be attempted in most cases. Alternatively, a double-J stent (a ureteral stent with two coiled ends) can be inserted, which will relieve obstruction until definitive treatment is performed (Fig. 61-2). However, in the setting of uncontrolled urinary tract infection, percutaneous nephrostomy (PCN) is the preferred option because it can be performed with local anesthesia and is less likely than endoscopic surgery to cause septicemia (Fig. 61-3). Rarely, an open procedure to remove a stone or a grossly infected kidney may be necessary.

Elective Surgical Intervention

Extracorporeal Shock Wave Lithotripsy

During ESWL, acoustic shock wave energy is delivered to a stone under fluoroscopic or ultrasound guidance. Treatment sessions typically last about 30 minutes, during which 1500 to 2500 shock waves are delivered. Sessions are performed on an outpatient basis with the patient under analgesia or intravenous sedation and can be repeated at intervals of 10 to 14 days. Stones up to 20 mm in size can be treated effectively, and stone-free rates of 60% to 98% have been reported. However, ESWL is operator dependent, and outcome is influenced by the size, composition, and location of the stone and the type of

Changing Use of Techniques for Stone Removal			
	1984	1990	1999
Location (%)			
Calyceal stones	35	43	46
Pelvic stones	42	20	13
Staghorn stones	8	3	1
Ureteral stones	15	34	40
Treatment Modality (%)			
ESWL	60	79	78
PCNL	20	5	2
Ureteroscopy	11	15	20
Open surgery	9	1	0.1

Table 61-1 Changing use of techniques for stone removal. The changes in the application of surgical techniques for stone removal since the introduction of extracorporeal shock wave lithotripsy (ESWL) and percutaneous nephrolithotomy (PCNL). *(Data from reference 1.)*

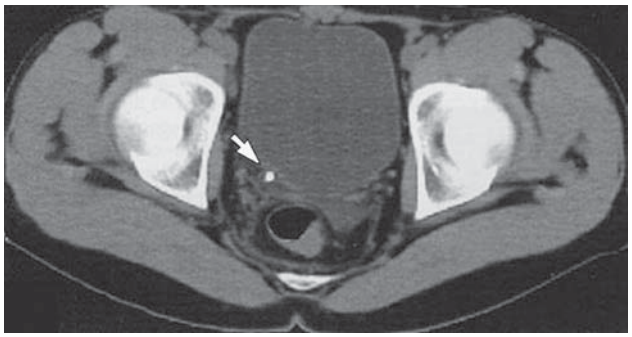

Figure 61-1 Computed tomography (CT) scan demonstrating a ureteral calculus. Non–contrast-enhanced CT scan showing a calculus *(arrow)* at the right vesicoureteral junction.

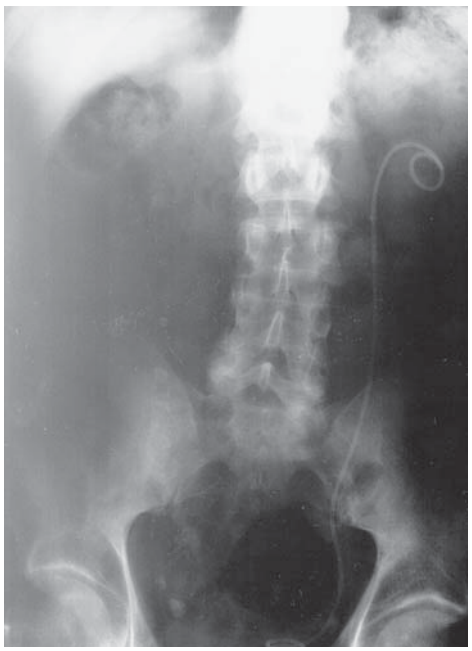

Figure 61-2 Ureteral stenting. Plain radiograph showing a double-J ureteral stent in the left ureter. Note that the curled ends of the stent remain in the pelvis despite ureteral peristalsis.

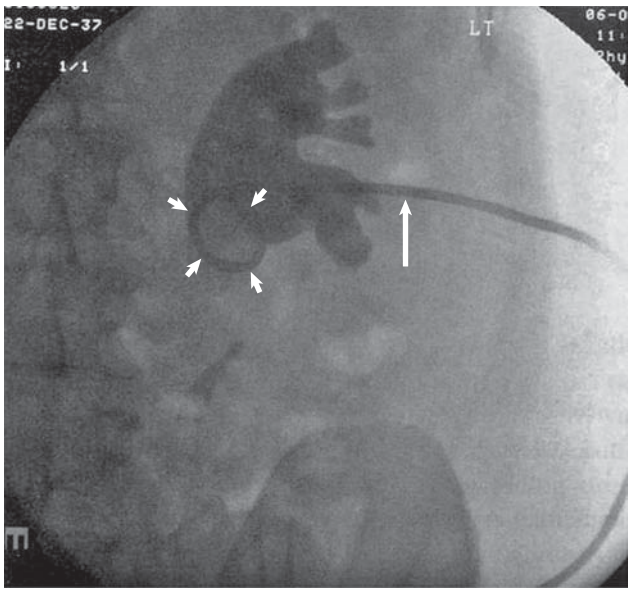

Figure 61-3 Nephrostogram in ureteral obstruction caused by a stone. Contrast material is injected through a percutaneous nephrostomy tube placed in the lower pole calyx *(arrow).* The contrast material outlines a single large calculus *(arrowheads)* producing complete obstruction at the pelviureteral junction.

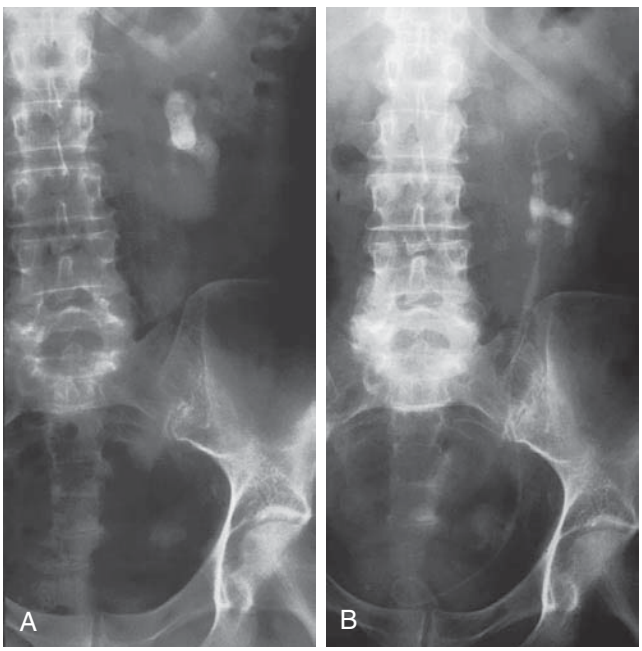

Figure 61-4 Extracorporeal shock wave lithotripsy (ESWL) complicated by Steinstrasse. A, Preoperative plain radiograph showing stones in the left renal pelvis. **B,** After ESWL, note the disappearance of the pelvic stone, the string of stone fragments throughout the length of the ureter, and the double-J ureteral stent placed to facilitate their passage.

lithotripter used. Cystine and calcium oxalate monohydrate stones are especially resistant. Targeting of the stone may be impossible in the presence of obesity and skeletal deformities (increased skin-to-stone distance), and ESWL is contraindicated in patients with aortic or renal artery aneurysm, uncontrolled urinary tract infection, or coagulation disorders and in pregnant women.

A double-J ureteral stent is sometimes placed endoscopically before ESWL treatment to prevent stone fragments from obstructing the distal ureter (*Steinstrasse,* literally "stone street"; Fig. 61-4). Other

Indications for Percutaneous Nephrolithotomy		
Composition*	Struvite stones	Complete removal necessary to eliminate infection and minimize stone recurrence
	Calcium oxalate monohydrate stones	Difficult to pulverize by ESWL
	Cystine stones	Difficult to pulverize by ESWL
Stone position	Lower pole stones	Fragments less easily evacuated from dependent lower pole calyces, especially if collecting system dilated
Anatomic abnormalities	PUJ obstruction Calyceal diverticula	Prevent passage of fragments after ESWL
Patient characteristics	Morbid obesity Ureteral obstruction	Stone cannot be placed in focal point of ESWL machine

Table 61-2 Indications for percutaneous nephrolithotomy. ESWL is the first choice for stone intervention, except in those circumstances that may favor PCNL. *ESWL,* Extracorporeal shock wave lithotripsy; *PCNL,* percutaneous nephrolithotomy; *PUJ,* pelviureteral junction. *Stone composition can be defined with certainty only by direct stone analysis, but advances in imaging may ultimately provide a means to accurately assess stone composition *in situ* before treatment, thus allowing the urologist to select the treatment most likely to be successful.

acute complications of ESWL include hemorrhage or hematoma, infection, and injury to adjacent organs. The risk for the later development of hypertension or renal impairment after ESWL remains controversial.

Extracorporeal shock wave lithotripsy is the first-line treatment for more than 75% of stone patients. Table 61-2 shows circumstances in which ESWL is less effective and PCNL becomes the preferred approach or a combination of the two modalities is used. For lower pole stones in particular, ESWL may not provide optimal clearance because of problems with the drainage of residual fragments. An RCT has shown that for lower pole stones larger than 10 mm, PCNL has much better clearance rates than ESWL (92% vs. 23%).[2]

Percutaneous Nephrolithotomy

During PCNL, a tract is created between the skin and the collecting system of the kidney and used as a working channel to remove stones. Preoperatively, IVU or CT, sometimes with three-dimensional reconstruction, is used to accurately localize calculi and neighboring organs (e.g., spleen, liver, large bowel, pleura, or lungs) and to plan access. The most frequently used access site is the dorsal calyx of the lower pole, and stone fragmentation is undertaken by ultrasound, pneumatic, or laser devices. The PCNL technique is modified for special circumstances, usually by altering the site of puncture (e.g., directly into a calyceal diverticulum) or, if there are ureteral stones, by using a higher-placed puncture to permit antegrade ureteroscopy. The percutaneous puncture may be facilitated by the preliminary placement of a retrograde ureteral catheter to dilate and to opacify the collecting system, which is then punctured under fluoroscopy. After completion of PCNL, a self-retaining balloon nephrostomy tube is used to tamponade the tract and to provide further access if needed. Hemorrhage can complicate PCNL (from renal or, rarely, intercostal arteries) and can usually be treated conservatively or by selective angiographic embolization. Other complications include sepsis; fluid overload (similar to transurethral resection syndrome); injury to spleen, pleura, or colon; and extravasation. PCNL usually results in minimal parenchymal injury, averaging only 0.15% of the total renal cortex.[3]

Indications for PCNL are shown in Table 61-2. These continue to evolve and are being challenged by developments in ureteroscopic techniques, which are allowing more upper ureteral and renal pelvic stones to be dealt with by a retrograde approach.

Open Stone Surgery

Although it is performed increasingly rarely, open surgery still has a place in the treatment of stone disease. It is reported that approximately 2% of stone patients are treated with open surgery, mainly when anatomic factors preclude the use of minimally invasive methods or when these techniques have failed. Other indications include complex stone burden and the presence of intrarenal anatomic abnormalities (e.g., pelviureteral junction obstruction). During surgery the renal pelvis as well as the parenchyma can be opened along avascular planes, and clamping of the renal vessels and hypothermia of the kidney may be needed. In selected patients a laparoscopic approach can be used for the treatment of stone disease.

Ureteroscopy

Recent advances in the design of endoscopes for ureteronephroscopy have rendered the entire urinary tract accessible to endoscopic examination and manipulation. Ureteroscopes may be semirigid or flexible, the latter allowing access to the renal pelvis and calyces. Stone fragmentation is achieved ideally by laser but also by ultrasound or pneumatic devices (lithoclast). Laser use is equally effective for all types of stones and has the additional advantages of a flexible fiber (allowing intrarenal stone fragmentation), low tissue penetration, and minimal stone displacement during use. Success rates for laser fragmentation of ureteral stones are high, in the region of 80%. Figure 61-5 highlights the increasing use of ureteroscopy in stone disease and also the increasing proportion of procedures in which a laser rather than ultrasound or a lithoclast is used to achieve stone fragmentation.

In the case of lower pole renal stones, although flexible ureteroscopes can access the lower pole to facilitate treatment, the stone-free rate in comparative studies is similar to that of ESWL.[4,5] Furthermore, patient preference is often ESWL in the first instance. As a result, it is common for patients to undergo ESWL before flexible ureteroscopy and lasertripsy. In the event of failed stone clearance after ureteroscopy, PCNL is commonly used next and is likely to remain an essential treatment for lower pole stones. Complications of ureteroscopy, particularly with use of graspers and baskets, include ureteral avulsion, perforation, extravasation, mucosal damage, hematuria, infection, and stricture. Advances in laser technology now enable stones to be reduced to dust-like particles, reducing the need for graspers and baskets and hence reducing complications.

Management of Staghorn Calculus

A staghorn calculus should usually be managed by intervention because reports of conservative therapy show a high rate of eventual nephrectomy (up to 50%) and an increase in associated morbidity (mainly renal failure) and mortality (up to 28%). Surgical options are ESWL monotherapy, complete endoscopic stone removal, and a combined approach with use of PCNL for debulking followed by ESWL. The advantage of the combined approach is the reduced need for additional renal access and secondary endourologic procedures.

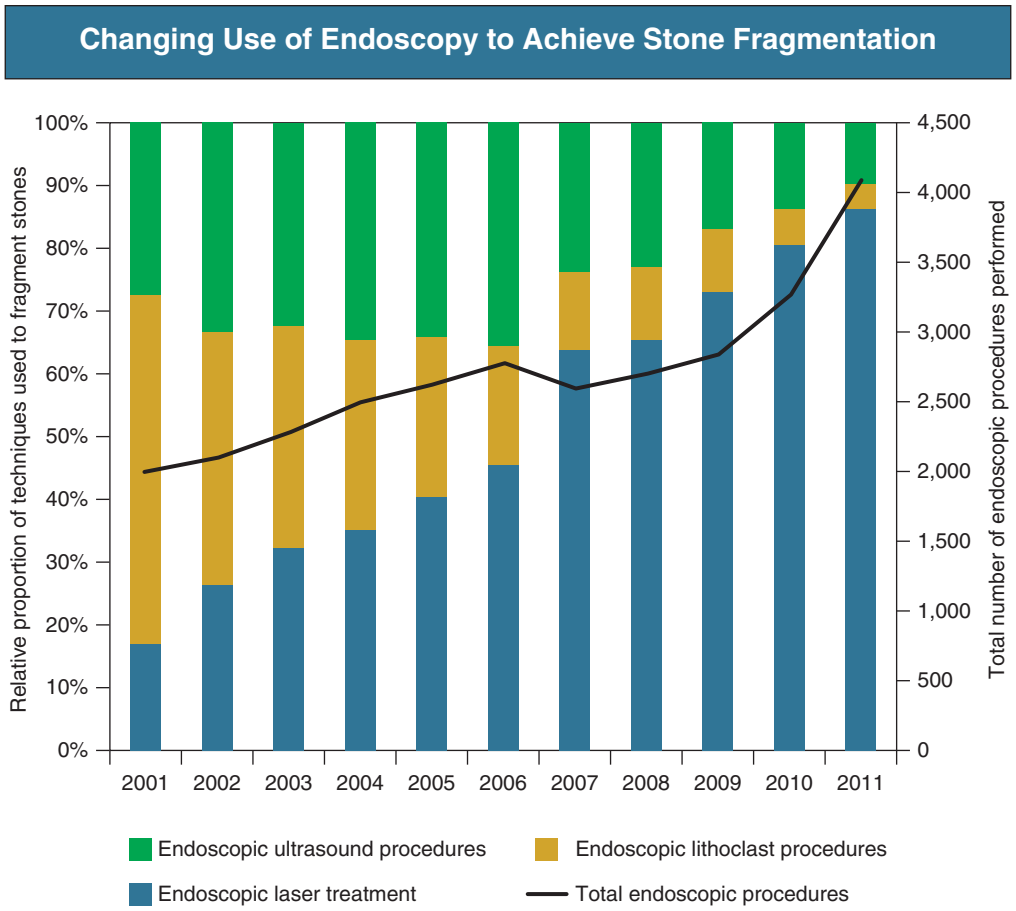

Figure 61-5 Changing use of endoscopy to achieve stone fragmentation. Chart showing the increasing use of endoscopy in stone surgery in addition to the increasing proportion of cases using lasers to achieve stone fragmentation. *(Data from UK Hospital Episode Statistics dataset.* http://www.hscic.gov.uk/hes. *Accessed June 9, 2012.)*

The choice of treatment depends on many factors, including the age and renal function of the patient. ESWL will not usually render the patient entirely stone free (the ideal goal of treatment), especially in the treatment of large staghorn stones; nevertheless, it can be considered successful when less than 40% of a staghorn calculus persisting as fragments is achieved. Rarely, open surgical removal of the stone may be indicated.

Stones in Transplanted Kidneys

The management of stone disease in a transplanted kidney is challenging because of the solitary kidney, the anatomic location within the pelvis, and the difficulty with retrograde access to the ureter and kidney. Early active intervention is indicated; prophylactic stenting, ureteroscopy, and PCNL are preferred to ESWL because stone targeting may not be possible. Open surgery may be needed in selected cases.

MANAGEMENT OF URINARY TRACT OBSTRUCTION

The causes of upper tract obstruction are listed in Chapter 60, Table 60-1, and a summary of the management of obstruction is given in Chapter 60, including Figure 60-7. Upper tract obstruction caused by malignant disease can be a result of direct tumor invasion or external compression by metastatic lymph node involvement or, rarely, true metastasis to the ureter. Some 70% of tumors causing ureteral obstruction are genitourinary (cervical, bladder, prostate) in origin; breast and gastrointestinal carcinomas and lymphoma constitute the majority of the remainder.[6] The presentation of a patient with obstruction may vary significantly, and hydronephrosis may develop progressively and insidiously and remain unrecognized until the patient develops anuria and uremia. Upper tract obstruction from malignant disease rarely presents with classic acute ureteral colic, which is typically seen with a benign cause such as a stone. Bladder outflow obstruction may be acute and dramatic, or chronic with few or no symptoms. To aid in understanding of the immediate needs and longer-term prognosis of these patients, the acute as well as the definitive management of the most common urologic diseases associated with obstruction and renal impairment are outlined.

Acute Management of Urinary Tract Obstruction

Relief of obstruction is crucial to reverse renal impairment and to preserve remaining renal function. In cases of bladder outflow obstruction, a urethral or suprapubic catheter is indicated; whereas in upper tract obstruction, a double-J ureteral stent is preferable, when possible. The most straightforward approach is endoscopic retrograde placement under fluoroscopy, with PCN reserved for

patients in whom the procedure fails. Bilateral stents should be placed if it is technically possible. However, tumor infiltration can distort trigonal anatomy, making identification of ureteral orifices for double-J stent insertion impossible at the time of cystoscopy. Furthermore, it has been suggested that stents fail to relieve obstruction in 40% to 50% of cases of external ureteral compression. Thus, these patients need to be closely monitored to ensure resolution of the obstruction. A new type of metallic, self-expanding stent, used alone or in conjunction with double-J stents, has had good results in maintaining ureteral patency and avoiding PCN in malignant ureteral obstruction.[6]

A stable patient with obstruction but without major signs of sepsis is a candidate for retrograde stent placement with use of general anesthesia. However, in a patient with sepsis, endoscopic manipulation can lead to bacteremia and rapid deterioration. Furthermore, such patients may not be fit for general anesthesia, in which case the preferred initial approach is PCN, which can then be followed after an interval with antegrade ureteral stenting. The success rate of this combined approach is high (>90%).[8] In patients with bilateral ureteral obstruction, it is not always necessary to insert bilateral PCN tubes. Significant palliation and return to nearly normal renal function can be accomplished by drainage of a single kidney, preferably the unit with the better preserved parenchyma as determined by CT scan or ultrasound. Once they have been placed, PCN tubes or double-J stents need to be replaced every 4 to 6 months. If they are left for a longer time, they become increasingly brittle and encrusted and are liable to fracture or break when they are manipulated. Complications of ureteral stents include migration, obstruction with proteinaceous material, infection, fragmentation, and rarely erosion through the urinary tract.[9] As many as 70% of patients with stents report lower urinary tract symptoms (LUITS), mainly urgency, frequency, and nocturia as well as pain along the urinary tract.

Morbidity after stenting or PCN is similar.[10] The main problem with indwelling stents is the increased risk of recurrent obstruction (11% for stents versus 1% for PCN). PCN may have an increased infection rate, and there may be psychological issues relating to the need for an external drainage bag.

Extra-anatomic stents are an alternative for patients in whom conventional stent insertion has failed or for whom permanent nephrostomy drainage is unacceptable. An extra-anatomic stent is placed by an initial percutaneous puncture and insertion of the upper end of a long (50-cm) double-J stent into the kidney. A subcutaneous tunnel is then created to bring the stent to the level of the iliac crest. Another tunnel is fashioned to bring the lower end of the stent out suprapubically, followed, finally, by suprapubic puncture of a full bladder and insertion of the lower end (Fig. 61-6).[11] Extra-anatomic stents are usually changed at 6-month intervals, and preliminary experience confirms their value in maintaining ureteral patency and avoiding PCN. Because of the effectiveness of minimally invasive methods, open surgery today is rarely indicated in the acute setting.

Pelviureteral Junction Obstruction

Surgical management of pelviureteral junction obstruction is aimed at obliterating the redundant (aperistaltic) portion of the ureter, allowing normalization of drainage from the affected kidney. The need for treatment is heralded by the onset of pain, infection, calculus formation, decline in renal function, or proven impaired excretion on MAG3 renography with impending decline in renal function. The gold standard treatment is now laparoscopic pyeloplasty, although traditional open techniques are still used. Robotic pyeloplasty and endoscopic treatments are also performed in some specialist centers.

Figure 61-6 Extra-anatomic stenting for malignant ureteral obstruction. Plain radiograph showing placement of an extra-anatomic stent for malignant obstruction of the right ureter. The upper end of the double-J stent has been placed in the right renal pelvis *(arrow)*. The stent then runs through a subcutaneous tunnel before the lower end enters the bladder *(arrowhead)*.

Retroperitoneal Fibrosis

Retroperitoneal fibrosis can be treated medically or surgically. A causative factor should be excluded (see Chapter 60). There are reports of favorable outcomes after immunosuppression with high doses of corticosteroids or azathioprine. Alternatively, surgery, consisting of ureterolysis (freeing the ureters from the fibrotic plaques) and omentoplasty (transposition of the ureters into the peritoneal cavity in omental wraps), can have good long-term results.

Malignant Obstruction

For upper tract transitional cell carcinoma, acute obstruction is best treated by internal stenting. PCN is avoided because of the risk of tumor seeding. Upper tract transitional cell carcinoma is an aggressive tumor and necessitates prompt extirpative surgery.

Bladder cancer can lead to hydronephrosis by invading the ureteral orifices and intramural ureter. Radical cystectomy is indicated, although temporary ureteral decompression may normalize renal function if neoadjuvant chemotherapy is planned. In selected cases, bladder preservation strategies combining systemic chemotherapy and radiotherapy can offer long-term control of the disease.

Prostate cancer causes obstruction by occluding the urethra or invading the ureteral orifices. Hormonal treatment can shrink prostatic tissue and malignant deposits and offer long-term remission of symptoms. Limited resection of the prostate may sometimes be indicated.

The decision to offer ureteral decompression for upper tract obstruction caused by cancer is not straightforward and requires input not only from the urologist but also from colleagues in radiation and medical oncology and the palliative care team. There must also be careful discussion of the options with the patient and family.

Percutaneous Nephrostomy for Malignant Obstructive Uropathy		
	Median Survival (wk)	5-yr Survival Rate (%)
Group I: primary untreated malignancy	27	10
Group II: recurrent malignancy with further treatment	20	20
Group III: recurrent malignancy with no further treatment	6.5	None survived longer than 1 yr
Group IV: benign disease as a result of previous treatment	Not stated	64
Overall	26	22

Table 61-3 Percutaneous nephrostomy for malignant obstructive uropathy. Outcome in 77 patients undergoing percutaneous nephrostomy for obstructive uropathy secondary to pelvic malignant disease. *(Data from reference 12.)*

Ureteral decompression is justified when radiotherapy and systemic chemotherapy remain therapeutic options after improvement in renal function but may also be justified for palliation of pain or ongoing renal tract sepsis.

A review of patients undergoing PCN for obstructive uropathy secondary to pelvic malignant disease identified a group of patients with very poor survival in whom ureteral decompression is usually not justified (Table 61-3).[12] Patients with gastric or pancreatic cancer survive a median of only 1.4 months after ureteral decompression, calling into question the benefit of such a procedure in this setting.[13] In another report, the average survival of patients with advanced malignant neoplasms undergoing endourologic diversion was only 5 months, half of which time was spent in the hospital.[14]

Benign Ureteral Strictures

These can be secondary to stone disease, iatrogenic, or caused by various benign diseases. The treatment of choice is endoscopic balloon dilation or ureterotomy. Open surgical repair or major reconstructive surgery may be needed in cases of recurrent strictures.

Bladder Outflow Obstruction

Bladder outflow obstruction in men is most frequently caused by either benign or malignant prostatic enlargement. Common presentations of both conditions include the onset of LUITS and acute (painful) or chronic (painless) retention of urine.

Chronic retention can be considered as the maintenance of voiding with incomplete bladder emptying. It is further classified into low- and high-pressure chronic retention. Low-pressure chronic retention occurs in the absence of upper tract compromise, whereas high-pressure chronic retention is associated with hydronephrosis and kidney injury.

In acute retention, low-pressure chronic retention, and LUITS caused by bladder outflow obstruction, medical therapy in the form of 5α-reductase inhibitors (finasteride, dutasteride) or α-adrenergic receptor blockers (tamsulosin, alfuzosin) is an accepted first-line treatment before surgery is offered.[15] Given the risk of worsening renal failure if medical therapy fails, it is not a safe management option in high-pressure chronic retention. Surgical management is reserved for patients who either derive no benefit from or are not willing to pursue medical therapy, those with acute and low-pressure chronic retention, and those with high-pressure chronic retention. Before surgery, evaluation of likelihood of success is essential. Patients with very high postvoid residual volumes of urine (more than 1 liter) are less likely to benefit from surgery because of the chronicity of their symptoms and consequent detrusor muscle weakness. These patients will be treated best with intermittent clean self-catheterization or a permanent urethral or suprapubic catheter.

The number of surgical management options available for bladder outflow obstruction is continually increasing. Although transurethral resection of the prostate (TURP) remains the gold standard procedure, the advancement of laser technology is likely to change this in the future. Holmium laser enucleation of the prostate (HoLEP) and vaporization of prostatic tissue (Green light laser) are being performed in specialist centers with favorable results with respect to reduced patient stay and postoperative catheterization. The widespread use of this technology is dependent on the results of ongoing comparative studies. A recently published 7-year follow-up study comparing TURP with HoLEP reported no significant difference in quality of life, maximum urinary flow, incontinence, or erectile dysfunction, with a reduced need for reoperation in the HoLEP arm of the study.[16]

Neurologic Diseases of the Lower Urinary Tract

Diseases of the central or peripheral nervous system can present with bladder underactivity or detrusor-sphincter dyssynergia and lead to bilateral hydroureter and hydronephrosis. Diabetes mellitus can also produce a flaccid denervated bladder through destruction of the peripheral nerves and can cause chronic retention and renal failure. Of diabetics who develop peripheral neuropathy, 75% to 100% will develop some neurogenic lower urinary tract dysfunction. The treatment of choice is generally intermittent clean self-catheterization, with a limited role for surgery.

INVESTIGATION OF HEMATURIA

Macroscopic, visible hematuria (macrohematuria) is perhaps the most important symptom in urologic practice, and quite apart from being alarming to the patient, it can be the first presenting sign of an underlying malignant condition of the urinary tract (most often a transitional cell tumor of the bladder). Studies show that 15% to 22% of patients with visible hematuria have an underlying genitourinary tract malignant neoplasm.

Patients with macrohematuria must be distinguished from those who have been found to have dipstick hematuria or microscopic hematuria, in whom the risk of malignant change is significantly lower (2% to 11%).

The outcome of full evaluation of a large group of patients (with both macrohematuria and microhematuria) attending a hematuria clinic is shown in Table 61-4.[17] In addition to a small but important group of patients in whom malignant disease was identified, there was a significant pickup rate of parenchymal renal disease (about 10%) presenting with both macrohematuria and microhematuria. It is also important to note the sizable proportion of patients in whom a definitive diagnosis could not be reached.

Evaluation of Macroscopic Hematuria

All adults with a single episode of macrohematuria require full urologic evaluation, including renal imaging and cystoscopy. The only

Outcome of Evaluation in a Hematuria Clinic			
Diagnoses Found	**All**	**Microscopic Hematuria**	**Macroscopic Hematuria**
No diagnosis	61	69	53
Renal cancer	0.6	0.3	0.9
Upper tract transitional cell carcinoma	0.1	0.1	0.1
Bladder cancer	12	5	19
Prostate cancer	0.4	0.2	0.6
Stone disease	4	4	3
Urinary tract infection	13	13	13
Renal parenchymal disease	10	9	10
Likelihood of Finding Malignancy			
		Microscopic Hematuria	**Macroscopic Hematuria**
Male, age >40 yr		8	24
Male, age <40 yr		2	7
Female, age >40 yr		5	19
Female, age <40 yr		0	0

Table 61-4 Outcome of evaluation in a hematuria clinic. Percentage of cases investigated, according to age. *(Data from reference 17.)*

exception to this rule occurs when an adult younger than 40 years gives a history characteristic of glomerular hematuria, such as is typically seen in IgA nephropathy, in which dark brown hematuria lasting 24 to 48 hours coincides with intercurrent mucosal infection, usually of the upper respiratory tract. This hematuria may be painless, or there may be bilateral loin ache. These young adults should be referred first for nephrologic assessment.

Evaluation of Microhematuria

Perhaps the greatest degree of overlap in practice between urologists and nephrologists occurs in the initial assessment of patients with microhematuria. Concurrent urinary tract infection will cause microhematuria and should be treated before further evaluation. Furthermore, features such as menstruation, vigorous exercise, viral illness, and trauma can themselves account for microhematuria. In the presence of a transient or treatable underlying cause other than urinary tract infection, repeat urinalysis should be performed 2 days later. In the presence of confirmed urinary tract infection, further urinalysis should be deferred until 6 weeks after treatment. If microhematuria resolves, no further investigation is required.

In 2012 the American Urological Association, after extensive systematic review of the literature, produced their guidance on the assessment and management of asymptomatic microscopic hematuria (AMH).

The definition of AMH for the purposes of these guidelines was the presence of three or more red blood cells per high power field on microscopic examination of one properly collected, noncontaminated urine sample. In addition to the benign causes listed, pyuria and bacteriuria should also be excluded with either dipstick or microscopy.

The most notable departure from previous guidance is the recommendation of urologic investigation after one episode of AMH, rather than waiting for two of three positive samples as previously suggested. There are currently no direct comparative studies identifying diagnostic yields in patients with one or more than one episode

Common Risk Factors for Urinary Tract Malignancy in Patients with Microhematuria
Male gender
Age (>35 years)
Past or current smoking
Occupational or other exposure to chemicals or dyes (benzenes or aromatic amines)
Analgesic abuse
History of gross hematuria
History of urologic disorder or disease
History of irritative voiding symptoms
History of pelvic irradiation
History of chronic urinary tract infection
History of exposure to known carcinogenic agents or chemotherapy such as alkylating agents
History of chronic indwelling foreign body

Box 61-1 Risk factors for malignancy in patients with microhematuria.

of AMH. Indirect comparison, however, reveals a diagnostic yield of urinary tract malignancy of 3.6% and 1.8% in patients with one or more than one episode of AMH, respectively.[18] Dipstick-positive hematuria may still herald significant disease in the absence of red cells on microscopy because red cells may lyse in alkaline or hypotonic urine before reaching the laboratory for analysis.[19] Urine microscopy is discussed further in Chapter 4.

Complete evaluation of microhematuria includes a history and physical examination, laboratory analysis, and radiologic imaging of the upper urinary tract, followed by cystoscopy (Fig. 61-7). In women, urethral and vaginal examinations should be performed to exclude local causes of microscopic hematuria. In uncircumcised men, the foreskin should be retracted to expose the glans penis, if possible. If a phimosis is present, a catheter specimen of urine may be required. Patients with urinary tract infection should be treated appropriately, and urinalysis should be repeated 6 weeks after treatment. If the hematuria resolves with treatment, no additional evaluation is necessary. An estimate of renal function should be obtained (estimated glomerular filtration rate [eGFR], creatinine, or blood urea nitrogen [BUN]) because intrinsic renal disease may have implications for consequent imaging and treatment. The remaining laboratory investigations are guided by specific findings of the history, physical examination, and urinalysis. Multiphase CT urography, which allows evaluation of renal parenchyma and also the collecting system, has been shown to have the highest sensitivity and specificity for imaging the upper tracts. If CT urography is unavailable, then IVU, and ultrasound combined with plain abdominal radiography are alternative imaging strategies. Cystoscopy is now advocated in all patients with AMH who are older than 35 years and those under the age of 35 years with risk factors for urologic malignancy or clinical suspicion of malignancy (Box 61-1). The use of adjuncts to AMH workup such as urine cytology and other urine biomarkers is no longer advocated.

Significant proteinuria (>0.3 g/24 h), red cell casts, predominance of dysmorphic red blood cells in the urine, or renal impairment should prompt referral to a nephrologist and evaluation for parenchymal renal disease. When present, red cell casts are virtually pathognomonic of glomerular bleeding, but they are often absent in low-grade glomerular disease. Accurate determination of red blood cell morphology requires inverted phase contrast microscopy. In general, glomerular bleeding is associated with more than 80%

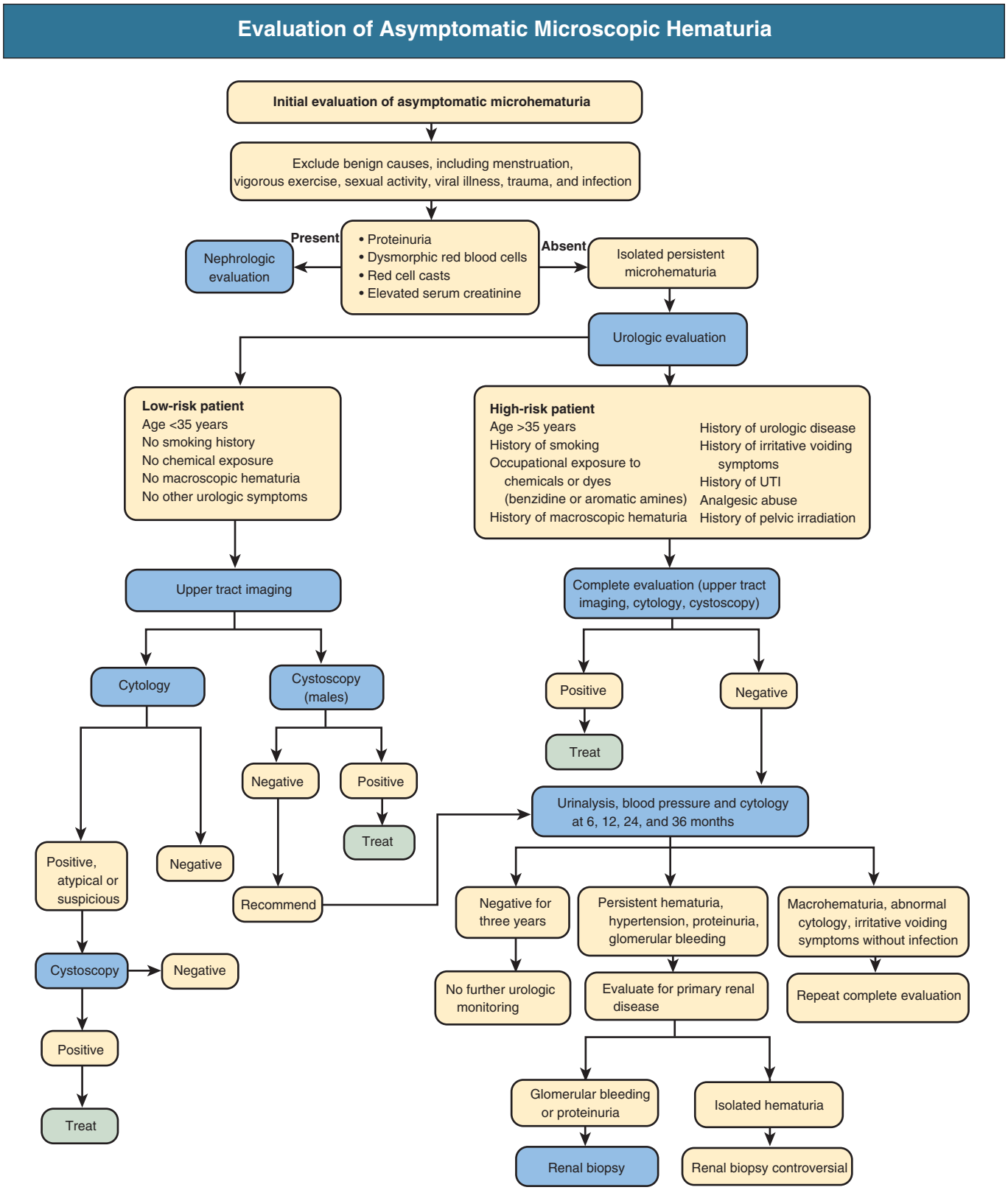

Figure 61-7 Evaluation of asymptomatic microscopic hematuria. *UTI,* Urinary tract infection.

dysmorphic red blood cells, and lower urinary tract bleeding is associated with more than 80% normal red blood cells.[20] This assessment is operator dependent. An alternative is to assess urinary red cell size by Coulter counter analysis because dysmorphic red cells are smaller than normal red cells, but this method is not useful when red cell numbers in the urine are small. Even in the absence of features of glomerular bleeding, many patients with isolated microscopic hematuria have glomerular disease, most commonly IgA nephropathy or thin basement membrane nephropathy.[21] Because there is a low risk of progressive renal disease, renal biopsy in this setting is not usually

recommended. Nevertheless, one study showed that microhematuria unexplained by urologic evaluation carries a twofold risk for eventual development of ESRD,[22] so these patients should be observed for the development of hypertension, renal impairment, or proteinuria.

Cyclophosphamide

Past treatment with cyclophosphamide increases the risk of bladder cancer up to ninefold, probably in a dose- and duration-dependent manner. Tumors have been reported 6 to 13 years after cyclophosphamide exposure and are often high grade. Hematuria is also common after cyclophosphamide in the absence of cancer. If full evaluation does not identify a cause of hematuria, there is no agreed-on surveillance protocol; it is not clear whether routine follow-up by cystoscopy and urine cytology is valuable, although a high index of suspicion should be maintained.

INVESTIGATION AND MANAGEMENT OF A RENAL MASS

The incidence of renal cancer has more than doubled in the last 30 years, and this cancer now accounts for 3% of all cancers. It is the third most common tumor of the urinary tract but is the most lethal. The apparent increased incidence is partly attributed to the widespread use of cross-sectional and sonographic imaging; more than 50% of new cases are incidental findings on CT, ultrasound, or magnetic resonance imaging (MRI).

The primary goal in investigating a renal mass is to exclude malignancy. Ultrasound has been reported to be 79% sensitive for the detection of renal parenchymal masses but does not detect lesions smaller than 5 mm. Until recently, the gold standard method of assessing renal masses was CT scanning with contrast enhancement, with use of no more than 5-mm slices. MRI, especially with T2-weighted images, may be superior to CT in the correct characterization of benign lesions.[23] Choice of imaging techniques and their interpretation are discussed further in Chapter 5.

Any solid mass larger than 3 cm should be regarded as malignant unless the radiologist can be confident that the mass is an angiomyolipoma because there is fat on CT images. A biopsy may be required if there is evidence suggestive of an alternative diagnosis (e.g., lymphoma or metastasis from another site) to guide appropriate management. In a recent study, in cases in which there was diagnostic uncertainty, a biopsy of the mass produced a high diagnostic accuracy rate (91.5%) with a low incidence of bleeding (2.8%) and no evidence of tumor seeding.[24]

The management of mixed cystic and solid masses is more of a problem. Table 61-5 shows the Bosniak classification of cystic renal masses.[25] This classification, based on CT appearances, provides the basis for management according to risk of malignancy. The evaluation of multiple cystic lesions in the kidney is discussed further in Chapter 47.

Tumor size is important; in a large retrospective study of 2935 patients with surgically treated solid renal tumors, 46% of lesions smaller than 1 cm were benign compared with 22% and 10% of tumors 1 to 2 cm and 4 to 5 cm, respectively. Furthermore, only 2.3% of cancers smaller than 1 cm were of high grade, whereas for tumors larger than 7 cm, the percentage was 58%.[26] Surveillance studies of small renal tumors have shown a median growth rate of 0.28 cm per year; about 30% of these lesions will not increase in size.

Traditionally, radical nephrectomy has been considered the gold standard treatment for localized renal cancers; however, partial nephrectomy for small renal masses is becoming increasingly popular. Comparison of these two approaches for lesions both smaller than 4 cm and 4 to 7 cm (T1 and T2 disease, respectively)

Classification and Management of Cystic Renal Masses

Bosniak Class	Features on Imaging	Comment	Management
Class I: simple benign cyst	Round or oval Uniform density <20 HU Unilocular No perceptible wall No contrast enhancement	Majority of asymptomatic cystic lesions	No further intervention required
Class II: benign cyst	One or two nonenhancing septa Calcifications in the wall or septum Hyperdense lesions (50-90 HU, resulting from the presence of blood, protein, or colloid) < 3 cm No contrast enhancement		No further intervention required
Class II F: probable benign cyst	Multiple hairline septa "Perceived" enhancement Nodular calcification Hyperdense lesions >3 cm	"Perceived" enhancement resulting from contrast within capillaries of septa	Surveillance with CT scans every 6-12 months
Class III: indeterminate cystic lesions	One or more of the following: Thick, irregular borders Irregular calcifications Thickened or enhancing septa Multilocular form Uniform wall thickening Small nonenhancing nodules	About 40% are neoplastic Magnetic resonance imaging may improve characterization	Surgical exploration
Class IV: presumed malignant cystic masses	Appear malignant Heterogeneous cysts Shaggy, thickened walls or enhancing nodules	Appearances result from necrosis and liquefaction of a solid tumor or a tumor growing in the wall	Surgical exploration

Table 61-5 Classification and management of cystic renal masses. Approach to renal mass found incidentally by ultrasound or computed tomography (CT) scanning. All patients with symptomatic renal masses should be referred for urologic assessment. Classification after Bosniak. *HU,* Hounsfield units. *(Data from reference 25.)*

has shown equal tumor outcome and a reduction in long-term cardiovascular complications with partial nephrectomy in younger patients.[27] Furthermore, increased early detection of small renal lesions with a possibility of late contralateral tumor development should be considered when surgery is planned. Radical nephrectomy should therefore be reserved for large renal cancers not amenable to partial nephrectomy.

Cryosurgery and radiofrequency ablation via open, laparoscopic, or percutaneous approaches are promising options for the treatment of localized renal cancers. There is currently no consensus on the maximum size of lesions amenable to these techniques, but they are usually reserved for tumors smaller than 4 cm in diameter. Laparoscopic cryotherapy was reported in one series to result in 5-year cancer-specific survival of 100%.[28] Radiofrequency ablation has also resulted in a 5-year recurrence-free survival rate of 93%.[29] Such treatments offer the advantages of nephron-sparing surgery in addition to their potential use in patients with high surgical risk. Disadvantages include absence of histologic confirmation of complete tissue destruction and potential for more difficult salvage surgery in the presence of local recurrence. These techniques to date have been used on a cohort of highly selected patients, and there are no comparative data or ongoing RCTs comparing radical and partial nephrectomy, cryosurgery, and radiofrequency ablation.

Adjunctive Therapy for Renal Cancer

The 5-year survival for patients diagnosed with localized renal cell carcinoma (RCC) is approximately 90%. However, up to one third of patients with RCC present with metastasis, and 5-year survival falls to 60% and 10% in the presence of regional and distant metastasis, respectively. Metastatic RCC (mRCC) is resistant to commonly used chemotherapeutic agents, and cytokine therapy with either interleukin (IL)–2 or interferon-α (IFN-α) was standard treatment for mRCC in the United States and Europe until 2005. Although more effective than traditional chemotherapy, it produced only modest response rates with significant toxicity.[30] Identification of the molecular pathways implicated in the progression from localized RCC to mRCC has led to the development of new targeted therapies directed against vascular endothelial growth factor (VEGF) (sorafenib, sunitinib, bevacizumab, pazopanib) and mammalian target of rapamycin (mTOR) (temsirolimus, everolimus). In Phase III trials these agents caused improvements when compared with cytokine therapy in both median progression-free survival (from 2 to 8 months to 4 to 11 months) and median overall survival (from 8 to 22 months to 11 to 26 months).[31-35] Furthermore, they caused improvements in progression-free survival and overall survival when used as second-line therapy for mRCC. There is not yet an international consensus on which agent or combination of agents is superior, although in the United Kingdom pazopanib is now considered first-line therapy in mRCC.[36] The adverse effects of pazopanib include hypertension, gastrointestinal hemorrhage, and fatigue.

Natural History of Renal Impairment After Surgical Treatment of Renal Cancer

It is well established that normal renal function can be preserved in the long term after donor transplant nephrectomy. However, donors are highly selected to minimize comorbidities and generally are younger than patients treated for renal tumors. After surgery for suspected renal cancer, when the residual renal mass is small, there is significant risk of late sequelae, including proteinuria, glomerulosclerosis, and progressive renal failure. These risks are greater when radical rather than partial nephrectomy is used. A retrospective survey studied 662 patients who underwent surgery for a tumor 4 cm or smaller, with normal preoperative serum creatinine concentration and a normal contralateral kidney on imaging[37]; 26% of patients had postoperative GFR lower than 60 ml/min, and mean GFR was 69 ml/min, significantly lower than reported after donor nephrectomy (92 to 103 ml/min). Postoperatively, the 3-year and 5-year probabilities that GFR remained above 60 ml/min were 80% and 67% after partial nephrectomy and 35% and 23% after radical nephrectomy. The probabilities that GFR remained above 45 ml/min were 95% and 93% after partial nephrectomy and only 64% and 57% for radical nephrectomy at 3 and 5 years postoperatively. Considering the excellent cancer-specific survival (>90%) of patients treated for renal tumors smaller than 4 cm, treatment-induced renal failure may have significant long-term consequences.

In another study, the effect of nephron-sparing surgery on solitary kidneys was assessed in a series of 400 patients.[38] Preoperatively, 56% of the patients had serum creatinine concentrations above 1.5 mg/dl (136 µmol/l). Transient renal failure was observed in 21% of patients postoperatively; hemodialysis was necessary in 3.5%. At a mean follow-up of 44 months, 38% had a greater than 50% increase in serum creatinine, although only 5% of patients progressed to end-stage renal disease (ESRD) requiring renal replacement therapy. Overall, patients with a congenital single kidney tolerated partial nephrectomy better than did patients with acquired solitary kidneys. Other factors affecting long-term renal function were age and the percentage of parenchyma resected but not the use of hypothermia or the duration of renal ischemia during surgery.

Renal Cell Carcinoma in von Hippel–Lindau Disease

von Hippel–Lindau disease (VHL) is a rare autosomal dominant condition with a predisposition to the development of RCC. The genetics, clinical manifestations, and general management of VHL are discussed further in Chapter 47. The incidence of RCC in patients with VHL is about 45%. On histologic examination, the tumors are of the clear cell type, often multifocal and bilateral, and can be solid or cystic. The mean age at diagnosis is 39 years, and there is a 30% to 35% risk for tumor progression, metastasis, and death.

A serial CT study[39] identified multiple lesions (on average, eight per patient) in VHL patients, of which 74% were classified as cysts, 8% as cysts with solid components, and 18% as solid masses. The solid components of cysts and the solid lesions almost always contained RCC. During a mean 2.4-year follow-up (range, 1 to 12 years), most cysts remained the same size (71%) or enlarged (20%), and 9% became smaller. On the contrary, 95% of solid masses increased in size. Although it is generally thought that the cysts are premalignant, the transformation of a simple cyst to a solid lesion was observed in only two patients. VHL patients require multidisciplinary management. Surgical intervention is deferred for tumors smaller than 3 cm because metastasis is rare. In addition, bilateral nephrectomy should be avoided, if possible, because of the substantial morbidity associated with renal replacement therapy. The standard of care for these patients is partial nephrectomy, and a 10-year survival rate of 81% has been reported.

The results of nephron-sparing surgery for VHL appear less satisfactory than for sporadic RCC because of a high risk of local tumor recurrence. Repeated surgery may be needed for new or growing lesions, and for this reason the use of minimally invasive methods is being investigated. Repeated ablation of tumors with radiofrequency and cryotherapy is possible with minimal morbidity; however, the long-term effectiveness of these methods has not yet been established.

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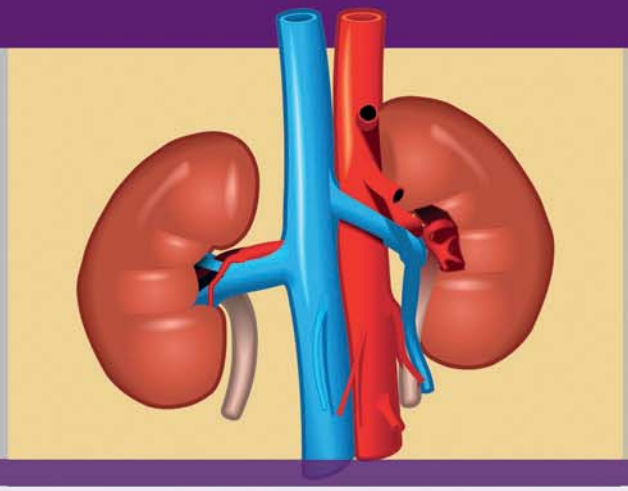

SECTION XI

Tubulointerstitial and Vascular Diseases

CHAPTER 62

Acute Interstitial Nephritis

Jerome A. Rossert and Evelyne A. Fischer

DEFINITION

Acute interstitial nephritis (AIN) is an acute, often reversible disease characterized by inflammatory infiltrates within the interstitium. AIN is a rare cause of acute kidney injury (AKI), but it should not be overlooked because it usually requires specific therapeutic interventions.

PATHOGENESIS

Most studies suggest that AIN is an immunologically induced hypersensitivity reaction to an antigen that is classically a drug or an infectious agent. Evidence for a hypersensitivity reaction in drug-induced AIN includes the following: it occurs only in a small percentage of individuals; it is not dose dependent; it is often associated with extrarenal manifestations of hypersensitivity; it recurs after accidental reexposure to the same drug or to a closely related one; and it is sometimes associated with evidence of delayed-type hypersensitivity reaction (renal granulomas). Similarly, AIN secondary to infections can be differentiated from pyelonephritis by the relative absence of neutrophils in the interstitial infiltrates and the failure to isolate the infective agent from the renal parenchyma, again suggesting an immunologic basis to the disease.

Studies of experimental models of AIN have shown that three major categories of antigens can induce AIN.[1] Antigens may be tubular basement membrane (TBM) components (such as the glycoproteins 3M-1 and TIN-Ag/TIN1), secreted tubular proteins (such as Tamm-Horsfall protein), or nonrenal proteins (such as from immune complexes).

Although some types of human AIN may be secondary to an immune reaction directed against a renal antigen, the majority of cases of AIN are probably induced by extrarenal antigens, being produced in particular by drugs or infectious agents. These antigens may be able to induce AIN by a variety of mechanisms. These mechanisms include binding to kidney structures ("planted antigen"); acting as haptens that modify the immunogenicity of native renal proteins; mimicking renal antigens, resulting in a cross-reactive immune reaction; and precipitating within the interstitium as circulating immune complexes.

Studies of experimental models of AIN show that their pathogenesis involves either cell-mediated immunity or antibody-mediated immunity (Fig. 62-1). In humans, most forms of AIN are not associated with antibody deposition, which suggests that cell-mediated immunity plays a major role. This hypothesis is reinforced by the fact that interstitial infiltrates usually contain numerous T cells and that these infiltrates sometimes form granulomas. Nevertheless, deposition of anti-TBM antibodies or of immune complexes can be observed occasionally in renal biopsy specimens, and antibody-mediated immunity may play a role in the pathogenesis of the disease in these cases.

Formation of immune complexes within the interstitium, or interstitial infiltration with T cells, will result in an inflammatory reaction. This reaction is triggered by many events, including activation of the complement cascade by antibodies and release of inflammatory cytokines by T lymphocytes and phagocytes (see Fig. 62-1). Although the interstitial inflammatory reaction may resolve without sequelae, it sometimes induces interstitial fibroblast proliferation and extracellular matrix synthesis, leading to interstitial fibrosis and chronic renal failure. Cytokines such as transforming growth factor β appear to play a key role in the latter process.

EPIDEMIOLOGY

Acute interstitial nephritis is an uncommon cause of AKI and is identified in only about 2% to 3% of all renal biopsy specimens, although this proportion could be increasing.[2] However, it may account for up to 10% to 25% of patients undergoing renal biopsy for unexplained or drug-induced AKI, respectively.[2] Although AIN can occur at any age, it appears to be rare in children.

Before antibiotics were available, AIN was most commonly associated with infections, such as scarlet fever and diphtheria. Currently, AIN is most often induced by drugs, particularly antimicrobial agents, proton pump inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs). Drug-induced AIN appears to account for about 75% to 90% of all cases.

DRUG-INDUCED ACUTE INTERSTITIAL NEPHRITIS

Clinical Manifestations

In the 1960s and 1970s, most cases of drug-induced AIN were caused by methicillin, and the clinical manifestations of methicillin-induced AIN were considered the prototypical presentation of AIN. Since then, many other drugs have been implicated in the induction of AIN (Box 62-1), of which antimicrobial agents (in particular, β-lactam antibiotics, sulfonamides, fluoroquinolones, and rifampin) and NSAIDs (especially fenoprofen) as well as cyclooxygenase-2 (COX-2) inhibitors have been most commonly involved. Antiulcer agents, diuretics, phenindione, phenytoin, and allopurinol have also been reported to cause AIN. There are increasing numbers of reports of AIN induced by proton pump inhibitors, with more than 70 reported biopsy-proven cases.[3] Recently, cases of drug-induced AIN have also been reported in human immunodeficiency virus (HIV)–infected patients treated with highly active antiretroviral therapy (HAART)[4] and in cancer patients treated with tyrosine kinase inhibitors.[5] Most other drugs have only rarely been linked with AIN (see Box 62-1). The clinical characteristics of drug-induced AIN are now recognized as much more varied and nonspecific than the spectrum seen in classic methicillin-induced AIN (Fig. 62-2).[2,6,7]

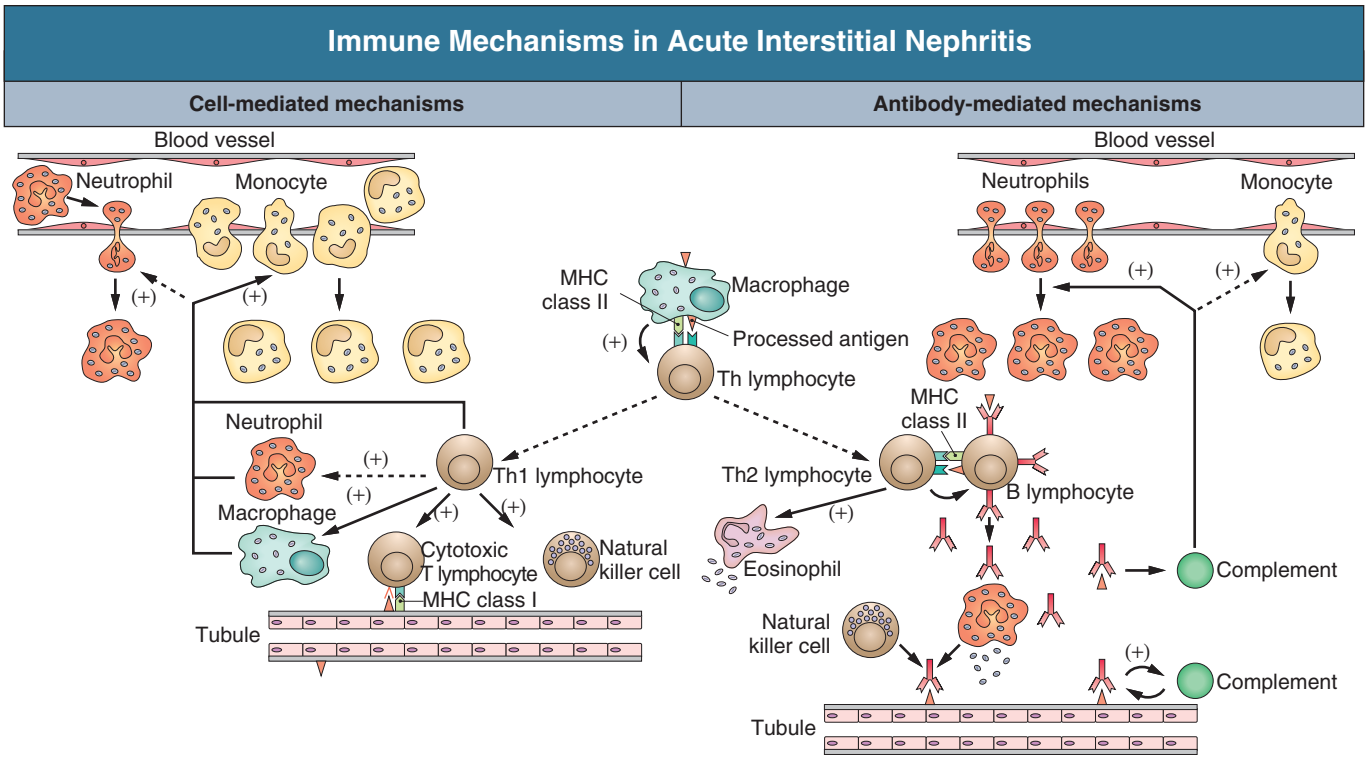

Figure 62-1 Immune mechanisms that can be involved in acute interstitial nephritis. Both cell-mediated and antibody-mediated mechanisms occur. The cell-mediated mechanism is primarily associated with macrophages and T cells. The antibody-mediated mechanism is frequently associated with neutrophil or eosinophil infiltration as well as with local complement activation. *MHC,* Major histocompatibility complex.

Renal Manifestations

Symptoms of AIN usually develop a few days to a few weeks after the inciting drug is started, although cases have occurred months after initial exposure to the drug. The typical presentation is sudden impairment in renal function, associated with mild proteinuria (<1 g/day) and abnormal urinalysis, in a patient with flank pain, normal blood pressure, and no edema. In patients with AIN not caused by methicillin, the clinical presentation is often incomplete (see Fig. 62-2), and AIN should be considered in any patient with unexplained AKI.[2,6,7] The renal dysfunction may be mild or severe; dialysis is required in about one third of patients. Hematuria and pyuria are present in a little more than half of the patients, and although leukocyte casts are common, hematuria is almost never associated with red blood cell casts. Flank pain, reflecting distention of the renal capsule, is observed in about one third of the patients and can be the main complaint on hospital admission. On occasion, patients have a low fractional excretion of sodium.

Standard imaging procedures show kidneys normal in size or slightly enlarged. Ultrasound usually discloses an increased cortical echogenicity (comparable to or higher than that of the liver).

Extrarenal Manifestations

Extrarenal symptoms consistent with a hypersensitivity reaction are occasionally observed, including low-grade fever, maculopapular rash (Fig. 62-3), mild arthralgias, and eosinophilia. If patients with methicillin-induced AIN are not considered, each of these symptoms is present in less than half of the patients (see Fig. 62-2), and all these symptoms are present together in less than 10% of patients.[2,6,7] With some drugs, other manifestations of hypersensitivity, such as hemolysis or hepatitis, can be present. Serum IgE levels may also be elevated.

The association of AKI either with clinical signs suggestive of hypersensitivity or with eosinophilia should lead to consideration of a diagnosis of AIN. However, signs of hypersensitivity can also be observed in patients with AKI not related to AIN, including patients with drug-induced acute tubular necrosis.

Other Specific Drug Associations

The clinical and biologic manifestations of AIN may have some specificity, depending on the drug involved.

As outlined earlier, methicillin-induced AIN is characterized by a high frequency of abnormal urinalysis and extrarenal symptoms and by good preservation of renal function. Renal failure has been reported in only about 50% of patients (see Fig. 62-2).

More than 200 cases of rifampin-induced AKI have been reported. Most have been observed either after readministration of rifampin or several months after intermittent administration of the drug. Renal failure is usually associated with the sudden onset of fever, gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), and myalgias. It may also be associated with hemolysis, thrombocytopenia, and less frequently hepatitis. Renal biopsy typically discloses tubular injury in addition to interstitial inflammatory infiltrates. Although circulating anti-rifampin antibodies are usually found in these patients, immunofluorescence staining of renal biopsy specimens has been negative in most cases, suggesting that cell-mediated immunity plays a key role in the induction of the nephritis. In a few cases, AIN developed after continuous treatment with rifampin for 1 to 10 weeks. It was almost never associated with extrarenal symptoms or with anti-rifampin antibodies, and renal biopsy specimens showed severe interstitial infiltrates but few tubular lesions.

Phenindione-induced AIN is generally associated with the development of hepatitis, which can be fatal.

Drugs Responsible for Acute Interstitial Nephritis (AIN)

Antimicrobial Agents

Penicillins

Amoxicillin
Ampicillin*
Aztreonam
Carbenicillin
Cloxacillin
Flucloxacillin
Methicillin*
Mezlocillin
Nafcillin
Oxacillin*
Benzylpenicillin*
Piperacillin

Cephalosporins

Cefaclor
Cefazolin
Cefotaxime
Cefotetan
Cefoxitin
Ceftriaxone
Cephalexin
Cephaloridine
Cephalothin
Cephradine

Quinolones

Ciprofloxacin*
Levofloxacin*
Moxifloxacin
Norfloxacin

Others

Acyclovir
Azithromycin
Clarithromycin
Colistin
Cotrimoxazole*
Erythromycin*
Ethambutol
Flurithromycin
Foscarnet
Gentamicin
Indinavir
Interferon
Isoniazid
Lincomycin
Linezolid
Minocycline
Nitrofurantoin*
Piromidic acid
Polymyxin B*
Quinine
Rifampin* (rifampicin*)
Spiramycin*
Sulfonamides*
Teicoplanin
Telithromycin
Tetracycline
Vancomycin*

NSAIDs Including Salicylates

Salicylates and Derivatives

Aspirin (acetyl salicylic acid)
Diflunisal*

Propionic Acid Derivatives

Benoxaprofen
Fenbufen
Fenoprofen*
Flurbiprofen
Ibuprofen*
Ketoprofen
Naproxen

Acetic Acid Derivatives

Indometacin* (indomethacin*)
Alclofenac
Diclofenac
Fenclofenac
Sulindac
Zomepirac

Enolic Acid Derivatives

Meloxicam
Piroxicam*

Fenamic Acid Derivatives

Mefenamic acid

Coxibs

Celecoxib
Rofecoxib

Others

Azapropazone
Mesalamine (mesalazine, 5-ASA)
Phenazone
Phenylbutazone
Sulfasalazine
Tolmetin

Antalgics

Aminopyrine
Antipyrine

Anticonvulsants

Carbamazepine*
Diazepam
Levetiracetam
Phenobarbital (phenobarbitone)
Phenytoin*
Valproic acid (valproate sodium)

Diuretics

Chlorthalidone
Etacrynic acid (ethacrynic acid)
Furosemide* (frusemide*)
Hydrochlorothiazide*
Indapamide
Triamterene*

Antiulcer Agents

H_2 Receptor Antagonists

Cimetidine*
Famotidine
Ranitidine

Proton Pump Inhibitors

Esomeprazole
Lansoprazole
Omeprazole
Pantoprazole
Rabeprazole

Others

Allopurinol*
Alpha methyl dopa
Amlodipine
Azathioprine
Betanidine (bethanidine)*
Bismuth salts
Captopril*
Carbimazole
Cetirizine
Chlorpropamide*
Clofibrate
Clozapine
Cyclosporine
Cytosine arabinoside
Deferasirox
Diltiazem
D-Penicillamine
Etanercept
Fenofibrate*
Fluindione
Gold salts
Griseofulvin
Interleukin-2
Lamotrigine*
Lenalidomide
Phenindione*
Phenothiazine
Phenylpropanolamine
Probenecid
Propranolol
Propylthiouracil
Sirolimus
Sorafenib
Streptokinase
Sulfinpyrazone
Sunitinib
Warfarin
Zopiclone

Box 62-1 Drugs responsible for acute interstitial nephritis. Drugs most commonly involved are in bold. *NSAIDs,* Nonsteroidal anti-inflammatory drugs. *Drugs that can cause granulomatous AIN.

Allopurinol-induced AIN appears to occur more often in patients with chronic kidney disease (CKD) and is usually seen in association with rash and liver dysfunction, and sometimes with full manifestations of the Stevens-Johnson syndrome. This severe allergic reaction is primarily observed in patients with the human leukocyte antigen (HLA)–B58 genotype. It has been suggested that the decreased excretion of oxypurinol, a metabolite of allopurinol, might favor the occurrence of AIN. There is also some experimental evidence that in the setting of renal impairment, allopurinol may precipitate as microcrystals or crystals and cause direct nephrotoxicity. Whether this can occur in humans is unknown, but it may provide an additional reason to reduce allopurinol doses in patients with CKD.

Acute interstitial nephritis occurring secondary to NSAIDs is associated with nephrotic syndrome in about three fourths of cases. This usually occurs in patients older than 50 years, and although it has been observed with all NSAIDs, including COX-2–selective

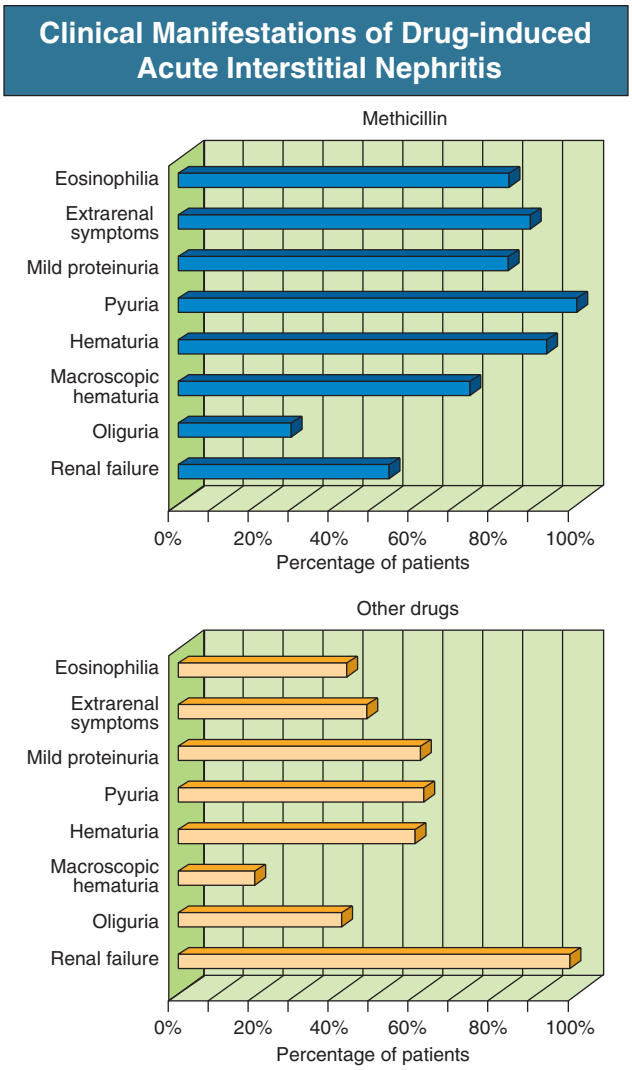

Figure 62-2 Clinical manifestations of drug-induced acute interstitial nephritis (AIN). Data were pooled from different case reports, including 95 patients with methicillin-induced AIN and more than 200 patients with other drug-induced AIN. Patients with AIN associated with a nephrotic syndrome are not included.

Figure 62-3 Maculopapular rash in a patient with drug-induced acute interstitial nephritis (AIN). Such cutaneous lesions occur in about 40% of patients with drug-induced AIN, but they can also be seen in patients with drug-induced acute tubular necrosis.

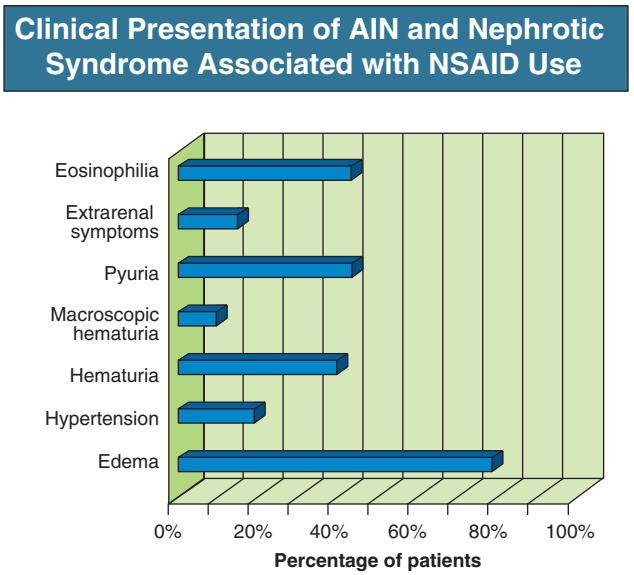

Figure 62-4 Clinical presentation of acute interstitial nephritis (AIN) and nephrotic syndrome associated with nonsteroidal anti-inflammatory drug (NSAID) use. Data were pooled from different case reports from more than 60 patients.

inhibitors, half of the incidents have been reported with fenoprofen. Most occurrences develop after the patient has taken NSAIDs for some months (mean, 6 months), but AIN can occur within days or after more than a year. With the exception of the heavy proteinuria and associated edema, the presentation of these patients is similar to that of patients with other drug-induced AIN (Fig. 62-4). The main difference is that extrarenal symptoms are present in only about 10% of patients. Renal disease caused by NSAIDs must be differentiated from other NSAID-induced nephropathies, including hemodynamically mediated AKI, papillary necrosis, and NSAID-induced membranous nephropathy. Drugs other than NSAIDs can rarely induce AIN associated with a nephrotic syndrome; a few cases have been reported after administration of ampicillin, rifampin, lithium, interferon, phenytoin, pamidronate, and D-penicillamine.

Pathology

The hallmark of AIN is the presence of inflammatory infiltrates within the interstitium (Fig. 62-5). These infiltrative lesions are often patchy, predominating in the deep cortex and in the outer medulla, but they can be diffuse in severe cases. They are composed mostly of T cells and monocytes-macrophages, but plasma cells, eosinophils, and a few neutrophilic granulocytes may also be present. The relative number of $CD4^+$ T cells and $CD8^+$ T cells is variable from one patient to another. In some cases, T lymphocytes infiltrate across the TBM and between tubular cells, mainly in distal tubules, and the resulting lesion is referred to as tubulitis.

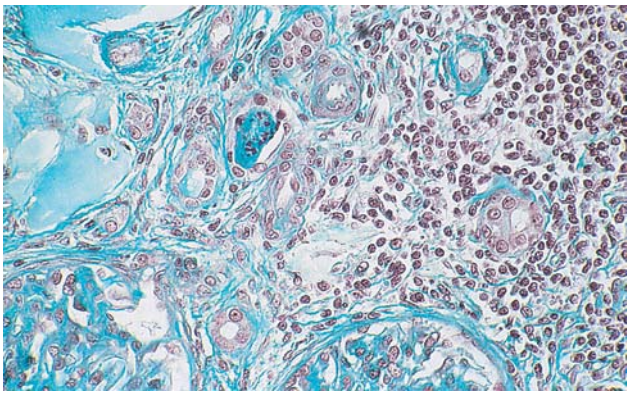

Figure 62-5 Drug-induced acute interstitial nephritis. On light microscopy, the characteristic feature is interstitial infiltration with mononuclear cells, with normal glomeruli. It is usually associated with interstitial edema and tubular lesions. *(Courtesy Dr. B. Mougenot, Paris VI University, Paris.)*

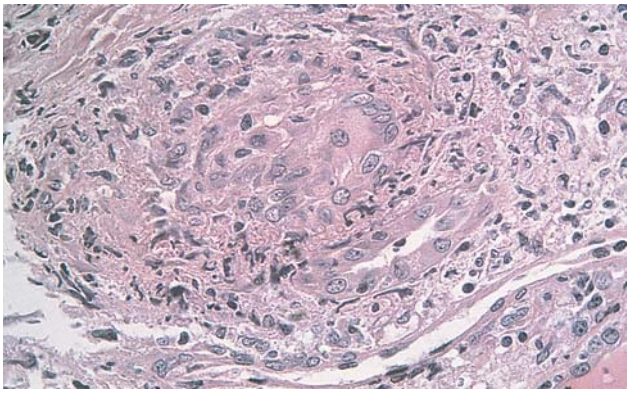

Figure 62-6 Drug-induced granulomatous acute interstitial nephritis. Some drugs can induce the formation of interstitial granulomas, which reflect a delayed-type hypersensitivity reaction. *(Courtesy Dr. B. Mougenot, Paris VI University, Paris.)*

In some cases of drug-induced AIN, renal biopsy shows interstitial granulomas (Fig. 62-6). These granulomas are usually sparse and non-necrotic, with few giant cells, and are associated with nongranulomatous interstitial infiltrates. Granulomas are also found in AIN related to infection (see Table 62-2), sarcoidosis, Sjögren syndrome, and Wegener granulomatosis.

Interstitial infiltrates are always associated with an interstitial edema, which is responsible for separating the tubules (see Fig. 62-5). They can also be associated with focal tubular lesions, which range from mild cellular alterations to extensive necrosis of epithelial cells and are sometimes associated with a disruption of the TBM. These tubular lesions usually predominate where the inflammatory infiltrates are most extensive.

Tubulointerstitial lesions are not associated with vascular or glomerular lesions. Even in AIN associated with a nephrotic syndrome, glomeruli appear normal on light microscopy; glomerular lesions are similar to those seen in minimal change disease (see Chapter 17).

In most patients with AIN, renal biopsy specimens do not show immune deposits, and both immunofluorescence and electron microscopy are negative. Nevertheless, staining of the tubular or capsular basement membrane for IgG or complement may occasionally be seen by immunofluorescence; the staining pattern is either granular or linear (Fig. 62-7). Linear fixation of IgG along the TBM indicates the presence of antibodies directed against membrane antigens or against drug metabolites bound to the TBM, and circulating anti-TBM antibodies have been detected in some cases. These linear deposits are seen mostly in patients taking methicillin, NSAIDs, phenytoin, or allopurinol.

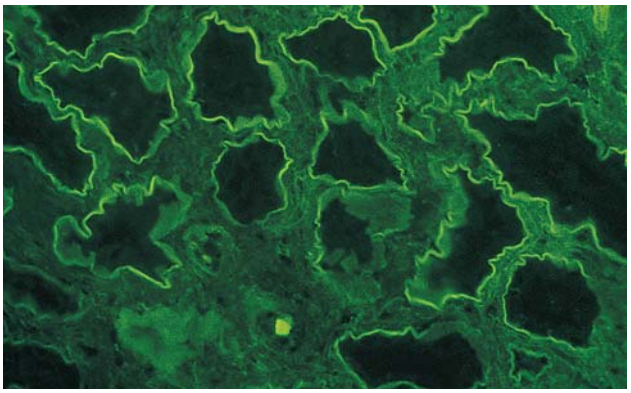

Figure 62-7 Linear deposits of IgG in methicillin-induced acute interstitial nephritis. Deposits along the tubular basement membrane (TBM) are shown on immunofluorescence microscopy. These antibodies recognize either a component of the TBM or a methicillin metabolite (dimethoxyphenylpenicilloyl) bound to the TBM. *(Courtesy Dr. B. Mougenot, Paris VI University, Paris.)*

Diagnosis

The most accurate way to diagnose AIN is by renal biopsy. However, both eosinophiluria and gallium scanning have been suggested as helpful in making the diagnosis.

Eosinophils can be detected in urine with use of either the Wright stain or the Hansel stain, both of which are eosin–methylene blue combinations, but the Hansel stain appears to be much more sensitive.[8,9] The result of this test is usually considered positive if more than 1% of urinary white blood cells are eosinophils. However, although eosinophiluria is frequently used to corroborate the diagnosis of drug-induced AIN, review of four large series shows that this test has rather poor sensitivity (67%) and a low positive predictive value, even when only patients with AKI are considered (50%) (Table 62-1).[8-11] In these series, the specificity of the test was 87%, and eosinophiluria was also observed in patients with acute tubular necrosis, postinfectious or crescentic glomerulonephritis (GN), atheroembolic renal disease, urinary tract infection, urinary schistosomiasis, and even pre-renal AKI. In particular, 28% of patients with urinary tract infection had eosinophiluria. Thus, whereas screening for eosinophiluria is still the commonly used screening test, it lacks sensitivity and specificity, and firm diagnosis requires renal biopsy and/or a clinical response on withdrawal of the drug of concern.

An increased renal uptake of gallium 67 has been reported in AIN.[12] Analysis of available series shows that in 45 patients with AIN, 88% had an abnormal renal scan (maximum after 48 hours), whereas it was normal in 17 of 18 patients with acute tubular necrosis. However, these studies were small and retrospective, and gallium 67 renal scanning is not specific for AIN and may be abnormal in patients with pyelonephritis, cancer, or glomerular diseases. Therefore, we also do not recommend use of gallium scanning as a diagnostic tool.

Because the clinical presentation of AIN may be polymorphic and because noninvasive diagnostic procedures have important limitations, renal biopsy is often essential for the diagnosis of AIN. Several studies have shown that prebiopsy diagnosis may be incorrect in a substantial number of patients.

Eosinophiluria in the Diagnosis of Acute Interstitial Nephritis (AIN)					
	Corwin et al.[8]	Nolan et al.[9]	Corwin et al.[10]	Ruffing et al.[11]	All series n (%)
Patients with AIN (n)	9	11	8	15	43
Eosinophiluria	8	10	5	6	29 (67%)
No eosinophiluria	1	1	3	9	14 (33%)
Patients without AIN (n)	56	81	175	184	496
Eosinophiluria	27	12	15	10	64 (13%)
No eosinophiluria	29	69	160	174	432 (87%)
Patients with Acute Kidney Injury					
Patients with AIN (n)	9	11	8	15	43
Eosinophiluria	8	10	5	6	29 (67%)
No eosinophiluria	1	1	3	9	14 (33%)
Patients without AIN (n)	14	46	84	23	167
Eosinophiluria	6	5	2	6	19 (11%)
No eosinophiluria	8	41	82	17	148 (89%)

Table 62-1 Eosinophiluria in the diagnosis of acute interstitial nephritis. The four large available series were analyzed to assess the value of eosinophiluria (defined by the presence of >1% of eosinophils in urine) for the diagnosis of drug-induced AIN. Only 67% of AIN was associated with eosinophiluria, whereas 13% of non-AIN was associated with eosinophiluria.

Identification of the Causative Drug

Identification of the causative drug is relatively easy when AIN occurs in a patient taking only one drug. However, patients are often taking more than one drug capable of inducing AIN. Two biologic tests have been used, primarily in research laboratories, to help identify the causative drug: the lymphocyte stimulation test and the identification of circulating antidrug antibodies.

Identification of circulating antidrug antibodies has been used mostly for patients thought to have AIN induced by rifampin. Antirifampin antibodies are present in most patients with rifampin-induced AIN; but unfortunately, they have also been detected in patients taking rifampin and having no adverse reaction to the drug, so this test has a limited diagnostic value.

The lymphocyte stimulation test has been used since the 1960s to identify a sensitizing drug. It is based on the measurement of lymphocyte proliferation in the presence of different drugs; a high proliferative index reflects a sensitization of T lymphocytes against the drug. However, this test lacks specificity and we do not recommend using it.

Natural History

Drug-induced AIN was long considered benign, with complete recovery of renal function if the inciting agent was removed. For example, with methicillin-induced AIN, a complete normalization of serum creatinine has been observed in about 90% of uremic patients. Nevertheless, although hematuria, leukocyturia, and extrarenal symptoms usually disappeared within 2 weeks, complete recovery of renal function was often delayed, with an average recovery time of about 1.5 months.

More recent studies show that with drugs other than methicillin, the course of AIN is not always benign and that serum creatinine remains elevated in about 40% to 50% of patients.[6,13] Moreover, as for methicillin, recovery of renal function can be delayed, and an increase in serum creatinine can persist for several weeks. Unfortunately, few prognostic factors are available. The severity of renal failure does not appear to be linked with the prognosis.[6] It has been suggested that the presence on renal biopsy of diffuse neutrophil- or macrophage-rich infiltrates, interstitial granulomas, or tubular atrophy is associated with a poor prognosis, but this has not been consistently found in all series. The best prognostic factors may actually be the duration of AKI and the severity of interstitial fibrosis.

Treatment

In addition to removal of the inciting agent, corticosteroids have been used to treat AIN. Most commonly, patients received an initial daily dose of 1 mg of prednis(ol)one per kilogram, which was then tapered during about 1 month; this oral therapy was sometimes associated with pulses of methylprednisolone. Analysis of series comparing patients who did or did not receive corticosteroids does not allow firm conclusion about the effect of corticosteroid therapy on long-term renal function, all the series being small, uncontrolled, and retrospective. However, some authors advocate an early and systematic use of a short course of corticosteroids.[7,13] In addition, it seems that a brief course of corticosteroids can hasten the recovery of renal function. In different series, corticosteroids rapidly induced a reduction in serum creatinine in patients whose renal function did not improve within about 1 week after discontinuation of the inciting agent. It is interesting to note that in patients with NSAID-induced AIN, corticosteroids do not seem to modify the course of the nephrotic syndrome.

On the basis of anecdotal case reports, some authors have also advocated use of mycophenolate mofetil in patients resistant to corticosteroids.[14]

We recommend administration of a short course of prednis-(ol)one in patients who are dialysis dependent or whose renal function fails to improve rapidly within 1 week after discontinuation of the inciting drug and return to baseline values, provided the diagnosis of AIN has been confirmed by renal biopsy. We initiate the treatment with a dose of prednis(ol)one of 1 mg/kg/day and not higher than 60 mg/day, and after 1 to 2 weeks, we progressively taper the dose so that the total duration of treatment is 4 to 6 weeks.

ACUTE INTERSTITIAL NEPHRITIS SECONDARY TO INFECTIOUS DISEASES

Infections were once the most common cause of AIN, but the frequency of AIN induced by an infection has dramatically decreased

with the widespread use of antibiotics. Nevertheless, the diagnosis of infectious AIN should not be overlooked, and AIN occurring in patients treated with antibiotics should not always be attributed to the drug.

Infectious agents can cause renal parenchymal inflammation by direct infection, resulting in acute pyelonephritis (see Chapter 53). However, many infectious agents may also induce an immunologically mediated AIN in the absence of direct invasion (Table 62-2). In this case, the clinical presentation depends mostly on the underlying infection. On histologic examination, lesions are identical to those described for drug-induced AIN, and they can also occasionally result in granulomas (see Table 62-2). Infection-associated AIN usually resolves with the treatment of the underlying infection, and corticosteroid therapy is not recommended.

An important cause of infection-associated AIN is hantavirus.[15] Hantavirus infections occur worldwide and are responsible for a disease that has been known as hemorrhagic fever with renal syndrome, epidemic hemorrhagic fever, and nephropathia epidemica. Rodents are the main reservoir of the virus, and humans are most probably infected by the airborne route. Extrarenal symptoms usually include fever, headache, lightheadedness, abdominal pain, nausea and vomiting, and thrombocytopenia; the last can be responsible for hemorrhagic complications. AKI is almost always associated with proteinuria, sometimes in the nephrotic range, and with hematuria. When a kidney biopsy is performed, it discloses not only interstitial inflammatory infiltrates, which predominate in the medulla, but also vascular congestion and interstitial bleeding (Fig. 62-8). In about 50% of the patients, immunofluorescence studies show granular immune deposits along the TBM and within glomeruli. Serum creatinine concentration usually starts to decrease after a few days, and a complete recovery of renal function is the rule. Nevertheless, in the more severe cases, recovery can be complicated by the occurrence of hemorrhagic complications or severe shock. The diagnosis is based on serologic test results, which become positive early (within weeks) in the course of the disease.

Tubulointerstitial lesions are common in HIV-positive patients who undergo a renal biopsy for AKI. Interstitial infiltrates are often associated with glomerular lesions, but they can also be isolated. These forms of AIN have been observed in both Caucasian and Black patients, and they might be related not only to drugs and opportunistic infections but also to the HIV infection itself.[16]

ACUTE INTERSTITIAL NEPHRITIS ASSOCIATED WITH SYSTEMIC DISEASES

Sarcoidosis

In sarcoidosis, renal impairment usually occurs as a complication of hypercalciuria and hypercalcemia, but granulomatous AIN associated with sarcoidosis has also been reported (Fig. 62-9).[17,18] The presentation is usually that of AKI, which can be isolated or associated with mild proteinuria and sterile leukocyturia. It is associated with extrarenal symptoms of sarcoidosis in about 90% of patients, most frequently with lymphadenopathy and lung, eye, or liver involvement. Nevertheless, only slightly more than half of the patients have hilar lymphadenopathy or pulmonary interstitial

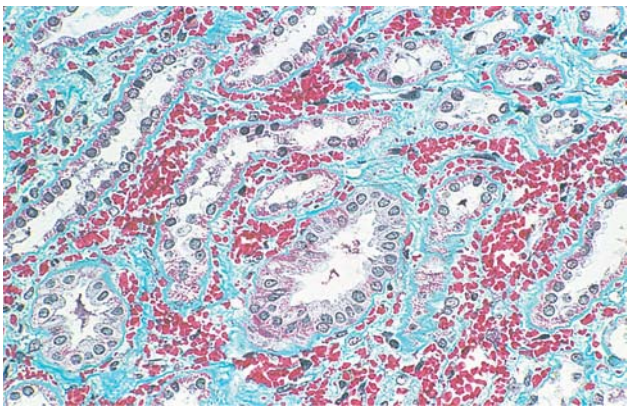

Figure 62-8 Acute interstitial nephritis secondary to hantavirus infection. Vascular congestion and foci of medullary hemorrhage are suggestive of the diagnosis. *(Courtesy Dr. B. Mougenot, Paris VI University, Paris.)*

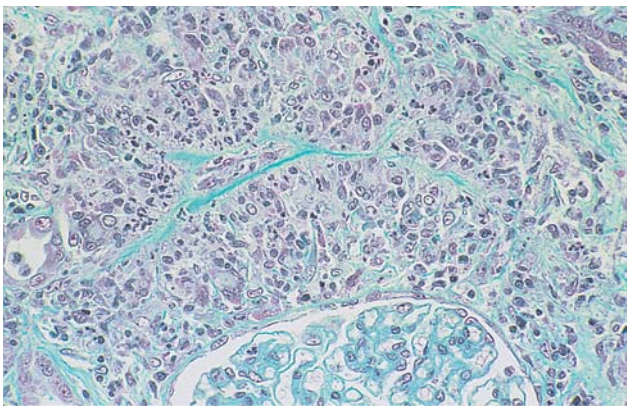

Figure 62-9 Granulomatous acute interstitial nephritis in a patient with sarcoidosis. *(Courtesy Dr. B. Mougenot, Paris VI University, Paris.)*

Infections that Can Be Associated with Acute Interstitial Nephritis

Bacteria	Viruses	Parasites	Others
Brucella species	Adenovirus	*Toxoplasma* species*	*Chlamydia* species
Campylobacter jejuni	Cytomegalovirus	*Leishmania donovani*	*Mycoplasma* species
Corynebacterium diphtheriae	Epstein-Barr virus*		
Escherichia coli	Hantavirus		
Legionella species	Hepatitis A virus		
Leptospira species	Hepatitis B virus		
*Mycobacterium tuberculosis**	Herpes simplex virus		
Salmonella species*	Human immunodeficiency virus		
Staphylococcus species	Measles virus		
Streptococcus species	Polyomavirus		
Yersinia pseudotuberculosis	Rickettsia		

Table 62-2 Infections that can be associated with acute interstitial nephritis. *Infections that can induce granulomatous AIN.

fibrosis at the time of diagnosis.[19] Treatment with high-dose corticosteroids quickly improves renal function, but most patients do not recover completely. The starting dose should be 1 mg of prednis(ol)one per kilogram daily and not higher than 60 mg/day, and corticosteroid therapy should be tapered slowly and not withdrawn before at least 1 year to prevent relapses. Whereas some authors advocate long-term maintenance therapy with low-dose corticosteroids, we usually stop corticosteroids after 2 to 3 years. Because of the risk of late relapse, these patients should be observed for a prolonged time.

Sjögren Syndrome

Clinically significant interstitial nephritis is rare in Sjögren syndrome and usually results in chronic tubular dysfunction.[20] Some patients may present with severe symptomatic hypokalemia with distal renal tubular acidosis. Rarely, Sjögren syndrome presents with AKI as a result of AIN. In these patients, treatment with high-dose corticosteroids may dramatically improve renal function.

Systemic Lupus Erythematosus

About two thirds of renal biopsies performed in patients with systemic lupus show some tubulointerstitial involvement, but significant tubulointerstitial injury in the setting of minimal glomerular abnormalities is rare, with only about 10 cases reported in the literature.[21] In these cases, renal biopsy shows typical features of AIN on light microscopy, and immunofluorescence staining always discloses immune deposits along the TBM, usually with a granular pattern. Renal function improves after high-dose corticosteroids, and additional immunosuppressive drugs are not usually required. However, azathioprine has been used as a corticosteroid-sparing agent.

Other Systemic Diseases

Among patients with cryoglobulinemia and AKI, a few exhibit significant interstitial inflammatory infiltrates associated with granular immune deposits in the interstitium and along the TBM. This AIN is usually associated with characteristic glomerular lesions and rarely lesions of the arterioles, and treatment is the same as for cryoglobulinemia-induced GN (see Chapter 21).

IgG4-related disease is a newly recognized systemic autoimmune disease that predominantly affects males older than 50 years of age. In the kidney, it is most commonly responsible for AIN characterized by the presence of interstitial infiltrates rich in IgG4-positive plasma cells and immune deposits along the TBM.[22] This interstitial nephritis can be associated with a membranous glomerulopathy, with the presence of renal inflammatory masses visible on radiographic studies, or with ureteral obstruction (see also Chapter 60). It usually responds very rapidly to treatment with corticosteroids.

Most renal lesions associated with small-vessel vasculitis consist of both an extracapillary GN and a tubulointerstitial nephritis (see Chapter 25). Nevertheless, a few patients with AIN and minimal glomerular lesions have been described.

ACUTE INTERSTITIAL NEPHRITIS ASSOCIATED WITH MALIGNANT NEOPLASMS

Infiltration of renal parenchyma by malignant cells is common in patients with leukemia or lymphoma. Most of the time, this infiltration is totally asymptomatic or only causes enlarged kidneys, but a few patients with AKI have been described.[23] Chemotherapy or radiotherapy may rapidly improve renal function in these patients, but before these treatments are started, it is important to exclude more common causes of AKI associated with neoplastic diseases (see Chapter 68).

IDIOPATHIC ACUTE INTERSTITIAL NEPHRITIS

More than 50 cases of idiopathic AIN with anterior uveitis have been reported (TINU syndrome).[24] This syndrome is found most commonly in girls of pubertal age but can also occur in pubertal boys and in adults. Initial symptoms may be ocular, with ocular pain and visual impairment, or pseudoviral, with fever, myalgia, and asthenia. AIN is responsible for AKI, ranging from mild to severe, that may or may not be associated with abnormal urinalysis. Renal biopsy shows diffuse interstitial inflammatory infiltrates, almost always without granulomas and without immune deposits. In children, renal prognosis is excellent, and serum creatinine usually returns to baseline values within a few weeks, with or without corticosteroid therapy. In adults, the renal prognosis seems to be less favorable, and corticosteroid therapy might be useful in preventing evolution to chronic renal impairment. Uveitis, which can occur at any time in respect to AIN, is usually responsive to topical corticosteroids, but it may relapse without any recurrence of AIN.

Cases of idiopathic AIN without uveitus have been reported. Immunofluorescence studies of renal biopsy specimens can show linear deposits of IgG along the TBM, granular deposits of IgG along the TBM, or no immune deposits, suggesting that this entity is heterogeneous. The treatment of patients with idiopathic AIN is still controversial. Patients who receive corticosteroids usually show a dramatic improvement of renal function, but others have recovered normal renal function without any treatment.

ACUTE INTERSTITIAL NEPHRITIS IN RENAL TRANSPLANTS

Acute rejection is by far the most common cause of AIN in renal allograft recipients (see Chapter 104). Nevertheless, AIN can also be induced by drugs or infections. Cases of drug-induced AIN have been reported even in the first weeks after transplantation, when immunosuppression is maximal.[25] Among patients with infectious AIN, the frequency of polyomavirus-induced AIN appears to be increasing, and it should be suspected in patients with acute deterioration of renal function and so-called decoy cells in urine (see Chapter 105).[26]

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CHAPTER 63

Primary Vesicoureteral Reflux and Reflux Nephropathy

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DEFINITION

Vesicoureteral reflux (VUR) is a congenital or acquired abnormality in which there is retrograde flow of urine from the bladder to the kidneys. This retrograde flow of urine, although normal in some animals, is not normal in humans. VUR may be primary (congenital) and associated with or without associated syndromes, or secondary, such as from increased bladder pressure resulting from obstructive uropathy or neurogenic bladder.

Vesicoureteral reflux may be suggested by fetal ultrasound in pregnancy (in which renal pelvis dilation is observed) or after urinary tract infection (UTI) in childhood. The presence of VUR increases the risk of upper tract UTI, and the two together can cause renal injury leading to scarring of the kidney termed reflux nephropathy (RN). RN may present as hypertension, toxemia of pregnancy, chronic kidney disease (CKD), and even end-stage renal disease (ESRD). Whereas RN involves primary injury to the renal parenchyma, some patients also have proteinuria as a result of secondary focal segmental glomerulosclerosis (FSGS).

Traditional management includes prompt treatment of UTI and long-term antimicrobial prophylaxis until the resolution of VUR. Surgical correction of the VUR may be recommended in those with high-grade VUR who have recurrent UTI in spite of antimicrobial prophylaxis or who are noncompliant with medical management. Debate persists on the superiority of one intervention over the other; most studies have concluded that long-term outcomes are similar.

CLASSIFICATION

Vesicoureteral reflux is classified by radiologic evaluation on voiding cystourethrography (VCU) into five grades as defined by the International Reflux Study in Children (Fig. 63-1 and Table 63-1).[1] Grade I is reflux into the ureter; grade II is reflux into the renal pelvis without any dilation of the calyces; grade III is reflux to the renal pelvis with mild dilation of the renal pelvis; grade IV is reflux to the renal pelvis with greater dilation of the renal pelvis; and grade V is reflux to the renal pelvis with ureteral and pelvic dilation. An example of grade V reflux is shown in Figure 63-2.

Grading of VUR is used to predict the outcomes of children with VUR. Because VUR may resolve spontaneously, grading is used to standardize management strategies as well as to compare clinical outcomes between institutions. Although it is widely used, the classification system is not perfect; differences between grade III and grade IV are not always obvious. The degree of reflux may be modified by how aggressively the bladder is filled during VCU. Ureteral dilation may also be present without calyceal dilation, leading to difficulties with grading.

EPIDEMIOLOGY

Vesicoureteral reflux is often first suggested by dilation of the fetal kidney during ultrasound examination. VUR is suspected when the fetal renal pelvis is more than 5 mm in anteroposterior diameter; a diameter of more than 10 mm is considered to be high-grade VUR. In neonates who had evidence of fetal dilation, as many as 13% to 22% will have VUR on VCU. Indeed, it is estimated that 1% to 2% of healthy children have VUR, with a higher frequency in boys and premature infants.[2] The incidence of renal dysplasia is also greater in male infants with VUR.[3] Most cases of grades I to III VUR will spontaneously resolve within the patient's first year of life, whereas grades IV and V are more likely to persist. Spontaneous resolution of VUR is greater in male infants.

Vesicoureteral reflux is also diagnosed in 30% to 40% of children presenting with UTI, predominantly girls. VUR is both less common and less severe in African American children.[4,5] Only about one third as many African American as Caucasian girls with UTI have VUR, and no significant differences in age or mode of presentation exist between the two races.

Renal scarring is responsible for 5% to 10% of ESRD in pediatric and adult patients.[6,7] In the Chronic Kidney Disease in Children (CKiD) study, in children with an estimated glomerular filtration rate (eGFR) of 30 to 90 ml/min/1.73 m^2, RN was the underlying cause for CKD in 14.8% of the patients.

ETIOLOGY AND PATHOGENESIS

Primary VUR is a congenital anomaly of the ureterovesical junction caused by a preexisting anatomic abnormality with shortening of the intravesical submucosal length of the ureter, leading to an incompetent valve (Fig. 63-3). The formation of the ureteral bud from the mesonephric duct signals the initial development of the metanephric kidney, the final stage of renal development. The ureteral bud interacts with the mesenchyme to give rise to the metanephric kidney. As the mesonephric duct is gradually absorbed into the enlarging urogenital sinus (the precursor of the developing bladder), the location of the ureteral bud plays a role in the eventual location of the ureteral meatus within the bladder. If the ureteral bud reaches the urogenital sinus too early because of the absorption pattern of the mesonephric duct, it is eventually located more laterally and proximally in the bladder. This location is associated with the development of reflux because there is reduction in the intravesical submucosal length of the ureter.

The ureterovesical junction is designed to prevent free reflux of urine from the bladder to the kidney. The ureters pass into the bladder through the detrusor in an oblique path. The distal end of

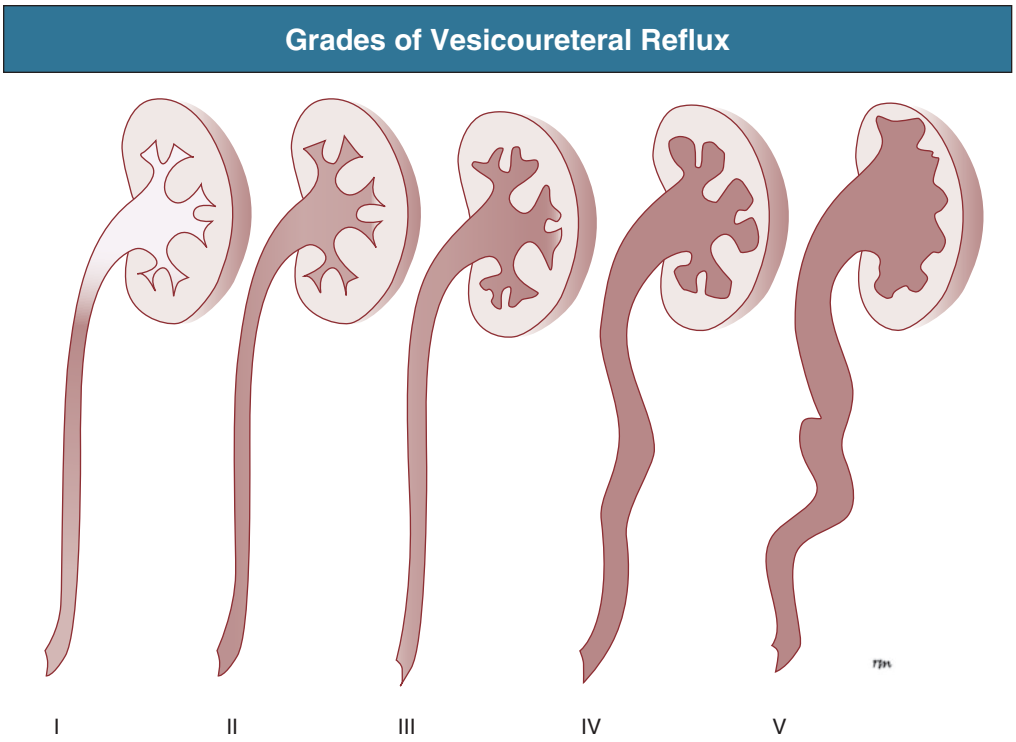

Figure 63-1 Grades of vesicoureteral reflux.

International Reflux Study in Children Classification of Vesicoureteral Reflux (VUR)	
Grade	**Degree of VUR**
I	Ureter only
II	Reflux into ureter, pelvis, and calyces with no dilation and with normal calyceal fornices
III	Mild or moderate dilation and/or tortuosity of the ureter and mild or moderate dilation of the pelvis; no or slight blunting of the fornices
IV	Moderate dilation and/or tortuosity of the ureter, and moderate dilation of the pelvis and calyces; complete obliteration of the pelvis and calyces; complete obliteration of the sharp angles of the fornices but maintenance of the papillary impressions in the majority of the calyces (see Fig. 63-7C)
V	Gross dilation and tortuosity of the ureter, pelvis, and calyces; the papillary impressions are no longer visible in the majority of calyces (see Fig. 63-2)

Table 63-1 Classification of VUR. The International Reflux Study in Children classification.

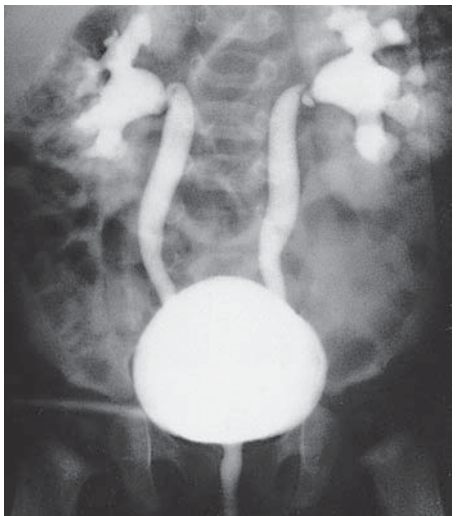

Figure 63-2 Gross vesicoureteral reflux (VUR) and intrarenal reflux. A voiding cystourethrogram shows grade V VUR with intrarenal reflux into several renal lobes in an infant.

the ureter is located submucosally within the bladder. The length of the submucosal ureter is critical in the prevention of VUR. The muscles of the ureter extend into the trigone of the bladder and mesh with the fibers from the opposite ureter. This intermingling of fibers helps anchor the ureters into the trigone of the bladder. The distal submucosal segment is compressed against the muscular bladder wall with bladder filling, acting as an additional mechanism to prevent reflux. Because urine is propelled antegrade down the ureter, the tone of the ureter and the meatus in the bladder also help prevent reflux.

Multiple genes are involved in the development of VUR. *PAX2* (necessary for ureteral budding in mice), glial-derived neurotrophic factor (GDNF), angiotensin II type 2 receptor, and uroplakin 3 (which is a component of tight junctions in uroepithelial cells) have been implicated in the development of VUR in mice; however, their role in human VUR remains controversial.[8,9] Neither autonomic innervation nor histology of the ureterovesical junction is different between patients with VUR and controls.[10]

Reflux Nephropathy

Reflux nephropathy is thought to result from one of two processes (Table 63-2).[51] Prenatal renal injury has been postulated to be secondary to the "water-hammer" effect of high-grade reflux and occurs in the absence of infection. This typically causes renal dysplasia. This form of renal scarring, which is also called congenital RN, is more

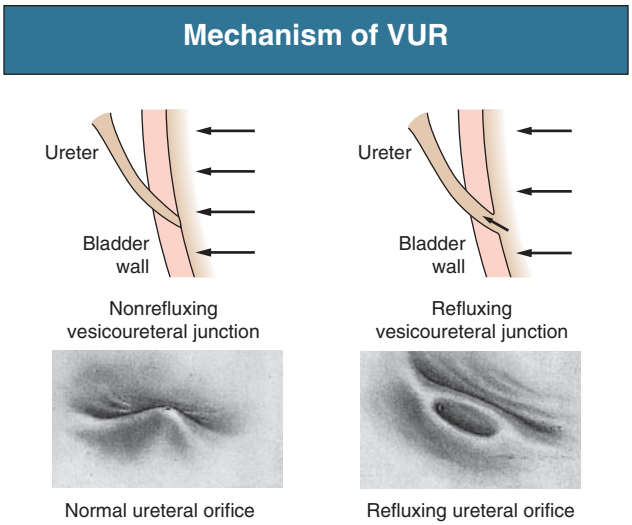

Figure 63-3 Pathogenesis of vesicoureteral reflux. Competent *(left)* and incompetent *(right)* vesicoureteral junctions and ureteral orifices.

Types of Renal Damage Associated with Vesicoureteral Reflux (VUR)

	Congenital	Acquired
Time of occurrence	Often prenatal	Postnatal, sometimes in adulthood
Previous urinary infection	Not usually	Usually
Gender	Usually boys	Usually girls (particularly after infancy)
Grade of VUR	Usually grades IV and V	Grades IV and V less common
Renal scarring	Often present	Present in minority of cases*
Associated bladder dysfunction	Hypercontractile bladder common	Less commonly, high-capacity bladder with incomplete voiding

Table 63-2 Types of renal damage associated with VUR. *Depends on unilateral versus bilateral involvement, and the severity of renal involvement. *(Adapted from reference 51, with permission.)*

commonly noted in infants with high-grade VUR, and there is a greater predominance of males in this cohort. The second mechanism for development of renal injury is the combination of VUR and repeated UTI, which is also called acquired RN. In these children, who are more commonly female, the combination of upper tract infection and reflux leads to renal inflammation and permanent scarring.

In both conditions, the damage to the kidney is likely to be greatest in children younger than 2 years, particularly in those with severe VUR.[11] Renal injury is more common in this age group because of delay in diagnosis of UTI as a result of the nonspecific clinical presentation, the difficulties in obtaining urine specimens, and the higher prevalence and severity of VUR in infants.

Reflux nephropathy is diagnosed by using technetium Tc 99m dimercaptosuccinic acid (DMSA) renal scanning as defects in the renal outline.[12] These defects can be seen in the absence of febrile UTIs. As noted previously, high-grade prenatal reflux can lead to renal injury in the absence of infection. Unfortunately, renal scarring secondary to UTI is indistinguishable by DMSA renal scan from that

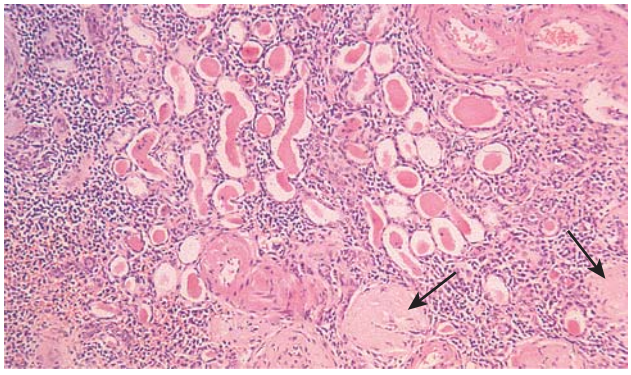

Figure 63-4 Histologic changes in reflux nephropathy. Sclerosed glomeruli *(arrows),* chronic inflammatory cell infiltration, and atrophic tubules with eosinophilic casts are present. (Hematoxylin-eosin; original magnification ×40.)

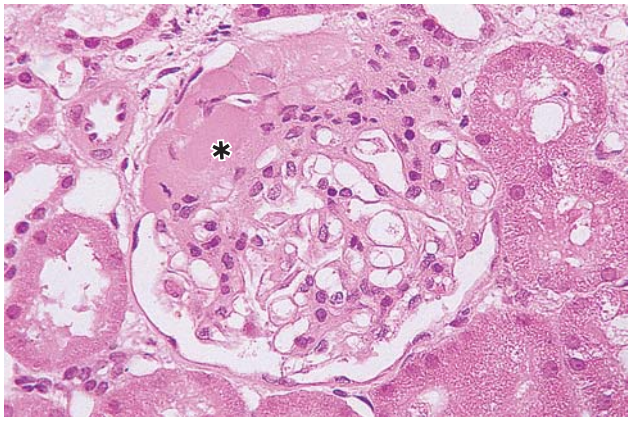

Figure 63-5 Focal segmental glomerulosclerosis (*) in reflux nephropathy. Light microscopy of a glomerulus from a patient with reflux nephropathy shows FSGS. (Hematoxylin-eosin; original magnification ×400.)

caused by prenatal renal dysplasia. In addition, renal injury can be noted after febrile UTI in the absence of identified VUR.

Finally, renal scarring as shown by technetium Tc 99m DMSA scan correlates more closely with the severity of VUR than with a history of UTI.[13]

PATHOLOGY

The process of renal scarring may take several years; in one study, the mean time from discovery of VUR to the appearance of a renal scar was 6.1 years.[14] Grossly, the injury favors the renal poles and is associated with clubbed calyces with medullary and cortical damage. The injury results from the local inflammatory response that may persist with chronic inflammation, tubular injury, local fibroblast activation, and interstitial collagen deposition (Fig. 63-4).[15] The loss of nephrons is associated with hyperfiltration and hypertension that result in proteinuria and progressive loss of renal function. This can also lead to the development of FSGS (Fig. 63-5).

CLINICAL MANIFESTATIONS

Presentation with Vesicoureteral Reflux

Patients with primary VUR may present in a variety of ways (Box 63-1). The three most common presentations are during follow-up

Clinical Presentations of Vesicoureteral Reflux (VUR)

- Complicated urinary infection—usually acute pyelonephritis in infants and children
- Asymptomatic
  - Detected by fetal ultrasound
  - Detected in the workup of members of an affected family
  - Detected in pregnant women with urinary tract infection
  - Detected during workup of kidney stones in children
  - Detected during assessment of other urologic congenital abnormalities

Box 63-1 Clinical presentations of VUR.

Prevalence of Vesicoureteral Reflux (VUR) in Patients with Urinary Tract Infection, According to Age

Age	Percentage with VUR
2-3 days	57
3-6 days	51
2-6 months	60
7-12 months	35
1-4 years	50
5-9 years	35
10-14 years	14
14 years	10
Adult	5

Table 63-3 Prevalence of VUR in patients with urinary tract infection, according to age. *(From reference 25.)*

for antenatal hydronephrosis, after a diagnosis of UTI, and on screening of a sibling of a patient with VUR.

Reflux Identified Secondary to Antenatal Hydronephrosis

Diagnosis of VUR may be suspected in utero with unilateral or bilateral hydronephrosis and confirmed at birth with VCU. There is a higher incidence of male infants diagnosed with VUR after identification of antenatal hydronephrosis.[16] Spontaneous resolution of the VUR occurs more commonly in boys with lower grades and unilateral reflux; infection rates are also lower in this cohort.[17] Female infants are more likely to have lower grades of VUR and are also less likely to develop renal damage compared with newborn boys. Reflux in newborn boys may be a result of elevated bladder pressures secondary to dyssynergia of the urethral sphincter, which improves with time with secondary resolution of even higher grades of VUR.[18,19]

Reflux Identified After a Urinary Tract Infection

Vesicoureteral reflux is most commonly found after UTI, particularly in a young child. The prevalence of VUR is higher in younger patients and decreases with age (Table 63-3). In neonates and toddlers, UTI may be manifested as failure to thrive as opposed to typical symptoms of dysuria and frequency. VUR is more common in patients with complicated or upper tract UTI. Because VUR may potentiate the effect of UTI in children, the recommendations for evaluation of

Algorithm for Evaluation of Young Children with Diagnosed UTI

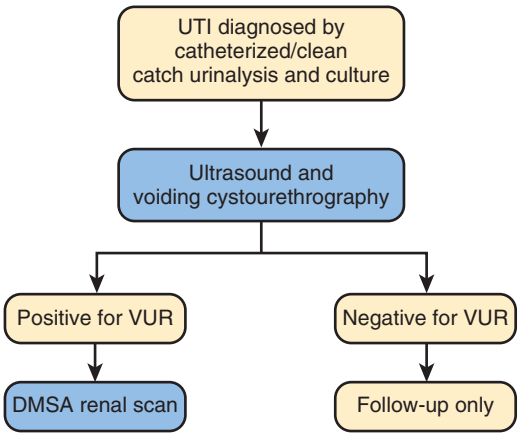

Figure 63-6 Current recommended algorithm for evaluation of young children with diagnosed urinary tract infection (UTI).

UTI have included ultrasound and VCU after resolution of the first UTI in both boys and girls (Fig. 63-6). However, in its most recent recommendations, the National Institute for Health and Care Excellence (NICE) from the United Kingdom and the American Academy of Pediatrics did not support routine voiding cystourethrogram (VCUG) in all children and children 2 to 24 months old, respectively, with first febrile UTI.[20]

Most children diagnosed with VUR after a UTI are younger than 7 years. UTI in these patients may be associated with modifiable host factors, such as voiding dysfunction and constipation. For example, toilet-trained children with VUR identified after a UTI have a 43% incidence of dysfunctional voiding.[21]

Sibling Vesicoureteral Reflux

Approximately one third of siblings of an index patient with VUR also have VUR.[22] There is a slightly higher incidence of VUR in female siblings of female index patients; 75% of children with VUR identified by sibling screening are asymptomatic. The incidence of renal damage is also lower in the siblings diagnosed with reflux compared with the index patient with VUR.[23] For example, UTI with progression of scar was noted in only 5% of siblings with VUR observed for 3 to 7 years, and most of those with grades I and II VUR had resolution.[23] The more "benign" course of sibling reflux compared with reflux identified after a UTI has led many to suggest limitation of those being screened. At this time, most suggest screening of younger siblings (younger than 2 years) of index children with VUR and reserve screening of older siblings for those who present with a UTI or other symptoms.

Reflux Nephropathy

Renal scarring can occur in patients with VUR and can be seen in those with or without proven UTI. This scarring is called reflux nephropathy.[24,25] Young children are particularly at risk of renal scarring. Renal scarring is more common with febrile UTI in children, and in those younger than 5 years, as many as 75% develop acute pyelonephritis and renal scarring. Renal cortical defects (by DMSA scanning) are present in 45% of children with febrile UTI and VUR compared with 24% with UTI without VUR.[25] In a large prospective

Clinical Presentations of Reflux Nephropathy

- Complicated urinary infection—usually acute pyelonephritis in infants and children
- Hypertension: may be accelerated
- During pregnancy: urinary infection, hypertension, preeclampsia
- Proteinuria
- Chronic renal impairment
- Urinary calculi
- Asymptomatic
  - Detected in the workup of members of an affected family
  - Detected by fetal ultrasound
  - Detected during assessment of other urologic congenital abnormalities

Box 63-2 Clinical presentations of reflux nephropathy.

study of a population-based cohort of 1221 children aged 0 to 15 years with symptomatic UTI, primary scarring during initial evaluation was even higher, occurring in 86% of the boys and 30% of the girls. Girls had significantly more recurrences of febrile UTIs and acquired renal scarring than boys.[26]

The clinical manifestations of RN are varied and may include complicated UTI, hypertension, proteinuria, and various manifestations of CKD (Box 63-2).

Hypertension

Hypertension occurs in 10% to 30% of children and young adults with RN,[26,27] and according to one study, hypertension may take 8 years to develop.[14] The exact cause of hypertension resulting from renal scarring is not known, but it is believed to be caused by impaired sodium excretion resulting from the renal injury. Hypertension is relatively uncommon in children with VUR, with an estimated probability of 2%, 6%, and 15% at 10, 15, and 21 years of age, respectively. However, hypertension increases in proportion to the degree of renal injury.[28] Renal scarring (noted by DMSA scans) was reported in 20% of newly diagnosed hypertension in children and adolescents.

Proteinuria

Patients may also present with microalbuminuria, persistent proteinuria, or rarely nephrotic-range proteinuria. The presence of proteinuria may suggest a histologic diagnosis of secondary FSGS, which can be confirmed by renal biopsy if kidney size is normal and diagnosis is uncertain (see Fig. 63-5).[29] Proteinuria is usually modest (0.5 to 4 g/day) and is commonly associated with hypertension and renal dysfunction. CKD progression often occurs gradually over 5 to 10 years.

End-Stage Renal Disease

According to the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) annual report of 2008, 3.5% of the 6491 children on dialysis had RN, which makes it the fourth most common cause of ESRD after FSGS; renal aplasia, hypoplasia, or dysplasia; and obstructive uropathy.[30,31] The number of pediatric patients with RN who present with ESRD as adults is not clear. According to one study of 123 adults with VUR diagnosed in childhood, the eGFR in those with nondilating VUR averaged 75 ml/1.73 m^2 and that in the dilating group was 72 ml/1.73 m^2; four patients (9%) in the nondilating group and 13 (17%) in the dilating group had eGFR below 60 ml/1.73 m^2.[30]

Presentation of Vesicoureteral Reflux in the Mother During Pregnancy

Vesicoureteral reflux may also first be manifested in the mother during pregnancy, when it can be associated with asymptomatic bacteriuria or symptomatic UTI, hypertension, preeclampsia, low-birth-weight babies, or miscarriage. VUR is present in approximately 5% of women with UTI in pregnancy and 4% to 5% of women with preeclampsia. VUR can be distinguished from the normal ureteral dilation that occurs in pregnancy, which preferentially affects the midportion of the ureter, and lack of involvement of the renal parenchyma.

Other Presentations

An increased risk of renal calculi has also been reported in children with VUR. Recurrent infections with urease-splitting organisms can lead to staghorn calculi. VUR or RN may also be discovered in adults after recurrent lower or upper UTI; indeed, about 5% of sexually active women with UTI have VUR.

DIAGNOSIS OF VESICOURETERAL REFLUX AND REFLUX NEPHROPATHY

An algorithm for diagnosis of VUR after the discovery of UTI is shown in Figure 63-6, and an example of the various tests in a child with UTI and VUR is shown in Figure 63-7. A similar approach should be performed in children after treatment of their first UTI.

Renal Ultrasound

Ultrasound is the initial modality for the evaluation of postnatal hydronephrosis and UTI in children. Ultrasound is also used as a screening tool in siblings of children with VUR to determine whether renal dilation suggestive of high-grade reflux is present. Whereas ultrasound can suggest the possibility of high-grade VUR, it has less sensitivity for diagnosis of acute pyelonephritis. In patients with acute pyelonephritis, abnormalities compatible with the diagnosis were reported in 20% to 69% by ultrasound compared with 40% to 92% by DMSA scintigraphy.[32] Nonetheless, ultrasound may be useful in detection of renal abscess and abnormalities of the perinephric space. Renal ultrasound is not diagnostic for VUR and is not a sensitive method for diagnosis of renal scars.

Voiding Cystourethrography

Voiding cystourethrography is the primary diagnostic modality for identification of VUR. It requires catheterization, which can lead to significant distress in both children and parents. The grading of VUR is based on radiographic appearance by VCU (see Fig. 63-1). In children with UTI, VCU should be performed as soon as the child has completed the course of antibiotic therapy. Evaluation with VCU has been suggested after the first febrile infection in children younger than 5 years.

The results of VCU can be affected by size, type, and position of the catheter; rate of bladder filling; height of the column of contrast media; state of hydration of the patient; and volume, temperature, and concentration of the contrast medium.

Nuclear cystography has been used to reduce the radiation exposure for children during follow-up of VUR. Nuclear cystography, although more sensitive, does not permit specific grading of VUR or reveal other anatomic defects, such as ureterocele and diverticulum. Therefore it is typically not the primary study performed

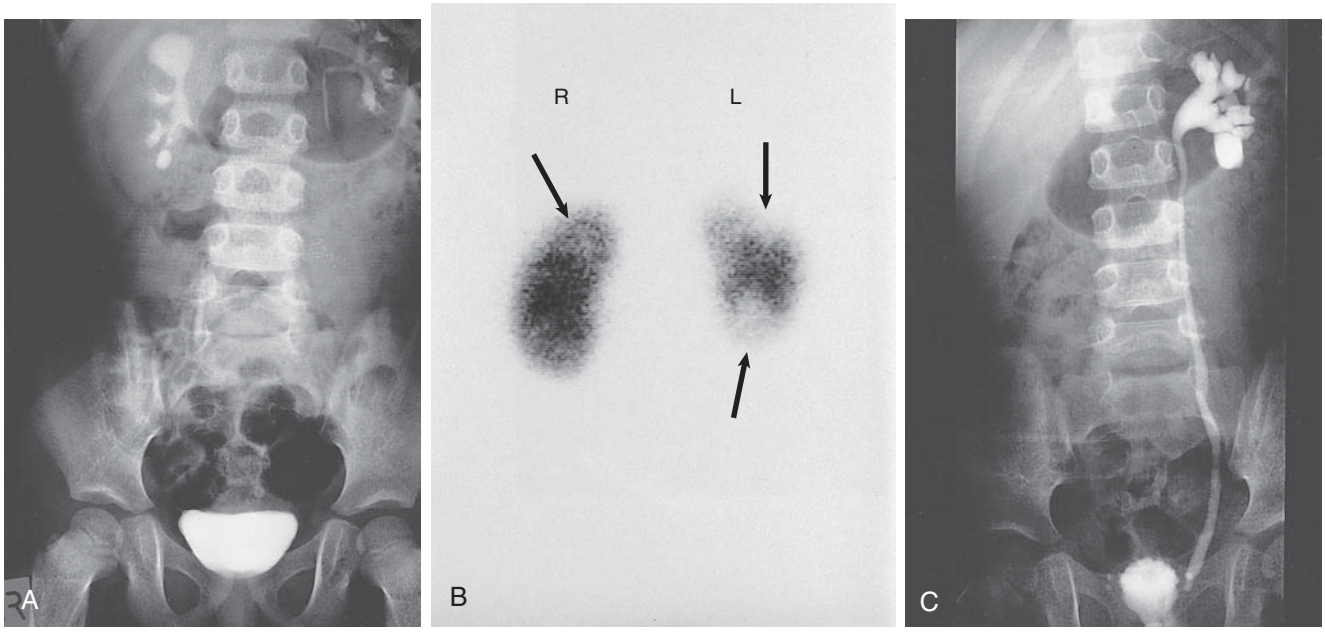

Figure 63-7 Investigation of reflux nephropathy. Investigation of a 3-year-old child with urinary tract infection. **A,** Intravenous urogram showing calyceal diverticulum in the upper pole of the right kidney and renal scarring in the upper pole and, probably, the lower pole of the left kidney. **B,** DMSA scintigraphy (posterior view) demonstrating upper and lower pole scarring *(arrows)* in the left kidney and scarring of the right upper kidney in association with the calyceal diverticulum *(arrowhead).* **C,** Voiding cystourethrogram showing grade IV vesicoureteral reflux on the left.

for identification of VUR, but it is useful in determining improvement or resolution of reflux during follow-up or after surgical correction.

DMSA Renal Scintigraphy

Use of DMSA scintigraphy is currently the accepted gold standard for diagnosis of acute pyelonephritis and renal scarring. Single-photon emission computed tomography (SPECT) DMSA scintigraphy is superior to planar imaging for detection of renal cortical damage.[34,35] The sensitivity of DMSA scintigraphy in experimentally induced acute pyelonephritis in a pig model was reported to be 92% when correlated with histologic findings.[35] By use of standardized criteria for its interpretation, high levels of intraobserver and interobserver agreement were reported.[36]

An abnormal DMSA scan during a febrile UTI allows the identification of children with renal inflammation who are at risk for development of renal scars. For acute pyelonephritis, DMSA scintigraphy can be performed within 2 to 4 weeks after the onset of UTI symptoms. However, routine use of DMSA renal scan after acute pyelonephritis is not encouraged because it does not change the clinical management. For renal scarring, DMSA scintigraphy to identify renal scarring should ideally be performed 6 months after acute infection to allow acute reversible lesions to resolve.[37,38]

Dysplasia secondary to congenital reflux will appear similar to renal scarring after postnatal infections. In the context of a child presenting with VUR, obtaining a baseline DMSA renal scan allows identification of renal dysplasia and scarring, which can then be observed over time.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has recently been used for the diagnosis of renal scars because it discriminates swelling from scarring, both of which would be interpreted by DMSA scintigraphy as renal scarring. MRI may also diagnose other coexisting conditions, such as nephrolithiasis,[38,39] which is not diagnosed by DMSA scintigraphy. Newer imaging methods that show promise in diagnosis of renal scarring include dynamic contrast-enhanced MRI and MRI using a gadolinium-enhanced short-tau inversion-recovery (STIR) sequence. However, routine use of MRI is less practical because of limited availability, especially for infants, need for prolonged sedation, and high cost. Gadolinium is also contraindicated in the presence of significant renal impairment (glomerular filtration rate below 30 ml/min/1.73 m^2).

Proteinuria as a Marker for Reflux Nephropathy

Proteinuria predicts CKD progression due to RN.[40] Persistent microalbuminuria is helpful in diagnosis of glomerular damage at a very early stage.[41] Microalbuminuria increases with increasing severity of VUR and renal scarring.[42] In children with bilateral VUR with renal scarring and normal creatinine clearance, microalbuminuria was detected in 54% of the cases.[43] Microalbuminuria screening offers the possibility of early intervention, such as the use of ACE inhibitors, aimed at retarding CKD progress. Proteinuria, when it is severe, is usually associated with FSGS.

NATURAL HISTORY OF VESICOURETERAL REFLUX AND REFLUX NEPHROPATHY

Primary VUR, especially grades I to III, generally improves with time, and this is attributed to the lengthening of the submucosal segment of the ureter. Spontaneous resolution of VUR is more common with non-Caucasian race, lower grades of reflux, absence of renal damage, and lack of voiding dysfunction. Resolution of VUR occurs more slowly in children with bilateral VUR in most but not all studies. In one study of children younger than 5 years with grades I to III VUR, the resolution rate of left unilateral VUR was better than for right VUR.[44] In another study, the mean time until

American Urologic Association Guidelines for Management of Vesicoureteral Reflux					
Grade of VUR	**I**	**II**	**III**	**IV**	**V**
<1 yr without UTI	Consider CAP	Consider CAP	CAP	CAP	CAP
<1 yr with UTI	CAP	CAP	CAP	CAP	CAP
>1 yr without BBD or UTI	Consider CAP	Consider CAP	Consider CAP	Possible surgery	Possible surgery
>1 yr without BBD *and* UTI	CAP/possible surgery	CAP/possible surgery	CAP/possible surgery	CAP/possible surgery	CAP/possible surgery
>1 yr with BBD *and* without UTI	Treat BBD/CAP	Treat BBD/CAP	Treat BBD/CAP / possible surgery when BBD improved	Treat BBD/CAP/ possible surgery when BBD improved	Treat BBD/CAP/ possible surgery when BBD improved
>1yr with BBD *and* UTI	Treat BBD/CAP/ change CAP	Treat BBD/CAP/ change CAP	Treat BBD/CAP/change CAP/possible surgery when BBD improved	Treat BBD/CAP/change CAP/possible surgery when BBD improved	Treat BBD/CAP/change CAP/possible surgery when BBD improved

Table 63.4 American urologic association guidelines for management of vesicoureteral reflux (VUR). *BBD,* Bladder/bowel dysfunction; *CAP,* continuous antibiotic prophylaxis; *possible surgery,* injectable materials or reimplantation for lower grades and reimplantation for higher grades. *Adapted from American Urological Association. Vesicoureteral reflux. Available at https://www.auanet.org/education/guidelines/vesicoureteral-reflux-a.cfm.*

spontaneous resolution in Black children was 15 months versus 21 months in Caucasian children.[45] Increasing age at presentation and bilateral VUR decrease the probability of resolution, and bilateral grade IV or grade V VUR has a particularly low potential for spontaneous resolution.[46]

The natural history of VUR in adults has been reported in few studies. In one study of adults (mean age of 24 years) with gross VUR diagnosed in infancy, proteinuria and CKD were present in 3 of the 13 patients with unilateral RN and 2 of the 4 patients with bilateral RN.[47] In another study of 127 adults (mean age of 41 years) with VUR diagnosed during childhood, 35% had unilateral renal scarring, 24% had bilateral renal scarring, 24% had albuminuria, and 11% had hypertension. Of the patients with bilateral renal scars, 83% had reduced GFR.[48] An increased frequency of UTI and abnormal voiding patterns has also been noted in adults with VUR. UTIs may also be increased in frequency in adults who have had surgical management of VUR.

TREATMENT

The management of VUR has been based on the premise that VUR predisposes to the development of recurrent UTI and renal parenchymal injury, but also has the potential for spontaneous resolution. Various treatment strategies have been used with the ultimate objective of preventing renal injury. The two main treatment modalities are long-term antimicrobial prophylaxis and surgical correction. Surgical correction of VUR was common until antimicrobial prophylaxis for childhood UTI was introduced in 1975.[49] Many subsequent studies have reported no significant differences in outcome with medical management of VUR versus surgical treatment in the prevention of renal injury. For example, in the International Reflux Study in Children, which involved 306 patients, no significant difference in outcome was found between medical and surgical management in terms of the development of new renal lesions or the progression of established renal scars.[50] Long-term follow-up of this cohort for a period of 5 years in the European arm of the study also indicated no difference in outcomes.[11]

The 2010 American Urological Association (AUA) guidelines reviewed seven treatment modalities used to manage VUR in children: intermittent antibiotic therapy; bladder training; continuous antibiotic prophylaxis; antibiotic prophylaxis and bladder training; antibiotic prophylaxis, anticholinergics, and bladder training; open surgical repair; and endoscopic repair. The key outcome measures were resolution of VUR, risk of pyelonephritis and scarring, and complications of medical versus surgical management. The study panel's recommendations are shown in Table 63-4. Antibiotic prophylaxis is recommended for all grades of VUR in children younger than 1 year because of a very high rate of spontaneous resolution. For children 1 to 5 years old, the study panel recommended antibiotic prophylaxis for all grades of VUR, with surgical options in grades III to V if VUR is bilateral or renal scarring is present. For children older than 6 years, the study panel recommended antibiotic prophylaxis for grades I and II (unilateral or bilateral) and unilateral grades III and IV, with surgical options if renal scarring is present, and surgical repair for bilateral grades III and IV and unilateral or bilateral grade V with or without scarring because the VUR has the lowest possibility of spontaneous resolution.[46]

Medical Management

Medical management involves long-term antimicrobial prophylaxis, appropriate management of voiding dysfunction and constipation, if present, and follow-up renal imaging to assess the resolution of VUR and the potential development of renal injury. The antimicrobial agents most appropriate for prophylaxis include trimethoprim-sulfamethoxazole (TMP-SMZ), trimethoprim alone, nitrofurantoin, and cephalexin. Follow-up of patients with VUR and UTI requires rapid evaluation (within 72 hours of the onset of fever) to allow early detection and prompt treatment of UTI. The timing of follow-up VCU is not well defined, but studies have suggested time intervals of 12 to 24 months. The treatment of voiding dysfunction or dysfunctional elimination syndrome (a syndrome consisting of constipation and urinary symptoms of frequency, urgency and incontinence that is associated with recurrent UTI in toilet-trained children) may include the use of laxatives and timed frequent voiding every 2 to 3 hours. Pelvic floor exercises, behavioral modification, or anticholinergic medication may be required. A combined conservative medical and computer game–assisted pelvic floor muscle retraining has been shown to decrease the incidence of breakthrough UTI and facilitate VUR resolution in children with voiding dysfunction and VUR. Treatment of constipation by dietary measures, behavioral therapy, and laxatives helps reduce UTI recurrence and resolve enuresis and uninhibited bladder contractions.

Antibiotic Prophylaxis Versus Surveillance Only

Some studies challenge the benefit of long-term antimicrobial prophylaxis in the prevention of renal injury in patients with VUR.

Surgical Techniques for Management of Vesicoureteral Reflux (VUR)			
Technique	**Success Rates**	**Pros**	**Cons**
Open reimplantation	95%	High success rates Limited requirement for follow-up VCU Reduction in hospital stays	Surgical incision Hospitalization required Catheters needed during postoperative management Need for pain control
Endoscopic injection Dextranomer and hyaluronidase (Deflux)	70%-80%	Reasonable success rates Outpatient management Minimal pain	Expensive Lower success rates Need for repeated procedures Need for follow-up VCU
Laparoscopic or robotic reimplantation	70%-90%	Reasonable success rates Small incisions Less discomfort	Lower success rates Requires hospitalization Need for follow-up VCU Long procedure Expensive equipment Significant surgical learning curve

Table 63-5 Surgical techniques for VUR. *VCU,* Voiding cystourethrography.

Concerns have been raised regarding the potential risks of long-term antibiotic use including the possibility of development of resistance or allergy.

In the last few years, six prospective randomized trials evaluated the role of antimicrobial prophylaxis in the prevention of recurrent UTI and renal scarring in children. Altogether 1435 patients were randomized, and included were 961 (67%) female patients. Four studies[13,52-54] reported no benefit with antimicrobial prophylaxis in children with or without VUR. One study[55] reported a decrease of 6 percentage points (95% confidence interval [CI] 1-13) in the number of UTIs with prophylaxis compared with placebo. The Swedish reflux trial[56,57] demonstrated that the rate of UTI recurrence in girls was higher than in boys, and that this rate can be decreased with antibiotic prophylaxis and endoscopic procedure. None of the five studies showed any difference in the rate of renal scarring with or without prophylaxis.

These trials, although suggestive, are not conclusive. Various study design limitations were present, including small study cohorts, short follow-up, lack of blinding, no evaluation of compliance, no use of placebo, urine collection by sterile bags in non–toilet-trained children, and exclusion of patients with high-grade VUR (who are normally associated with the highest risk of renal injury) as well as the issue of interobserver variability in the interpretation of DMSA renal scans.

Hypertension and Proteinuria

Appropriate management of hypertension and proteinuria includes the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) as in other renal diseases (see Chapter 80). ACE inhibitors reduce proteinuria in patients with RN and also can reverse microalbuminuria. Combinations of ACE inhibitors and ARBs may provide additional lowering of proteinuria.[58] However, it is not known whether this antiproteinuric effect slows the progression of the renal disease. Historically, some patients also occasionally had their scarred kidney removed to help control hypertension, provided the contralateral kidney was healthy. However, this is exceptionally rare these days because of the availability of many potent antihypertensive agents.

Surgical Management

Surgical management of VUR is now a second-line management strategy and is reserved for patients whose medical management with antimicrobial prophylaxis and follow-up has failed. Current indications for surgical management of VUR are recurrent infections despite compliance with a prophylactic antibiotic regimen, worsening of renal scars, as judged by DMSA scanning, after a UTI, and repeated failure to comply with a prophylactic regimen. The recent introduction of minimally invasive modalities for the management of VUR has made some clinicians consider surgical correction a potential first-line therapy. Immediate correction could potentially offset the need for antibiotic prophylaxis in children. Although most surgical techniques have high success rates, most studies indicate that surgical correction of VUR does not prevent UTI or eventual renal scarring.[59] A review of surgical techniques is presented in Table 63-5.

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CHAPTER 64

Chronic Interstitial Nephritis

Masaomi Nangaku

DEFINITION

Chronic interstitial nephritis is a histologic entity characterized by progressive scarring of the tubulointerstitium, with tubular atrophy, macrophage and lymphocytic infiltration, and interstitial fibrosis. Because the degree of tubular damage accompanying interstitial nephritis is variable, the term *tubulointerstitial nephritis* is used interchangeably with *interstitial nephritis. Tubulitis* refers to infiltration of the tubular epithelium by leukocytes, usually lymphocytes.

There are many primary as well as secondary causes of chronic interstitial nephritis (Table 64-1). Tubulointerstitial injury is clinically important because it is a better predictor than the degree of glomerular injury of present and future renal function. Although any glomerular disease can injure the tubulointerstitium secondarily through mechanisms involving the direct effects of proteinuria and ischemia, in this chapter we discuss only primary chronic interstitial nephritis.

PATHOGENESIS

The tubulointerstitium can be injured by toxins (e.g., heavy metals), drugs (e.g., analgesics), crystals (e.g., calcium phosphate, uric acid), infections, obstruction, immunologic mechanisms, and ischemia. Regardless of the initiating mechanism, however, the tubulointerstitial response shows little variation. Tubular injury results in the release of chemotactic substances and the expression of leukocyte adhesion molecules that attract inflammatory cells into the interstitium. Tubular cells express human leukocyte antigens, serve as antigen-presenting cells, and secrete complement components and vasoactive mediators, all of which may further stimulate or attract macrophages and T cells. Growth factors released by tubular cells and macrophages, such as platelet-derived growth factor and transforming growth factor β, may stimulate fibroblast proliferation and activation, leading to matrix accumulation.[1] The source of fibroblasts in renal interstitial fibrosis remains controversial but may include an intrinsic fibroblast population, migration of circulating fibrocytes from perivascular areas, and transdifferentiation of tubular cells, pericytes, and endothelial cells into fibroblasts. Over time, a loss of peritubular capillaries and decreased oxygen diffusion caused by expansion of the interstitium render the kidney hypoxic, and progressive apoptosis leads to local hypocellularity and fibrosis.[2] Renal function becomes severely decreased, and renal replacement therapies are required.

EPIDEMIOLOGY

Whereas chronic interstitial nephritis occurs with progressive renal disease of all causes, primary chronic interstitial nephritis is not a common cause of end-stage renal disease (ESRD); reports range from 42% in Scotland to 3% to 4% in China and the United States.[3-5] This variability in incidence may relate to differences in how diagnoses are made, causes and toxin or drug exposure, and treatment modalities.

In several localized regions of the world, marked increases in the incidence of chronic interstitial nephritis have been reported. These include Sri Lanka, some coastal areas of Central America, and the Balkan region in Europe.

PATHOLOGY

The pathologic features of chronic interstitial nephritis are nonspecific. They include tubular cell atrophy or dilation; interstitial fibrosis that is composed of interstitial (types I and II) collagens; and mononuclear cell infiltration with macrophages, T cells, and occasionally other cell types (neutrophils, eosinophils, and plasma cells). Tubular lumina vary in diameter but may show marked dilation, with homogeneous casts producing a thyroid-like appearance, hence the term *thyroidization.*

Whereas a noncaseating granulomatous pattern is typical of sarcoidosis, interstitial granulomatous reactions also occur in response to infection of the kidney by mycobacteria (Fig. 64-1), fungi, or bacteria; drugs (including rifampin, sulfonamides, and narcotics); and oxalate or uric acid crystal deposition. Interstitial granulomatous reactions also have been noted in renal malacoplakia, Wegener granulomatosis, and heroin abuse and after jejunoileal bypass surgery.

CLINICAL MANIFESTATIONS

The impaired renal function is often insidious, and the early manifestations of the disease are those of tubular dysfunction, which may go undetected (Box 64-1).[6] Diagnosis is often made incidentally on routine laboratory screening or during evaluation of hypertension, in association with reduced glomerular filtration rate (GFR). Proteinuria is commonly less than 1 g/day. The urinalysis may show only occasional white blood cells and, rarely, white blood cell casts. Hematuria is uncommon. Anemia may occur relatively early because of loss of erythropoietin-producing interstitial cells.

The tubular dysfunction is often generalized, but some conditions may present with proximal tubular defects including aminoaciduria, phosphaturia, proximal renal tubular acidosis (RTA), or, rarely, a complete Fanconi syndrome. Distal tubular defects can be associated with distal RTA (type 1 or type 4) (see Chapter 12). Concentrating defects (increased urinary frequency and nocturia) can be a sign of medullary dysfunction and may be severe enough to result in nephrogenic diabetes insipidus. Some patients will also have an inability to conserve salt on a low-salt diet with a subsequent salt-wasting syndrome. Others, particularly with microvascular disease, may

Major Causes of Chronic Interstitial Nephritis	
Diseases in Which the Kidneys Are Macroscopically Normal	**Diseases in Which the Kidneys Are Macroscopically Abnormal**
Drugs and toxins (e.g., aristolochic acid, lithium, cyclosporine, tacrolimus, indinavir, cisplatin)	Analgesic nephropathy
Metabolic (hyperuricemia, hypokalemia, hypercalcemia, hyperoxaluria, cystinosis)	Chronic obstruction (see Chapters 60 and 63)
Heavy metals (lead, cadmium, arsenic, mercury, gold, uranium)	Hereditary (nephronophthisis, medullary cystic kidney disease, familial juvenile hyperuricemic nephropathy, autosomal dominant polycystic kidney disease, autosomal recessive polycystic kidney disease)
Radiation	Infection (chronic pyelonephritis, malacoplakia, xanthogranulomatous pyelonephritis; see Chapter 53)
Balkan nephropathy	
Immune-mediated conditions (systemic lupus erythematosus, Sjögren syndrome, sarcoidosis, Wegener granulomatosis, other vasculitides)	
Vascular diseases (atherosclerotic kidney disease) (see Chapter 66)	
Transplantation (chronic transplant rejection)	
Hematologic disturbances (multiple myeloma, light-chain deposition disease, lymphoma, sickle cell disease, paroxysmal nocturnal hemoglobinuria) (see Chapters 27, 51, and 65)	
Progressive glomerular disease of all causes (e.g., glomerulonephritides, diabetes, hypertension)	
Idiopathic	

Table 64-1 Major causes of chronic interstitial nephritis. Note that kidneys of any clinical entity can be shrunken at end stage. Some diseases categorized as macroscopically normal can in later stages result in macroscopically abnormal kidneys. For example, kidneys of sickle cell nephropathy are macroscopically normal unless papillary necrosis is present.

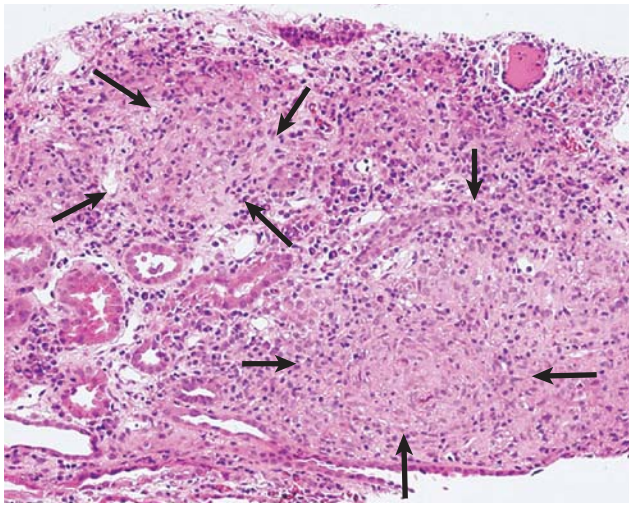

Figure 64-1 Renal tuberculosis. Noncaseating granulomas with epithelioid cells in miliary tuberculosis (arrows show the peripheries of the granulomas). Although the typical pathologic change is granuloma with caseous necrosis with Langerhans-type giant cells, these atypical granulomas can be observed in tuberculosis and should be differentiated from sarcoidosis. (Hematoxylin-eosin stain.) *(Courtesy Dr. Noriko Uesugi, Ibaraki, Japan.)*

Functional Manifestations of Chronic Interstitial Nephritis
Deterioration of glomerular filtration rate with insidious onset
Tubular proteinuria mainly composed of low-molecular-weight protein (generally <1 g/day)
Inactive urinary sediment
Renal anemia at a relatively early stage
Proximal tubular dysfunction (aminoaciduria, phosphaturia, proximal renal tubular acidosis, Fanconi syndrome)
Distal tubular dysfunction (type IV renal tubular acidosis)
Medullary dysfunction (concentrating defects)
Salt-wasting syndrome
Salt-sensitive hypertension

Box 64-1 Functional manifestations of chronic interstitial nephritis.

have a relative inability to excrete salt with resultant salt-sensitive hypertension.[7]

Clues to the causes of tubulointerstitial nephritis by history and physical examination are shown in Table 64-2.[8]

TREATMENT

Treatment includes identification and elimination of any exogenous agents (drugs, heavy metals), metabolic causes (hypercalcemia), or conditions (obstruction, infection) potentially causing the chronic interstitial lesion. Specific treatments may be required for a condition, such as corticosteroids for sarcoidosis. General measures include control of blood pressure. Most clinicians favor the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), which reduce glomerular and systemic pressures, decrease proteinuria, and increase renal blood flow. Specific therapies for each clinical entity are discussed later.

DRUG-INDUCED CHRONIC INTERSTITIAL NEPHRITIS

Several drugs and herbs can cause chronic interstitial nephritis. Cyclosporine- and tacrolimus-induced nephropathy is discussed in

Clues to Causes of Tubulointerstitial Nephritis by History and Physical Examination		
Feature	**Symptom, Sign, or Historical Clue**	**Potential Diagnosis**
Occupational history	Exposure to heavy metals (e.g., batteries, alloys)	Lead or cadmium nephropathy
Alcohol	History of moonshine ingestion	Lead nephropathy
Social history	Country of origin	Balkan nephropathy
Past history	Systemic lupus erythematosus Sjögren syndrome Sarcoidosis Inflammatory bowel disease Autoimmune pancreatitis Chronic pain syndrome Gouty attack	Disease-associated chronic interstitial nephritis Analgesic nephropathy Lead nephropathy
Medication	Prescribed Over-the-counter (NSAIDs) Herbal Indinavir	Drug-induced chronic interstitial nephritis Analgesic nephropathy Aristolochic acid–associated nephropathy Crystal nephropathy
Physical examination	Dry eyes	Sjögren syndrome
Laboratory examination	Hyperuricemia Hypokalemia Hypercalcemia High serum IgG4 levels	Chronic uric acid nephropathy Hypokalemic nephropathy Hypercalcemic nephropathy IgG4-related sclerosing disease
Radiologic examination	Decreased volume, bumpy contours, and papillary calcification on CT Microcysts on MRI or ultrasound Nephrocalcinosis on CT	Analgesic nephropathy Lithium nephropathy Hypercalcemic nephropathy

Table 64-2 Clues to tubulointerstitial nephritis by history and physical examination. *CT,* Computed tomography; *MRI,* magnetic resonance imaging; *NSAIDs,* nonsteroidal anti-inflammatory drugs. *(Modified from reference 8.)*

Chapters 101, 107, and 111; aristolochic acid as a cause of aristolochic acid–associated nephropathy (formerly known as *Chinese herbs nephropathy*) is discussed in Chapter 78.

Lithium Nephropathy

Definition and Epidemiology

Lithium is commonly used in the treatment of bipolar disorder. Complications of lithium treatment include nephrogenic diabetes insipidus, acute lithium intoxication, and chronic lithium nephrotoxicity. A meta-analysis of the data of 14 studies involving 1172 patients receiving chronic lithium therapy showed that the prevalence of reduced GFR was 15%.[9]

Pathogenesis

Diabetes insipidus results from accumulation of lithium in the collecting tubular cells after entry into these cells through sodium channels in the luminal membrane. Lithium blocks vasopressin-induced reabsorption by inhibiting adenylate cyclase activity, and hence cyclic adenosine monophosphate production, and also by decreasing the apical membrane expression of aquaporin 2, the collecting tubule water channel. Chronic lithium-induced interstitial nephritis may also occur, possibly because of inositol depletion and inhibition of cell proliferation.

Pathology

Biopsies show focal chronic interstitial nephritis with interstitial fibrosis, tubular atrophy, and glomerular sclerosis. Whereas similar histologic changes have been reported in psychiatric patients without a history of lithium therapy, patients with lithium exposure often show microcystic changes in the distal tubule; interstitial inflammation and vascular changes are relatively minor. The degree of interstitial fibrosis is related to the duration of administration and cumulative dose.

Clinical Manifestations

Lithium-associated Diabetes Insipidus The most common presentation of lithium-induced nephrotoxicity is nephrogenic diabetes insipidus, characterized by resistance to vasopressin, polyuria, and polydipsia. Impaired renal concentrating ability is found in about 50% of patients, and polyuria resulting from nephrogenic diabetes insipidus occurs in about 20% of patients chronically treated with lithium.

Lithium is also rarely a cause of hypercalcemia, which could potentially exaggerate the tubular concentrating defect and contribute to the development of chronic interstitial nephritis in lithium-treated patients. Nephrogenic diabetes insipidus in lithium treatment may be associated with distal RTA, although this partial functional defect is virtually never of clinical importance.

Chronic Lithium Nephropathy Nephrogenic diabetes insipidus induced by lithium may persist despite the cessation of treatment, indicating irreversible renal damage.

In one study, the mean serum creatinine concentration of patients with biopsy-proven chronic lithium nephrotoxicity was 2.8 mg/dl (247 μmol/l) at the time of biopsy, and 42% of patients had proteinuria greater than 1 g/day.[10] After renal biopsy, all but one patient discontinued treatment with lithium, but seven patients nevertheless progressed to ESRD. A study of 74 lithium-treated patients in France showed that lithium-induced nephropathy developed slowly during several decades, with an average latency between the start of therapy and ESRD of 20 years.[11]

Magnetic resonance imaging, in particular the half-Fourier acquisition single-short turbo spin-echo T2-weighted sequence, without the use of gadolinium, or ultrasound may help in the detection of the characteristic microcysts in the kidney.[12]

Treatment

After other potential causes of polyuria and polydipsia have been excluded, particularly psychogenic polydipsia, the first step to

consider is a reduction in lithium dosage. The potassium-sparing diuretic amiloride improves the polyuria and also blocks lithium uptake through sodium channels in the collecting duct. Thiazide diuretics should be avoided because they increase the risk for acute lithium intoxication because of the resultant volume contraction and an increase in sodium and lithium reabsorption in the proximal tubule.

Patients undergoing long-term lithium treatment should have renal function and 24-hour urine volume measured yearly (serum creatinine and estimated GFR [eGFR]). Lithium has a narrow therapeutic index, so levels should be monitored and maintained between 0.6 and 1.25 mmol/l. The severity of chronic lithium intoxication correlates directly with the serum lithium concentration and may be categorized as mild (1.5 to 2.0 mmol/l), moderate (2.0 to 2.5 mmol/l), or severe (>2.5 mmol/l). Once-daily regimens are less toxic than multiple daily administration schedules, perhaps because of the possibility of renal tubular regeneration with a once-daily administration schedule.[13] Prevention of volume depletion is also important.

Because progressive renal injury with reduced GFR in patients without prior acute lithium intoxication is relatively unusual, raised serum creatinine concentration should initially be treated by a dose reduction. If serum creatinine is persistently elevated, a renal biopsy should be considered, although the findings rarely mandate the complete cessation of lithium treatment. At all times, the risk for discontinuation in a patient with a severe unipolar or bipolar affective disorder needs to be balanced with the relatively low risk of progressive renal injury.

Analgesic Nephropathy

Definition and Epidemiology

Analgesic nephropathy resulted from the abuse of analgesics, commonly mixtures containing phenacetin, aspirin, and caffeine, that were available as over-the-counter preparations in Europe and Australia. It is now rare; indeed, some doubt that new cases are still presenting, following restrictions in compound analgesic sales.[14] Long-term use of aspirin alone is not associated with analgesic nephropathy, and although long-term nonsteroidal anti-inflammatory drug (NSAID) use has been associated with chronic interstitial nephritis in a small number of patients, a large-scale case-control study found no increased risk of ESRD in users of combined or single formulations of phenacetin-free analgesics.[15] A large study in the United States also showed no association between use of current analgesic preparations and increased risk of chronic renal dysfunction,[16] although it does increase the risk of acute kidney injury (see Chapter 69).

Pathogenesis and Pathology

The primary injury in analgesic nephropathy is medullary ischemia caused by toxic concentrations of phenacetin metabolites combined with relative medullary hypoxia, aggravated by inhibition of vasodilatory prostaglandin synthesis. The main pathologic consequence is papillary necrosis, with secondary tubular atrophy, interstitial fibrosis, and a mononuclear cellular infiltrate (Fig. 64-2).

Clinical Manifestations

Analgesic nephropathy is five to seven times more common in women than in men. Renal manifestations are nonspecific and consist of slowly progressive chronic kidney disease (CKD) with impaired urine concentrating ability, urinary acidification defects, and impaired sodium conservation. Urinalysis shows sterile pyuria and mild proteinuria. Patients with analgesic nephropathy are at increased risk for transitional cell carcinoma of the uroepithelium. Recent prospective analysis of the Nurses' Health Study and the Health Professionals Follow-up Study also showed association of regular use of nonaspirin NSAIDs with an increased renal cell carcinoma risk, whereas aspirin and acetaminophen use were not.[17]

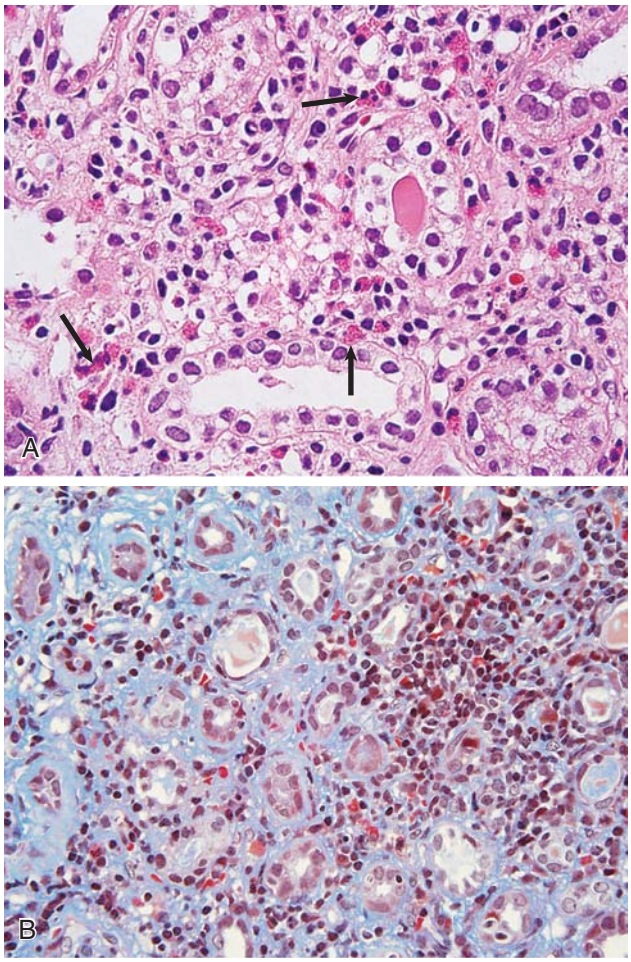

Figure 64-2 Histologic changes in analgesic nephropathy. A, Interstitial nephritis in a patient with analgesic nephropathy associated with marked mononuclear cellular infiltrate including eosinophils *(arrows).* (Hematoxylin-eosin stain; original magnification ×600.) **B,** Analgesic nephropathy with interstitial fibrosis and inflammatory cell infiltration. (Masson trichrome stain; original magnification ×400.) *(Courtesy Drs. Akira Shimizu and Hideki Takano, Nippon Medical School, Tokyo.)*

Diagnosis

Papillary necrosis is present histologically in almost all patients, but it can be detected radiologically only if part or all of the papilla has sloughed. Papillary necrosis is not pathognomonic of analgesic nephropathy; it is also seen in diabetic nephropathy (particularly during an episode of acute pyelonephritis), sickle cell nephropathy, urinary tract obstruction, and renal tuberculosis. Non–contrast-enhanced computed tomography (CT) demonstrates a decrease in renal mass with either bumpy contours or papillary calcifications (Fig. 64-3; see also Fig 52-3, *C*).[18]

Treatment

Management consists of stopping or at least reducing the intake of analgesic medications. Because of the increased incidence of uro-

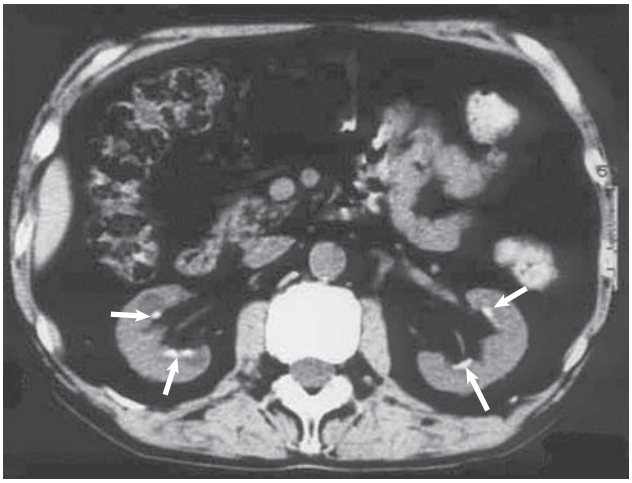

Figure 64-3 Papillary calcifications in analgesic nephropathy. Non–contrast-enhanced computed tomography scan of a patient with long-time analgesic abuse shows thinning of the renal parenchyma and typical papillary calcifications *(arrows). (Courtesy Dr. Yoshifumi Ubara, Toranomon Hospital, Tokyo.)*

epithelial tumors, close follow-up is necessary. New hematuria requires early referral for urologic evaluation.

Analgesic nephropathy associated with over-the-counter medicines is also discussed in Chapter 78.

CHRONIC INTERSTITIAL NEPHRITIS CAUSED BY METABOLIC DISORDERS

Metabolic disorders that cause interstitial nephritis are discussed here. Hyperoxaluria is described in Chapter 59 and cystinosis in Chapter 48.

Chronic Uric Acid Nephropathy

Definition and Epidemiology

Historically, chronic interstitial nephritis associated with chronic hyperuricemia was called *gouty nephropathy* and was ascribed to the medullary deposition of crystals with surrounding inflammation and fibrosis. Later this concept was challenged, and the renal disease associated with gout was thought to be secondary to coexistent hypertension, vascular disease, or aging-associated renal injury. In addition, independent of a specific chronic uric acid nephropathy with crystal deposition, recent epidemiologic studies document that an elevated serum uric acid is a risk factor for the *de novo* development of CKD.[20] These increases in risk remain significant even after adjustment for eGFR, proteinuria, age, and components of the metabolic syndrome. These studies suggest that chronic hyperuricemia may be both a true risk factor for the development of CKD and also a risk factor for progression of established CKD.[21]

Pathogenesis

Chronic gout and severe hyperuricemia can be associated with the deposition of uric acid crystals in the renal medulla (Fig. 64-4). However, independent of crystal deposition, experimental studies indicate that hyperuricemia causes chronic renal injury by activating the renin-angiotensin system (RAS) and inducing oxidative stress, resulting in glomerular hypertension and impaired renal autoregulation.[22] Although uric acid can function as an antioxidant in the extracellular environment, within the cell uric acid has pro-oxidant effects and can lead to endothelial and mitochondrial dysfunction.

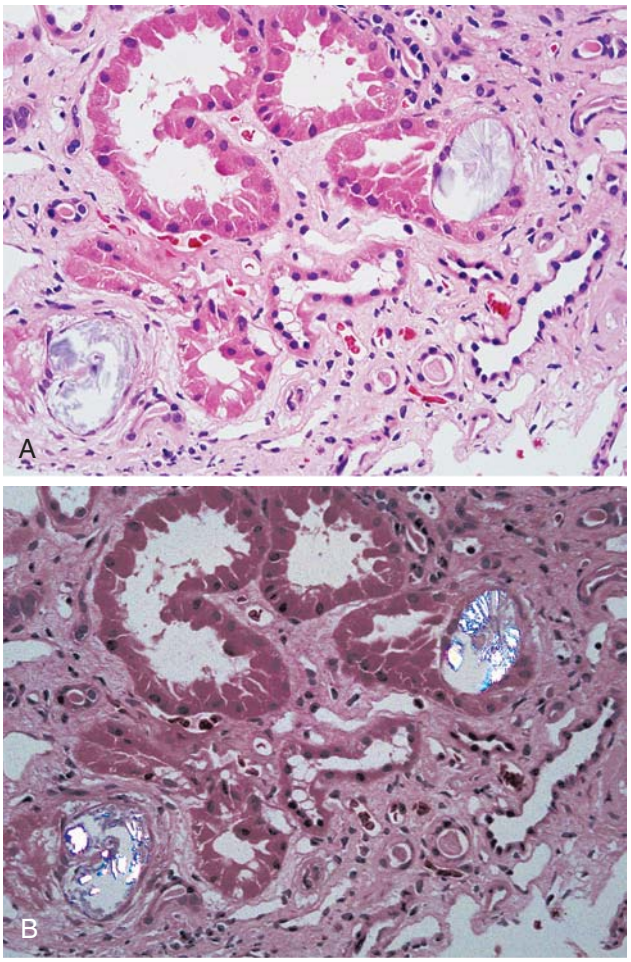

Figure 64-4 Chronic uric acid nephropathy. A, Large collections of elongated or fragmented uric acid crystals are present in association with atrophic tubules. (Hematoxylin-eosin stain; original magnification ×400.) **B,** The crystalline masses are refractile under polarized light. *(Courtesy Drs. Akira Shimizu and Hideki Takano, Nippon Medical School, Tokyo.)*

Pathology

Renal functional abnormalities are observed in 30% to 50% of patients who have had gout for many years, and histologic changes are observed in more than 90%.[23] The most consistent histologic findings are arteriolosclerosis, focal or global glomerulosclerosis, and chronic tubulointerstitial disease. Uric acid crystals can also be occasionally found within both tubules and in the interstitium (see Fig. 64-4), especially in the outer medulla, and on rare occasions medullary renal tophi can be found on gross anatomic dissection. Experimental studies question whether the uric acid crystals themselves are responsible for the disease.

Clinical Manifestations

Patients with chronic uric acid nephropathy present with hypertension with mildly impaired renal function, mild proteinuria, unremarkable urinary sediment, and minor tubular dysfunction (usually impairment of urine concentrating ability manifested as isosthenuria). Uric acid nephropathy should particularly be considered if there is a disproportionate elevation in serum uric acid in relation to the degree of renal impairment (Table 64-3).[24]

Serum Creatinine and Uric Acid Levels in Chronic Kidney Disease			
Serum Creatinine		**Serum Uric Acid**	
mg/dl	**μmol/l**	**mg/dl**	**μmol/l**
<1.5	<132	9	536
1.5-2.0	132-176	10	595
>2.0	>176	12	714

Table 64-3 Serum creatinine and uric acid levels in chronic kidney disease. Uric acid levels higher than those shown should alert the clinician to the possibility of chronic uric acid nephropathy, although they are not diagnostic. *(Modified from reference 23.)*

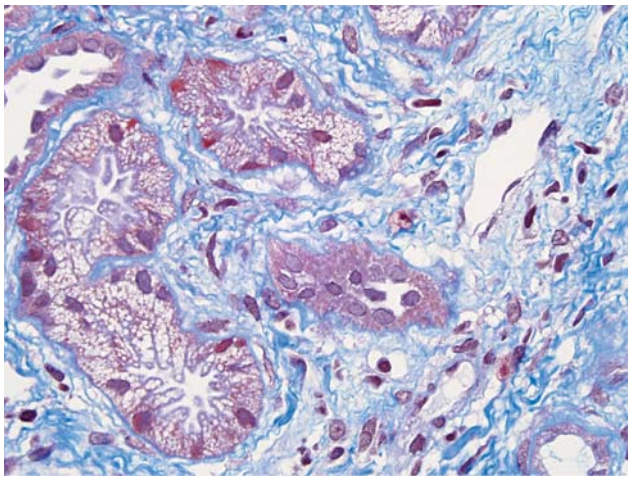

Figure 64-5 Hypokalemic nephropathy. Vacuolization of the renal tubules is observed in association with interstitial fibrosis in a patient with hypokalemic nephropathy. (Masson trichrome stain; original magnification ×400.) *(Courtesy Drs. Akira Shimizu and Hideki Takano, Nippon Medical School, Tokyo.)*

Diagnosis

The most important differential diagnosis for chronic uric acid nephropathy is chronic lead nephropathy. Familial juvenile hyperuricemic nephropathy is a rare autosomal dominant disease that mimics chronic gouty nephropathy but presents in adolescence or during early childhood (see Chapter 50).

Treatment

It remains controversial whether lowering uric acid can improve kidney disease in patients with gout or hyperuricemia. One prospective, randomized trial demonstrated that allopurinol therapy is associated with preservation of eGFR in CKD, although the treatment did not show any effects on the defined study end point, which was ESRD.[25] Withdrawal of allopurinol from patients with stable CKD has resulted in worsening of hypertension and acceleration of kidney dysfunction, especially in patients who were not on ACE inhibitors.[26] Lowering uric acid in patients with asymptomatic hyperuricemia is also associated with an increase in eGFR.[27] There have also been reports that lowering uric acid may reduce the risk of cardiovascular disease in patients with CKD.[25,28] However, to date all studies have involved small numbers of patients, and more definitive studies are required before treatment of hyperuricemia with uric acid–lowering therapy can be recommended routinely.

One reason for caution is the accumulation of xanthine in renal failure, which will be aggravated by the xanthine oxidase inhibitor allopurinol and which can precipitate in the kidney and cause acute kidney injury. To minimize this complication, it is recommended to initiate allopurinol at a dose of 50 to 100 mg/day, increasing to 200 or 300 mg/day after several weeks if it is tolerated. Another adverse effect of allopurinol use is a hypersensitivity reaction (Stevens-Johnson–like syndrome) that may be more common in patients with impaired renal function. The newer xanthine oxidase inhibitor febuxostat does not require modification of dose in renal failure and appears to be less frequently associated with hypersensitivity or nephrotoxicity, but more studies are required before it can be recommended as first-line therapy.

Hypokalemic Nephropathy

Definition and Epidemiology

Hypokalemia, if persistent for prolonged periods, can induce renal cysts, chronic interstitial nephritis, and progressive loss of renal function, known as *hypokalemic nephropathy,* which can be inherited or acquired. Hypokalemic nephropathy occurs in 15% to 20% of individuals with anorexia nervosa.[29]

Pathology

The characteristic finding is vacuolation of the renal tubules as a result of dilation of cisternae of the endoplasmic reticulum and basal folding, which is usually limited to the proximal tubular segments (Fig. 64-5). This abnormality generally requires at least 1 month to develop and is reversible with potassium supplementation. More prolonged hypokalemia can lead to more severe changes, predominantly in the renal medulla, including interstitial fibrosis, tubular atrophy, and cyst formation. There is experimental evidence that hypokalemic injury may be caused by hypokalemia-induced renal vasoconstriction with ischemia. Local ammonia production stimulated by hypokalemia may also lead to intrarenal complement activation that may contribute to the renal injury. Furthermore, the associated intracellular acidosis can stimulate cell proliferation, which may account for the occasional development of cysts in hypokalemic patients.

Clinical Manifestations

Impaired urine concentration, presenting with nocturia, polyuria, and polydipsia, may occur, particularly when serum potassium concentration is consistently below 3.0 mmol/l for months or years. The average duration of hypokalemia reported in patients with chronic hypokalemic nephropathy is 3.5 to 9 years. The renal defect is associated with decreased collecting tubule responsiveness to vasopressin, possibly because of decreased expression of aquaporin 2.

Diagnosis

Although degenerative changes in proximal tubular cells are a consistent but nonspecific finding in hypokalemic nephropathy, a particularly characteristic finding is vacuolar changes in the proximal tubules (see Fig. 64-5). Similar vacuolization of the convoluted tubules is observed in ethylene glycol poisoning.

Treatment

Hypokalemia can usually be treated with oral potassium supplements. The treatment of hypokalemia is discussed in Chapter 9. Coarse cytoplasmic vacuoles may persist for some time after normalization of serum potassium values.

Hypercalcemic Nephropathy

Definition and Epidemiology

Hypercalcemia can cause both a transient and reversible renal vasoconstriction with a decrement in renal function and a chronic interstitial nephritis secondary to tubular cell necrosis and intratubular obstruction. In addition, hypoparathyroidism (especially after surgical treatment of hyperparathyroidism) can also result in marked hypercalciuria and a similar syndrome in the absence of hypercalcemia.

Pathology

Focal degeneration and necrosis of the tubular epithelium, primarily in the medulla where calcium is concentrated, develop soon with persistent hypercalcemia. Although focal degenerative and necrotic lesions of the tubular epithelium can be observed with acute hypercalcemia, the most distinctive histologic feature of longstanding hypercalcemia is calcific deposits in the interstitium (nephrocalcinosis; Fig. 64-6). Deposition begins in the medullary tubules, followed by deposition in the cortical proximal and distal tubules and within the interstitial space, and secondarily leads to mononuclear cell infiltration and tubular necrosis.

Clinical Manifestations

Macroscopic nephrocalcinosis is often detected on radiography or ultrasound. A defect in urinary concentration is the most notable tubular dysfunction and manifests as polyuria and polydipsia. The mechanism is incompletely understood, but the impairment relates both to a reduction in medullary solute content and to interference with the cellular response to vasopressin. Reversible impairment of renal function can result from either acute or chronic hypercalcemia by decreased renal blood flow and GFR. Irreversible renal failure is a rare consequence of longstanding hypercalcemia and is almost invariably associated with calcium crystal deposition in the interstitium of the kidney.

CHRONIC INTERSTITIAL NEPHRITIS CAUSED BY HEREDITARY DISEASES OF THE KIDNEY

Nephronophthisis (NPHP) and medullary cystic kidney disease (MCKD) (or the NPHP-MCKD complex) are hereditary diseases associated with renal cysts at the corticomedullary junction. These disorders are described in detail in Chapter 47.

CHRONIC INTERSTITIAL NEPHRITIS ASSOCIATED WITH HEAVY METAL EXPOSURE

Lead Nephropathy

Definition and Epidemiology

Acute lead intoxication is rare but may present with abdominal pain, encephalopathy, hemolytic anemia, peripheral neuropathy, and proximal tubular dysfunction (Fanconi syndrome). In contrast,

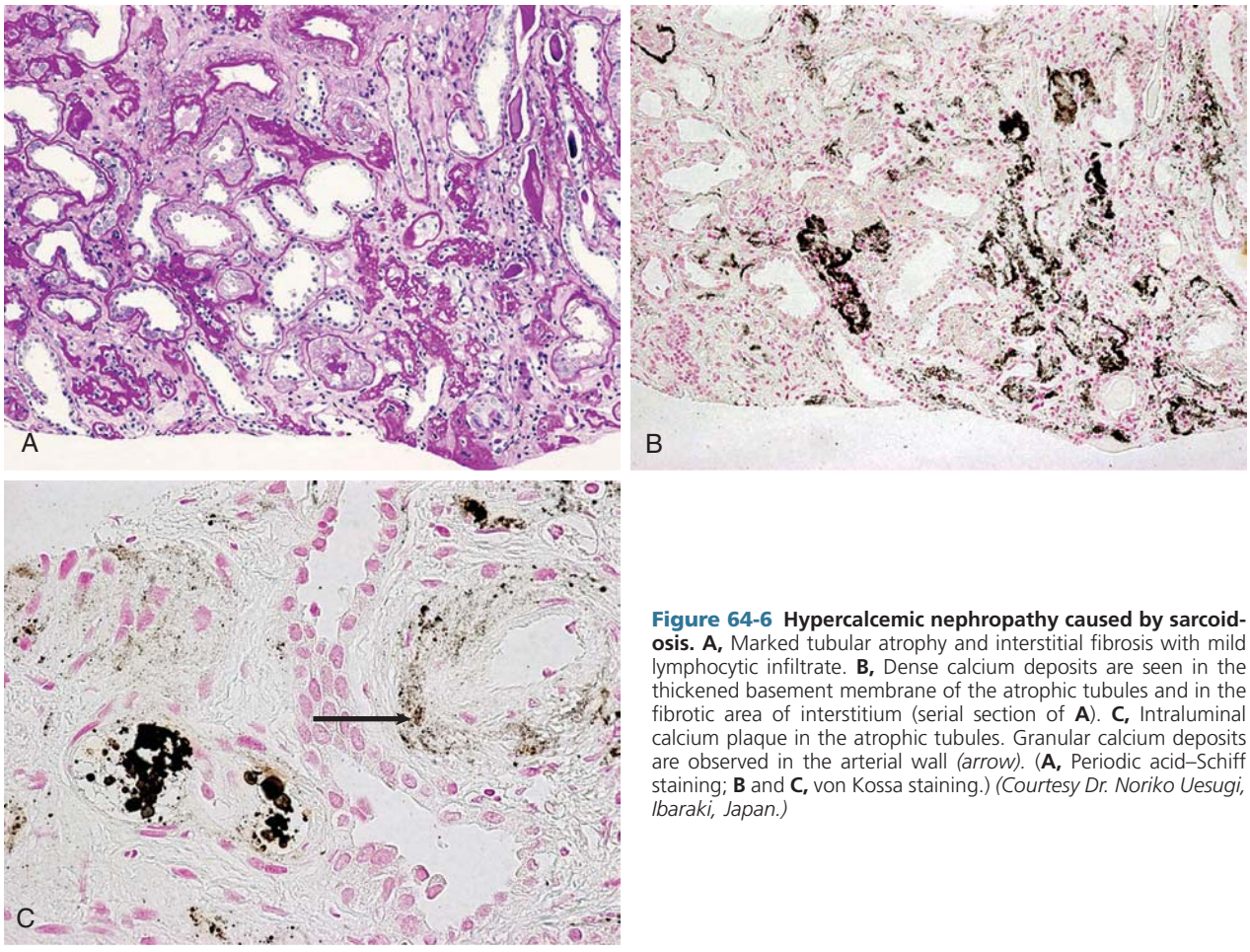

Figure 64-6 Hypercalcemic nephropathy caused by sarcoidosis. A, Marked tubular atrophy and interstitial fibrosis with mild lymphocytic infiltrate. **B,** Dense calcium deposits are seen in the thickened basement membrane of the atrophic tubules and in the fibrotic area of interstitium (serial section of **A**). **C,** Intraluminal calcium plaque in the atrophic tubules. Granular calcium deposits are observed in the arterial wall *(arrow)*. (**A,** Periodic acid–Schiff staining; **B** and **C,** von Kossa staining.) *(Courtesy Dr. Noriko Uesugi, Ibaraki, Japan.)*

chronic low-level exposure to lead has been associated with CKD, often with hyperuricemia. Because lead has a biologic half-life of several decades, both intermittent acute poisoning and low-level environmental exposure result in chronic cumulative lead poisoning.

Although some epidemiologic studies have suggested that low-level exposure may be associated with CKD or hypertension,[30-32] data indicating that lead causes CKD leading to ESRD are relatively sparse.[33] The pathogenesis of the renal disease may be related to the accumulation of reabsorbed lead in the proximal tubule cells, effects of chronic lead exposure on the vasculature, or lead-induced hyperuricemia. Additional well-controlled longitudinal studies with adequate exposure and effect variables are awaited to confirm that lead exposure causes deterioration of renal function and eventual ESRD.

Pathology

The kidneys are granular and contracted. The characteristic morphology is chronic interstitial nephritis demonstrating nonspecific tubular atrophy, interstitial fibrosis, and a paucity of inflammatory cells. The earliest histologic finding is proximal tubular injury, with intranuclear inclusion bodies composed of a lead-protein complex. Glomerular scarring can be observed as a secondary event, and arteries and arterioles demonstrate medial thickening and luminal narrowing, probably related to hypertension. Immunofluorescence studies are noncontributory.

Clinical Manifestations

Chronic lead nephropathy is usually identified when a source of high exposure is known (occupational hazard or consumption of illicitly distilled spirits [moonshine]). Hyperuricemia is common because of impaired uric acid excretion. Urine sediment is benign, and urinary protein excretion is less than 2 g/day. Hypertension is almost always present, and in the absence of appropriate testing or a careful exposure history, lead nephropathy is often misdiagnosed as hypertensive kidney disease. Gouty arthritis ("saturnine gout") affects about half of patients. Patients with chronic lead intoxication may occasionally manifest other signs, including peripheral motor neuropathies, anemia with "basophilic" stippling, and perivascular cerebellar calcifications.

Diagnosis

Lead nephropathy may be underdiagnosed because no simple diagnostic blood test is available. Lead nephropathy is easily confused with chronic uric acid nephropathy, in which uric acid deposits (tophi) may form in the renal interstitium. All patients with hyperuricemia and renal impairment should have a history of occupational lead exposure excluded. The blood lead concentration is an insensitive measure of cumulative body stores. A clinical diagnosis of lead nephropathy is based on a history of exposure, evidence of renal dysfunction, and an abnormal calcium disodium edetate ($CaNa_2$ EDTA) lead chelation test. The association with gout and CKD is strong enough to merit lead chelation screening in patients with CKD who have gout and risk of lead exposure. $CaNa_2$ EDTA is administered (two doses of 0.5 g in 250 ml 5% dextrose given 12 hours apart), and urine is collected for 3 days because urinary excretion is slowed in the setting of renal failure. Normal urinary lead levels are less than 650 µg/3 days. X-ray fluorescence, which provokes the emission of fluorescent photons from the target area, is an alternative method that detects increased bone lead levels, which are also a reflection of cumulative lead exposure. Although x-ray fluorescence measurements allow a rapid, noninvasive estimation of lead in bone, detection equipment remains available at only a small number of centers, making availability of this method limited.

Treatment

Treatment involves the infusions of $CaNa_2$ EDTA together with removal of the source of lead. The likelihood of a satisfactory response to $CaNa_2$ EDTA is influenced by the degree of interstitial fibrosis that has already occurred.

In industrial and occupational settings, such as in foundry workers and individuals working with lead-based paints and glazes, preventive measures to minimize exposure and low-level absorption are essential. Some studies in children show success with the oral chelating agent succimer (Chemet). Chelation therapy may slow progressive CKD, even in patients with mild lead intoxication.[34] However, the chelation therapy has not been widely used because of adverse drug effects and concerns about the effects of remobilized lead. It is generally not indicated for adults with blood lead concentrations of less than 45 µg/dl. Because of a lack of controlled clinical trials demonstrating efficacy of chelation and concerns about potential side effects, recommendations for treatment with chelating agents are empiric, and decisions to use chelation therapy for lead intoxication can be controversial.

Other Heavy Metal–induced Nephropathies

Cadmium is a metal with a wide variety of industrial uses, including the manufacture of glass, metal alloys, and electrical equipment. Cadmium is preferentially concentrated in the kidney, principally in the proximal tubule, in the form of a cadmium-metallothionein complex that has a biologic half-life of about 10 years. Cadmium contamination may be an important contributor to the high risk of chronic interstitial nephritis in some agricultural communities in the developing world. A major outbreak of cadmium toxicity occurred in Japan as a result of industrial contamination. The disease was called *itai-itai,* or "ouch-ouch," because bone pain was the major clinical manifestation. Other manifestations included proximal tubular dysfunction, renal stones caused by hypercalciuria, anemia, and progressive chronic interstitial nephritis. The mechanism by which cadmium elicits chronic inflammation and fibrosis in the kidney is relatively unstudied. The diagnosis is suggested by a history of occupational exposure, increased urinary β_2-microglobulin, and increased urinary cadmium levels (>7 µg of cadmium per gram creatinine). Once manifested, renal injury tends to be progressive, even if exposure is discontinued. Chelation has not been effective in humans, and prevention is the only effective treatment.

Arsenic, used as a poison gas in the First World War, is present in insecticides, weed killers, wallpaper, and paints. Chronic arsenic toxicity most commonly manifests as sensory and motor neuropathies, distal extremity hyperkeratosis, palmar desquamation, diarrhea and nausea, Aldrich-Mees lines (white bands on the nails), and anemia. In rare cases, it may cause renal disease, manifested by both proximal RTA and chronic interstitial fibrosis. Diagnosis is made by demonstration of an elevated urinary arsenic level.

Mercury is found in alloy plants, mirror plants, and some batteries, and mercury intoxication usually occurs as a result of accidental exposure to mercury vapor. Mercury has been shown to induce membranous nephropathy (MN) in experimental animals and has been reported with the use of mercury-containing skin-lightening creams.[35] Neither elemental mercury nor the mercurous salt (Hg_2Cl_2) produces sustained renal tubular injury, but mercury dichloride ($HgCl_2$) may produce acute tubular necrosis and subsequent chronic interstitial nephritis. However, a report of endemic methyl mercury poisoning in Japan revealed a clinical picture dominated by neurologic sequelae; renal disease in these patients was surprisingly benign, consisting only of tubular proteinuria without changes in serum creatinine.

ENDEMIC CHRONIC INTERSTITIAL NEPHRITIS

A number of localized epidemics of CKD caused by chronic interstitial nephritis have been reported. The longest known is Balkan endemic nephropathy, which is described in Chapter 78 along with the other manifestations of aristolochic acid nephropathy.

Another epidemic has been identified in agricultural communities on the Pacific coast of Central America, especially in Nicaragua, Honduras, and El Salvador. The disease is observed primarily in men working in the sugar cane fields, but it also occurs in others working outside in hot environments. The cause remains unknown but does not appear to relate to pesticides, aristolochic acid, or heavy metals. It has been proposed that the disease may result from leptospirosis infection or from chronic or recurrent episodes of dehydration, possibly in conjunction with the use of NSAIDs.

An epidemic has also been described recently in agricultural communities in Sri Lanka; the cause remains uncertain, but heavy metal contamination may be involved.

RADIATION NEPHRITIS

Definition and Epidemiology

Although radiation nephritis was relatively common decades ago, the incidence has decreased considerably because recognition of radiation-induced renal damage has altered protocols for the administration of therapeutic radiation. In general, direct exposure of the kidney to 20 to 30 Gy (1 Gy = 100 rad) during 5 weeks or less will produce radiation nephritis.

Pathology

The initial target of ionizing radiation within the kidney appears to be endothelial cells, leading to endothelial cell swelling. Vascular occlusion then develops with resultant tubular atrophy. Electron microscopy reveals a split appearance of the capillary wall caused by the mesangial interposition and widening of the subendothelial space by a nondescript fluffy material. These features are shared by hemolytic uremic syndrome and thrombotic thrombocytopenic purpura, suggesting a common pathogenic mechanism originating from endothelial injury. Severe disease is characterized by progressive interstitial fibrosis and the presence of interstitial inflammatory cells.

Clinical Manifestations

In general, vascular and glomerular lesions of thrombotic microangiopathy may predominate. However, tubulointerstitial changes of varying severity are also usually present. Hypertension is commonly observed. Progression to a "chronic" form of radiation nephritis may occur if resolution of acute radiation nephritis is incomplete. These patients present with proteinuria, progressive CKD, and eventual development of ESRD several years after irradiation in the absence of an acute phase.

Treatment

Prevention is the best approach. The risk for development of radiation nephritis can be minimized by shielding the kidneys or fractioning the total-body irradiation into several small doses over several days. No specific treatment is available for established radiation nephritis; consequently, the general approach is control of hypertension and supportive treatment of CKD.

INTERSTITIAL NEPHRITIS MEDIATED BY IMMUNOLOGIC MECHANISMS

Sjögren Syndrome

Definition and Epidemiology

Sjögren syndrome may be associated with chronic interstitial nephritis. The reported prevalence of renal involvement in Sjögren syndrome has varied widely, ranging from 2% to 67%, principally owing to different definitions of kidney involvement or disease. Recent analysis of 130 patients with primary Sjögren syndrome in China showed an 80% incidence of biopsy-proven chronic interstitial nephritis.[36]

Pathology

The lesion is characterized histologically by infiltration of lymphocytes and plasmacytes in the interstitium with tubular cell injury and, rarely, granuloma formation. This progresses to tubular atrophy and interstitial fibrosis over time. Immunofluorescence reveals granular deposits of IgG and C3 along the tubular basement membrane (TBM).

Clinical Manifestations

The clinical and biochemical manifestations of interstitial nephritis may be the presenting or only features of Sjögren syndrome. Serum creatinine concentration is generally only mildly elevated in association with a bland urine sediment and abnormalities in tubular function, including Fanconi syndrome, distal RTA, hypokalemia, and nephrogenic diabetes insipidus. Sjögren syndrome is one of the most common causes of acquired distal (type 1) RTA in adults, and the hypokalemia may be marked, resulting in a clinical presentation of severe weakness. Hypokalemia may occur in the absence of RTA, resulting from salt wasting and secondary hyperaldosteronism.

Treatment

Treatment with corticosteroids at the stage of cellular infiltration is frequently beneficial for protecting renal function. Although the renal disease has a slow and protracted course and CKD develops over time, progression to ESRD is rare.

Sarcoidosis

Definition and Epidemiology

Histologic evidence of interstitial nephritis with noncaseating granulomas is common in patients with sarcoidosis, but the frequency of clinically significant disease is low.[37] It may present as either an acute interstitial nephritis or a chronic interstitial nephritis.

Pathogenesis and Pathology

Renal biopsy reveals normal glomeruli; interstitial infiltration, mostly with mononuclear cells; tubular injury; and with more chronic disease, interstitial fibrosis. Whereas the classic finding is noncaseating granulomas in the interstitium, they are uncommon and nonspecific. An analysis of 18 patients with granulomatous interstitial nephritis showed that in five the disorder was associated with sarcoidosis; in two, tubulointerstitial nephritis and uveitis; in two, medication; and in nine, the condition was idiopathic.[38] Immunofluorescence and electron microscopic studies typically show no immune deposits.

Recent studies suggest that renal sarcoidosis may reflect an impaired immune response to certain bacteria, especially *Propionibacterium acnes*. Confirmatory studies are needed, and it is not known if antibiotic treatment aimed at *P. acnes* provides any benefit.

Clinical Manifestations

Most affected patients have clear evidence of diffuse active sarcoidosis, although some present with an isolated elevation in serum creatinine and only minimal extrarenal manifestations. The urinalysis, if findings are not normal, shows only sterile pyuria or mild proteinuria.

In addition, hypercalcemia induced by increased production of calcitriol (1,25-dihydroxyvitamin D_3) by activated mononuclear cells (particularly macrophages) in the lung and lymph nodes occasionally results in renal problems (see the previous discussion of hypercalcemic nephropathy).

The serum ACE level is used best not as a primary diagnostic tool but as a marker of disease activity and response to therapy. A normal serum ACE level does not exclude renal sarcoidosis.

Treatment

Corticosteroid therapy tends to improve renal function, although recovery is often incomplete. Rapid tapering of corticosteroids can result in relapse.

Systemic Lupus Erythematosus

Definition and Epidemiology

Interstitial nephritis with immune complexes is defined by granular deposits of immunoglobulins and complement in the TBM, interstitium, or both. Systemic lupus erythematosus is the most common reason for this type of interstitial nephritis (Fig. 64-7), and interstitial involvement is present in half of kidney biopsy specimens in lupus. Rarely, tubulointerstitial immune complex disease may be the only manifestation of lupus nephritis.

Clinical Manifestations

The presentation may be as an acute or a chronic interstitial nephritis. The possibility of interstitial involvement (without glomerular disease) is suggested by a rising serum creatinine concentration and a bland urine sediment. Interstitial involvement may be accompanied by signs of tubular dysfunction, such as distal RTA (type 1 or type 4); by isolated hyperkalemia resulting from impaired distal potassium secretion; or by hypokalemia resulting from salt wasting. The potentiating effects of sodium wasting on potassium secretion include an increase in sodium delivery to the potassium secretory site in the collecting tubules and associated volume depletion with subsequent stimulation of aldosterone secretion.

Treatment

Corticosteroid therapy is usually effective in suppressing tubular dysfunction and preserving renal function.

Inflammatory Bowel Disease

Although the most frequent renal complications of Crohn disease are calcium oxalate stones and renal amyloidosis, interstitial nephritis has been reported in patients treated for chronic inflammatory bowel disease. Aminosalicylates (5-aminosalicylic acid, mesalazine, and sulfasalazine) are responsible for most of these cases, but nephrotoxicity of these agents is very uncommon (mean rate only 0.3% per patient-year).[39] Nephrotoxicity most often occurs in the first 12 months of treatment with aminosalicylate, but a delayed presentation after several years has also been reported. There is no clear relationship between aminosalicylate dose and the risk of nephrotoxicity, suggesting that this is an idiosyncratic response. Some patients have been reported to have biopsy-proven interstitial nephritis before the diagnosis of Crohn disease.

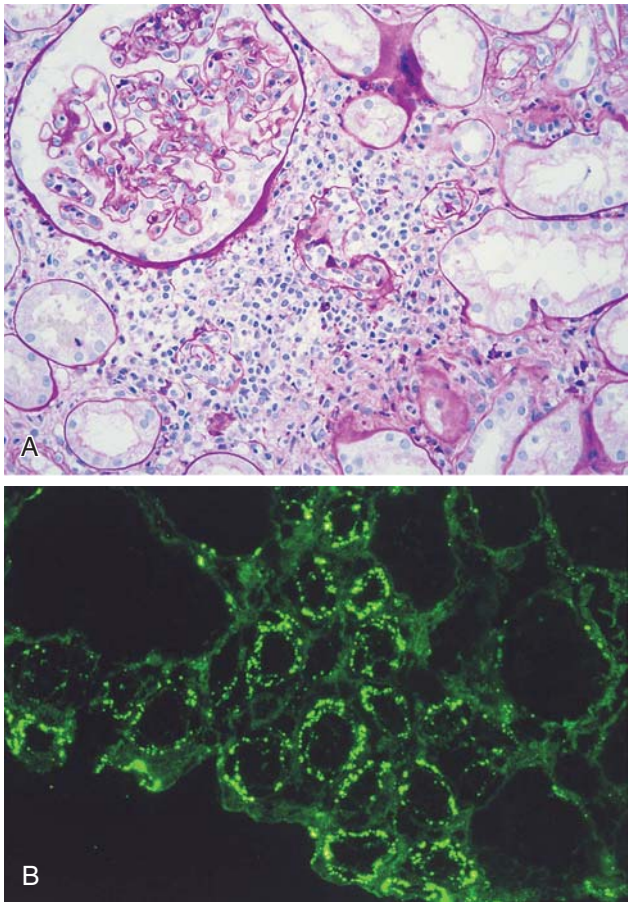

Figure 64-7 Chronic interstitial nephritis in systemic lupus. A, Interstitial nephritis observed in patients with systemic lupus erythematosus. (Periodic acid–Schiff staining; original magnification ×400.) **B,** Immunofluorescence study of the same patient revealed deposition of IgG in the interstitium, in tubular cells, and along the tubular basement membrane. *(Courtesy Drs. Akira Shimizu and Hideki Takano, Nippon Medical School, Tokyo.)*

Aminosalicylates should be withdrawn when renal impairment develops in a patient with inflammatory bowel disease; if this does not result in a fall in serum creatinine, renal biopsy should be considered. Corticosteroids are recommended when renal function does not respond to drug withdrawal.

IgG4-related Kidney Disease

Definition and Epidemiology

On the basis of histologic and immunohistochemical examination of various organs of patients with autoimmune pancreatitis, a novel clinicopathologic entity of IgG4-related sclerosing disease has been proposed.[40] This is a systemic disease that is characterized by extensive IgG4-positive plasma cells and T lymphocyte infiltration of various organs (Fig. 64-8). Initial reports of IgG4-related sclerosing disease came from Japan, but it has now been described in Europe and the United States and is considered to be a worldwide entity.

Pathogenesis

Whether IgG4 is pathogenic or is a "bystander" remains unknown. IgG4 does not activate the classical complement pathway effectively. However, immune complex formation may play a pathogenic role, raising the possibility of complement fixation via the lectin pathway or activation of the classical pathway of complement by some unknown mechanism.

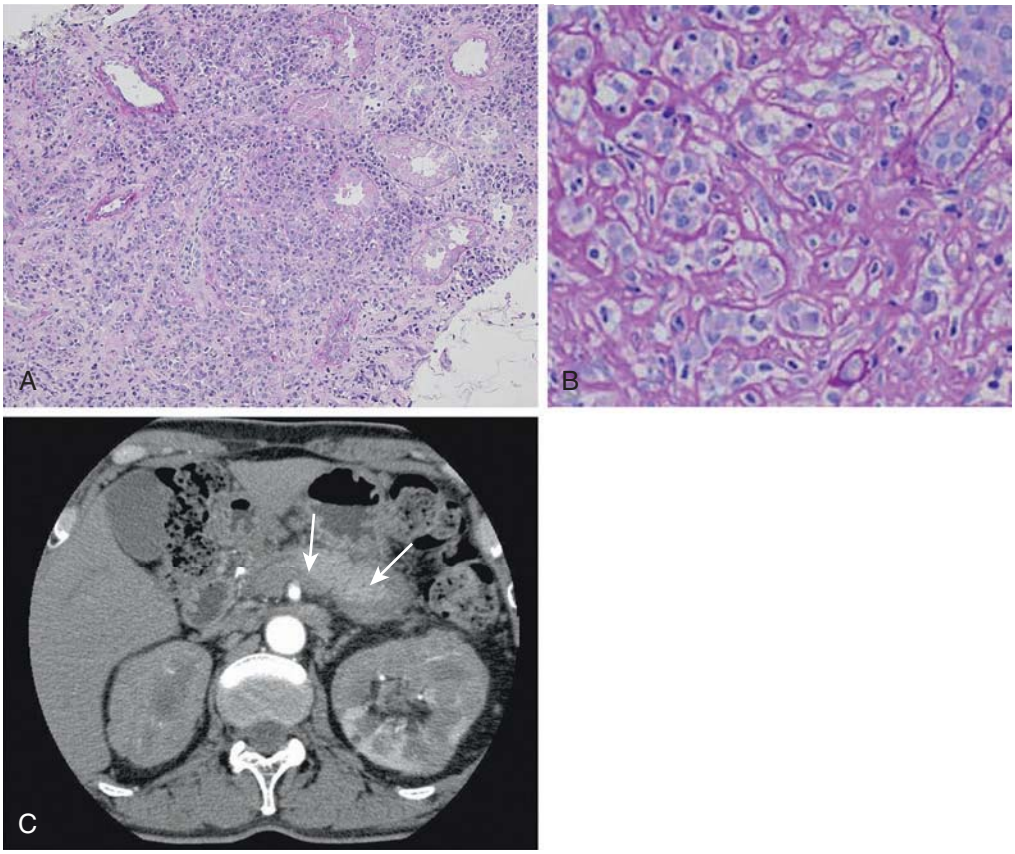

Figure 64-8 Chronic interstitial nephritis in IgG4-related sclerosing disease. A, Interstitial nephritis with numerous mononuclear cell infiltrates observed in a patient with autoimmune pancreatitis. Many of these cells are positive for IgG4 in typical cases. (Periodic acid–Schiff staining; original magnification ×200.) **B,** Small nests of swollen plasma cells or individual plasma cells are encircled by collagenous tissue. The features resemble a maple wood grain pattern called "bird's eye." Plasma cells look like birds' eyes in the wood, whereas fibrotic tissues correspond to branches of the wood. **C,** Computed tomography scan of the patient revealed pancreatic swelling *(arrows). (**A** and **C** courtesy Dr. Hiroshi Nishi, University of Tokyo, Tokyo. **B** from reference 41.)*

Pathology

The most common pattern of involvement by IgG4-related kidney disease is tubulointerstitial nephritis with dense infiltration of IgG4-positive mononuclear cells. Distinctive features of the tubulointerstitial nephritis include (1) well-demarcated borders between involved and uninvolved areas; (2) involvement of the cortex and deep medulla, often extending beyond the renal capsule; (3) interstitial inflammatory cells comprising predominantly plasma cells and lymphocytes, with a high prevalence of IgG4-positive cells often admixed with fibrosis; (4) peculiar features of interstitial fibrosis resembling a "bird's-eye" pattern; and (5) deposits visible by light microscopy and immunofluorescence in the TBM, Bowman capsule, and interstitium.[41] Immunofluorescence shows granular TBM staining for IgG accompanied by C3 of lesser staining intensity. MN has also been described as a manifestation of IgG4-related kidney disease.[42]

Clinical Manifestations

Clinical manifestations are observed in various organs, with presentations including sclerosing cholangitis, cholecystitis, sialadenitis, and retroperitoneal fibrosis. IgG4-related tubulointerstitial nephritis can be mass forming, similar to IgG4-related inflammatory lesions in other organs. Of patients with IgG4-related disease, 80% are reported to have had radiographic renal abnormalities: bilateral and multiple small low-attenuation lesions, a mass, or bilateral renal enlargement.[43] Whereas most IgG4-related sclerosing disease is associated with autoimmune pancreatitis, cases without pancreatic involvement have also been described. The disease occurs predominantly in older men. Serum IgG4 levels are raised, and IgG4-positive cells are found in the interstitium. The finding of an elevated serum IgG4 is not specific, however, because this may occur in 5% of the normal population. The patients often show hypocomplementemia and eosinophilia. Recently proposed diagnostic criteria are shown in Table 64-4.

Treatment

The response to corticosteroids is generally favorable. There is no correlation between histologic pattern and response to therapy, and even patients with extensive fibrosis on biopsy have shown a response to corticosteroid therapy.[44]

Other Forms of Immune-mediated Interstitial Nephritis

Primary anti–TBM nephritis is an extremely rare form of interstitial nephritis that usually is acute and characterized by linear deposits of immunoglobulins, commonly IgG, and complement in the TBM, together with tubular interstitial inflammation and anti-TBM antibodies in the serum. Anti-TBM antibodies, usually IgG, may also be found in 50% to 70% of patients with anti–glomerular basement membrane nephritis and occasionally in patients with MN, systemic lupus, IgA nephropathy, minimal change disease, and malignant hypertension.

Diagnostic Criteria for IgG4-related Tubulointerstitial Nephritis (TIN)	
Histology	Plasma cell–rich tubulointerstitial nephritis with >10 IgG4-positive plasma cells per high-power field in the most concentrated field* Tubular basement membrane immune complex deposits by immunofluorescence, immunohistochemistry, and/or electron microscopy†
Imaging	Small peripheral low-attenuation cortical nodules, round or wedge-shaped lesions, or diffuse patchy involvement Diffuse marked enlargement of kidneys
Serology	Elevated serum IgG4 or total IgG level
Other organ involvement	Includes autoimmune pancreatitis, sclerosing cholangitis, inflammatory masses in any organ, sialadenitis, inflammatory aortic aneurysm, lung involvement, retroperitoneal fibrosis

Table 64-4 Diagnostic criteria for IgG4-related TIN. Diagnosis of IgG4-TIN requires the histologic feature of plasma cell–rich TIN with increased IgG4+ plasma cells and at least one other feature from the categories of imaging, serology, or other organ involvement. *Mandatory criterion. †Supportive criterion, present in >80% of cases. *(From reference 43.)*

OBSTRUCTIVE UROPATHY

Complete or partial urinary tract obstruction is accompanied by pathologic changes in both the tubulointerstitium and glomeruli consisting of interstitial fibrosis, tubular atrophy, and occasionally focal glomerular sclerosis. Details are discussed in Chapter 60.

VASCULAR DISEASES

Ischemia resulting from intrarenal vascular involvement causes tubular atrophy, interstitial fibrosis, and cellular infiltration. This is further discussed in Chapter 66. Chronic ischemia in the tubulointerstitial compartment also plays a crucial role in the progression of a variety of glomerular and tubulointerstitial diseases.[2]

INFECTION-ASSOCIATED CHRONIC INTERSTITIAL NEPHRITIS

Although a variety of bacterial and viral infections can be associated with acute interstitial nephritis (see Chapter 62), chronic interstitial nephritis secondary to infectious agents appears to be rare. Insidious *Mycobacterium tuberculosis* infection can cause chronic granulomatous tubulointerstitial nephritis.[45] Chronic bacterial infections can result in xanthogranulomatous pyelonephritis or renal malacoplakia (see Chapter 53).

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CHAPTER 65

Myeloma and the Kidney

Ashley B. Irish

Myeloma is an uncommon hematologic malignancy, accounting for 1% of total and 10% of hematologic malignancies. African Americans have twice the incidence of Caucasians, and males predominate over females. It is a disease of the elderly, with a median age of diagnosis of older than 65 years. The characteristic feature of myeloma is the dysregulated overproduction of immunoglobulin (Ig), and especially the light-chain (LC) component, which can be nephrotoxic. Various causes and manifestations of acute kidney injury (AKI) are possible in myeloma (Table 65-1), but the major risk is myeloma cast nephropathy (MCN), which is a medical emergency that requires prompt diagnosis and intervention to prevent irreversible renal failure.

ETIOLOGY AND PATHOGENESIS OF MYELOMA

Myeloma is a B cell–derived malignancy of incompletely differentiated plasma cells that have two prominent features: increased production of monoclonal Ig, and bone destruction. Normally plasma cells derive from mature uncommitted B cells and after antigen stimulus undergo heavy chain class switching from μ (IgM) expression to α, δ, ε, or γ. Whole Ig production requires the intracellular assembly of two heavy chains and two LCs, kappa (κ) or lambda (λ), to derive whole IgG, IgA, IgD, and IgE immunoglobulin. Normally LCs are excreted in slight excess, with a κ:λ ratio of approximately 2:1. In myeloma a clone of cells secretes excessive quantities of a specific Ig and/or LC (the paraprotein or M protein). The genetic and somatic abnormalities underlying this malignant clone are complex and remain incompletely understood but have important implications for prognosis and treatment.[1] Both deregulation of cell cycling and impaired apoptosis account for their progressive and dysfunctional accumulation within the bone marrow, and occasionally other organs. Plasma cells express little surface Ig and are recognized by surface expression of CD38 and CD138; they normally reside only in the bone marrow. In myeloma, unrestrained plasma cell growth is supported by a complex milieu of autocrine and paracrine cytokines, especially interleukin (IL)–6. These cytokines are secreted from stromal cells, endothelial cells, and/or osteoclasts and maintain myeloma cell growth, survival, and migration; they also contribute to local organ dysfunction—for example, bone resorption, fracture, and anemia.[2]

ETIOLOGY AND PATHOGENESIS OF RENAL DISEASE

Free light chains (FLCs) circulate as monomers (predominantly κ, approximately 25 kD) and dimers (predominantly λ, approximately 50 kD) with a very short half-life (2 to 6 hours) because of free glomerular filtration, whereas the much larger whole Ig circulates intact for several weeks. The filtered FLC is reabsorbed in the proximal tubule cell (PTC) by receptor-mediated endocytosis after binding with the glycoprotein receptor cubilin (Fig. 65-1).[3] LCs in excess can induce an inhibitory effect on endocytosis *in vitro* and are associated with lysosomal overload and rupture, releasing enzymatic contents into the cytosol, manifesting histologically by evidence of crystallization, vacuolation, and desquamation of the PTC. Endocytosis of light chains induces the release of the proinflammatory cytokines IL-6, IL-8, and monocyte chemoattractant protein 1 (MCP-1) via the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in the PTC.[4] This mechanism suggests that LC overload induces factors promoting interstitial injury and fibrosis, as described in other proteinuric states. LC may also be cytotoxic to the PTC via direct DNA injury and the induction of apoptosis.[5] Less common manifestations of PTC injury include Fanconi syndrome, which is invariably associated with specific variant κ LCs and often with pathologic evidence of crystalline inclusions.[6]

Injury to the PTC allows escape or overflow of LCs to the distal nephron where they can interact with the Tamm-Horsfall protein (THP) secreted by the cells of the thick ascending loop of Henle (TAL). Variations in the specificity of the complementarity-determining region 3 (CDR3) of different LCs modify the affinity of the LC for binding with the specific single FLC-binding domain of THP, which could in part explain the variable nephrotoxicity (cast formation) of different LCs.[7] This specificity of the individual LC for THP was illustrated by the finding that the intraperitoneal installation of LC isolated from humans with specific renal LC-associated disease induces the same renal injury in animals.[8] Although renal injury occurs only in the presence of urinary LC, not all LCs are associated with injury, and neither the amount nor the type of urinary LC correlates with the severity of cast formation. Nevertheless, in general, the higher the urinary excretion of LC, the greater the risk of renal failure and reduced response to chemotherapy.[9-11] In addition to LC-specific factors, tubular solute composition and tubular flow rates modulate the risk for cast formation. In animals, urinary acidification, furosemide, increased urinary sodium increased urinary calcium concentration may affect the tendency to increased binding or aggregation of LC with THP, whereas colchicine may reduce this tendency in animals but not in humans.[12,13] The formation and passage of casts distally can occlude the tubule and allow intratubular obstruction, with rupture and even backflow of contents (Fig. 65-2).

EPIDEMIOLOGY

Most myeloma presents *de novo,* although a small number of cases evolve in patients with monoclonal gammopathy of undetermined significance (MGUS) each year. In patients with newly diagnosed myeloma, the prevalence of IgG, IgA, IgD, and FLC-only myeloma was 52%, 21%, 2%, and 16%, respectively.[9] IgM and IgE myeloma are extremely uncommon. Approximately 70% of patients with myeloma

also have a urinary M protein. At the time of diagnosis of myeloma, up to 50% of patients have evidence of impaired renal function judged by increased serum creatinine; approximately 25% present with serum creatinine exceeding 2 mg/dl (177 µmol/l).[9,10] In unselected series, 2% to 10% of patients present with severe renal failure necessitating dialysis; this figure is higher in series reported from renal units. In contrast to the general distribution of M-protein types in myeloma, LC and IgD myeloma are particularly associated with the risk of renal disease, being present in nearly 50% of patients with severe renal disease who require dialysis.[14]

Etiology of Renal Injury and Clinical Manifestations

	Cause	Manifestation
Pre-renal		
Volume depletion	Hypercalcemia Gastrointestinal losses (nausea and vomiting) Sepsis	Polyuria and polydipsia Hypotension Fever
Hemodynamic	Hemodynamic from NSAIDs	Oliguria, hyperkalemia
Other	Hyperviscosity (IgA, IgG3) Hyperuricemia	Mental state alterations Tumor lysis
Renal	Proximal tubular injury from light chains, uric acid, distal tubular injury from casts Glomerular disease (LCDD, amyloid)	Fanconi syndrome Tubular proteinuria Crystalluria Nephrotic proteinuria Hematuria, active sediment
Post-renal	Calculi	Colic

Table 65-1 Etiology of renal injury and clinical manifestations. *LCDD,* Light-chain deposition disease; *NSAIDs,* nonsteroidal anti-inflammatory drugs.

CLINICAL PRESENTATION

Most patients present with constitutional symptoms (fatigue, weight loss) and skeletal pain, especially back pain. Renal impairment is common and has a variety of causes (see Table 65-1). In a smaller proportion of patients, renal failure is the presenting manifestation of myeloma, and the diagnosis of myeloma is made or suggested by the renal biopsy. In general these patients have more advanced

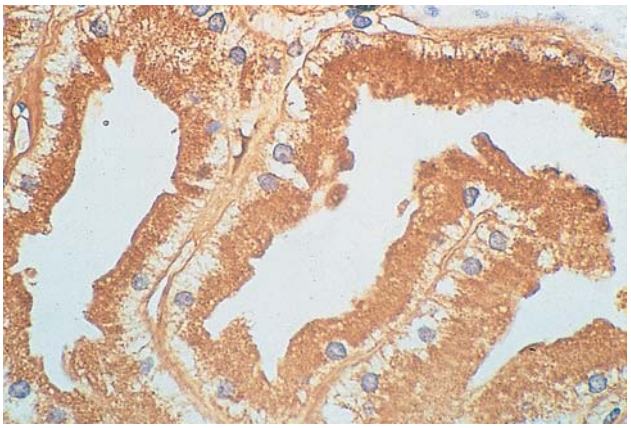

Figure 65-1 Uptake of light chains by proximal tubular cells. Renal biopsy from a patient excreting κ light chains. Immunoperoxidase staining showing κ light chains along the brush border and in the cytoplasm of PTC (brown stain).

Renal Injury Caused by Light Chains

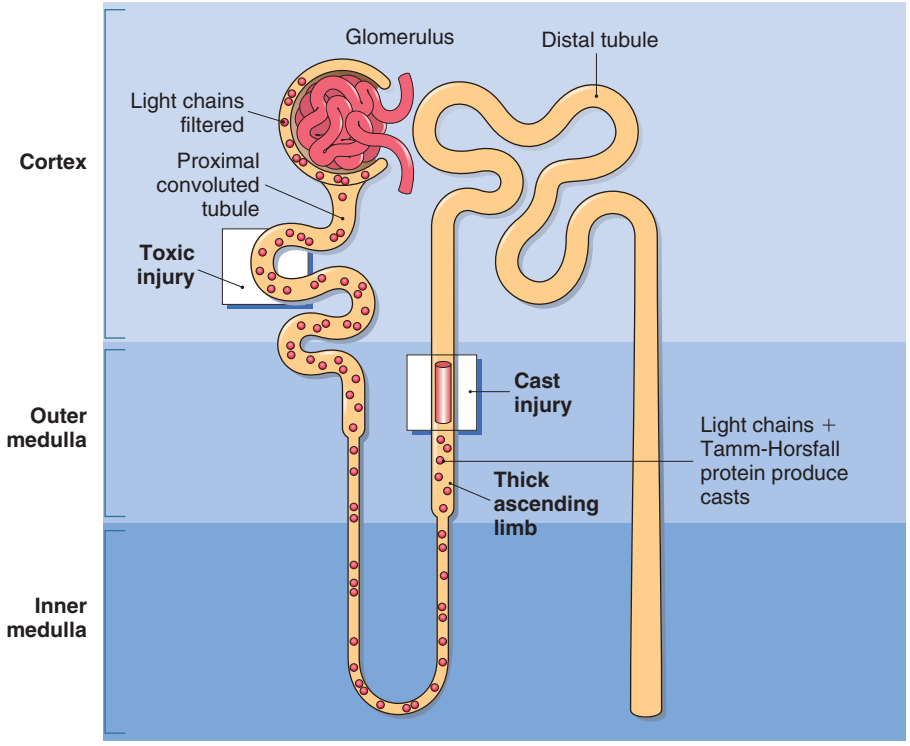

Figure 65-2 Renal injury caused by light chains. Sites *(shaded boxes)* where light chains injure the tubule. In the proximal tubule there is direct tubular cytotoxicity. In the distal tubule there is cast injury.

Differentiating Features of Myeloma Kidney and Other Monoclonal Immune Deposition Diseases (MIDDs)		
	Myeloma Kidney	**Other MIDDs**
Proteinuria	<3 g/l	>3 g/l
Hematuria	Rare	LCDD, occasional Amyloidosis, rare
Hypercalcemia	Common	Absent
Hypertension	Uncommon	LCDD, common Amyloidosis, uncommon
Cytopenias	Anemia very common Leukopenia and thrombocytopenia, occasional	Uncommon
Immunoparesis*	Very common	Uncommon
Lytic bone lesions	Very common	Absent
Renal impairment	Common	Common
Associated whole immunoglobulin	IgA, IgD, IgG	None
Type of light chain	Either	Amyloid λ > κ LCDD κ > λ
Serum light chain elevation	>500 mg/l	<500 mg/l

Table 65-2 Clinical features of myeloma kidney versus MIDDs. *LCDD,* Light-chain deposition disease. *Defined as a reduction in the nonparaprotein globulin fractions.

Renal Disease in Patients with Multiple Myeloma	
Histologic Finding	**Prevalence**
Myeloma kidney (myeloma cast nephropathy)	30%-50%
Interstitial nephritis or fibrosis without cast nephropathy	20%-30%
Amyloidosis	10%
Light-chain deposition disease	5%
Acute tubular necrosis	10%
Other (uric acid nephropathy, tubular crystals, hypercalcemia, FSGS)	5%

Table 65-3 Renal disease in patients with multiple myeloma. *FSGS,* Focal segmental glomerulosclerosis. *(From references 26, 66 to 71.)*

Histologic Features of Myeloma Kidney
Many eosinophilic, often fractured casts (medullary portion of the distal nephron predominantly)
Intratubular and interstitial macrophages and giant cells in response to casts
Interstitial inflammation, fibrosis, tubular atrophy, crystalline inclusions
Minimal glomerular abnormality
Minimal or no vascular changes

Box 65-1 Histologic features of myeloma cast nephropathy.

disease with high morbidity and mortality.[14] Renal findings are nonspecific, usually including normal size kidneys and bland urine. Urinary total protein excretion may be markedly increased because of the presence of LCs (Bence Jones protein), whereas urinary dipstick or albumin quantification may be misleading because they measure albumin only. This discrepancy between albumin and total protein measurements may alert clinicians to the diagnosis of myeloma. Normal or elevated ionized calcium, a decreased serum anion gap, lytic bone lesions on x-ray examination, hypogammaglobulinemia or reductions in levels of other immunoglobulin classes (immune paresis), an abnormal serum FLC ratio, and significant cytopenias or blood film changes (plasma cells and/or leukoerythroblastic film) are suggestive of myeloma. Clinical and laboratory findings that may distinguish MCN from other monoclonal immunoglobulin deposition diseases (MIDD) are listed in Table 65-2 and discussed in Chapter 27.

PATHOLOGY

Histologic examination of the kidney in myeloma has diagnostic and prognostic utility, although it is not always required, and the risk of complications after biopsy may be increased in patients with AKI who require dialysis. Biopsy is useful for the initial evaluation of AKI and to guide treatments designed to reverse AKI. Table 65-3 lists the likely findings and prevalence of renal injury noted at histologic or autopsy sampling. MCN is the commonest histologic finding, occurring in 30% to 50% of patients (Box 65-1 and Fig. 65-3, *A*). MCN is characterized by many distal tubular casts, which are strongly eosinophilic and consist of the monoclonal LC and laminated THP, which often appear fractured after fixation. Casts promote local inflammation with giant cell formation.[15,16] In 30% of patients, cast formation may not be prominent despite extensive tubulointerstitial injury (Fig. 65-3, *B* and *C*).[17] Glomeruli are usually spared unless there is associated LC deposition disease or amyloidosis (see Chapter 27).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The International Myeloma Working Group (2003) diagnostic criteria for symptomatic myeloma require (1) the detection and quantification of a monoclonal protein by serum electrophoresis (SEP) and characterization by immunofixation electrophoresis (IFE); (2) bone marrow (clonal) plasma cells or biopsy-proven plasmacytoma; and (3) the demonstration of any end-organ damage not otherwise explained by other pathology (including hypercalcemia, renal failure, anemia, and lytic bone disease).[18] The monoclonal M protein is the key abnormality required for diagnosis, and 97% of patients have an intact Ig and/or a free LC by SEP and IFE. The quantity of the M protein is estimated from the SEP and may be used for both diagnosis and to monitor response to therapy. Urinary LC (Bence Jones protein) is determined from a concentrated sample, but despite this, LC may still be below the level of detection by IFE. The specific quantitative FLC assay (which measures only LC not bound to whole Ig) for both urine and serum is significantly more sensitive than SEP and IFE alone and is an automated assay that allows rapid diagnosis.[19-21] An abnormal monoclonal FLC clone increases the specific LC fraction and may suppress the other LC, which alters the normal ratio of FLC (0.26 to 1.65 κ:λ) to reflect the oversecretion of the abnormal LC clone (i.e., <0.26 for λ FLC clone, >1.65 for κ clone). The normal serum levels of FLC are very low (7 to 13 mg/L), but in patients with impaired renal function, accumulation of both

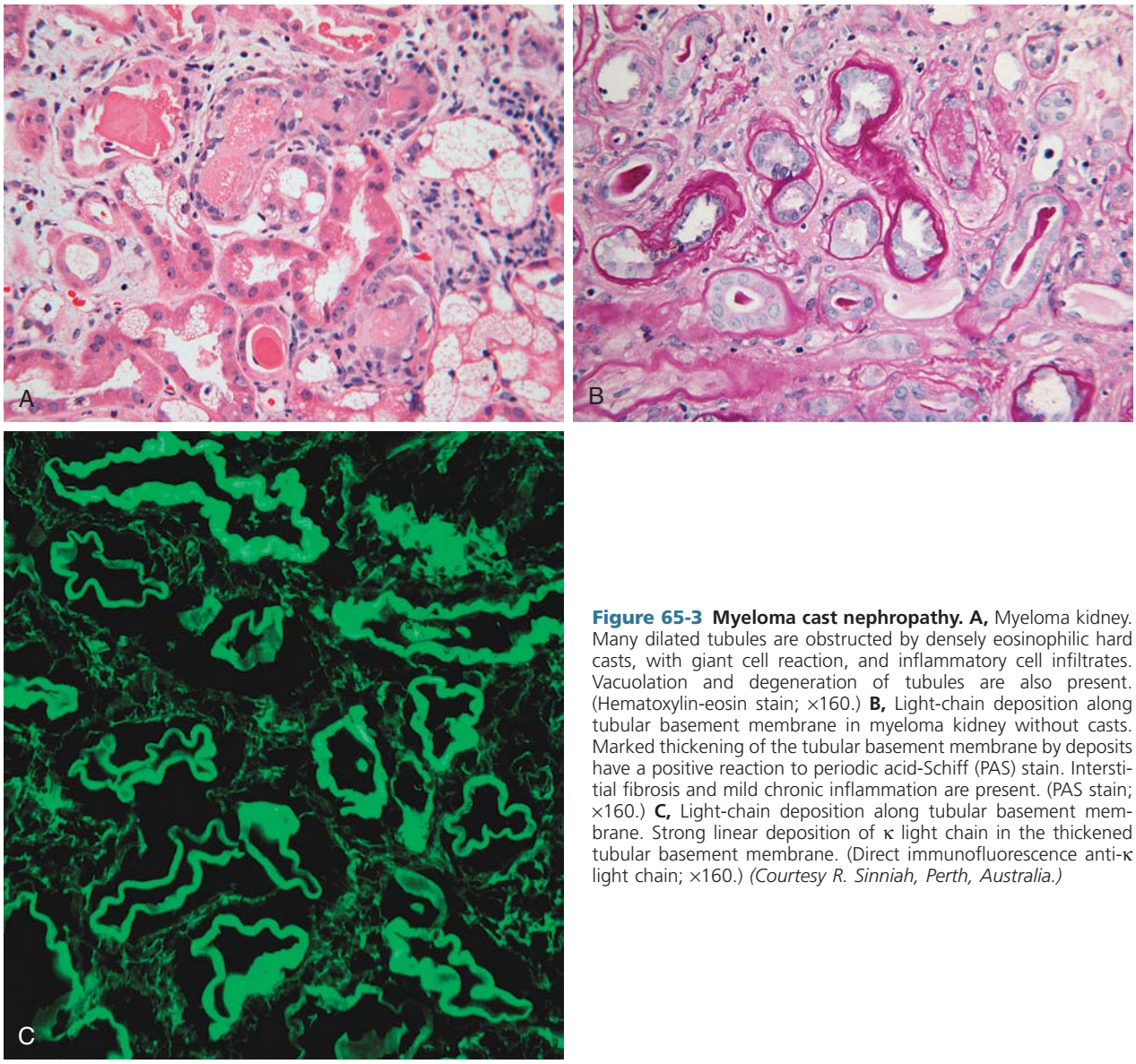

Figure 65-3 Myeloma cast nephropathy. A, Myeloma kidney. Many dilated tubules are obstructed by densely eosinophilic hard casts, with giant cell reaction, and inflammatory cell infiltrates. Vacuolation and degeneration of tubules are also present. (Hematoxylin-eosin stain; ×160.) **B,** Light-chain deposition along tubular basement membrane in myeloma kidney without casts. Marked thickening of the tubular basement membrane by deposits have a positive reaction to periodic acid-Schiff (PAS) stain. Interstitial fibrosis and mild chronic inflammation are present. (PAS stain; ×160.) **C,** Light-chain deposition along tubular basement membrane. Strong linear deposition of κ light chain in the thickened tubular basement membrane. (Direct immunofluorescence anti-κ light chain; ×160.) *(Courtesy R. Sinniah, Perth, Australia.)*

(κ and λ) FLCs occurs as a result of reduced excretion, and the ratio generally remains within the normal range. However, because λ FLCs tend to circulate as dimers, their clearance is reduced more than the monomeric κ FLCs, and this may alter the ratio. Therefore, an extended reference range of 0.37 to 3.1 is considered normal in the patient with renal failure, and use of this cutoff improves diagnostic sensitivity for myeloma to 99% with 100% specificity.[21] The absolute value of the serum monoclonal LC is of lesser importance in diagnosis, but in general, patients with renal failure without myeloma have polyclonal increases in FLC on the order of 10 to 20 times normal. In contrast, in biopsy-proven cast nephropathy the ratios are highly abnormal and the absolute increases in FLC are 100 to 200 times normal with typical values exceeding 500 mg/l (usually exceeding 1000 mg/l) at presentation (Fig. 65-4).[21] Measurement of serum FLC has significant advantages over SEP and IFE and is now incorporated into international clinical guidelines for the diagnosis and management of myeloma.[22]

Diagnostic difficulties can arise in elderly patients who are evaluated for newly diagnosed renal impairment and in whom routine SEP reveals an M protein. Approximately 3% of the population over 70 years of age will have a serum M protein, most consistent with MGUS. A diagnosis of MGUS is more likely if the serum level of the M protein is low (<3 g/dl), urinary LCs are absent or very low (<1 g/24 h), and the FLC ratio is normal with the absence of end-organ injury (no lytic lesions, <10% plasma cells on bone marrow aspirate).[23] This distinction is important because most patients with MGUS will die from an unrelated disease, and only 1% a year progress to myeloma.[24] The majority of renal disease in patients with MGUS is unrelated to the M protein,[25] although rare cases of focal segmental glomerulosclerosis (FSGS) have been associated with a dysproteinemia.[26] Evidence supportive of alternative causes of the renal disease (most commonly diabetes or vascular disease), along with a period of observation, may clarify the significance of the M protein, although renal and/or bone marrow biopsy may be required when diagnostic uncertainty persists.

NATURAL HISTORY

The majority of patients with renal impairment at presentation will show resolution of these predominantly functional changes with therapeutic measures that include withdrawal of nephrotoxins,

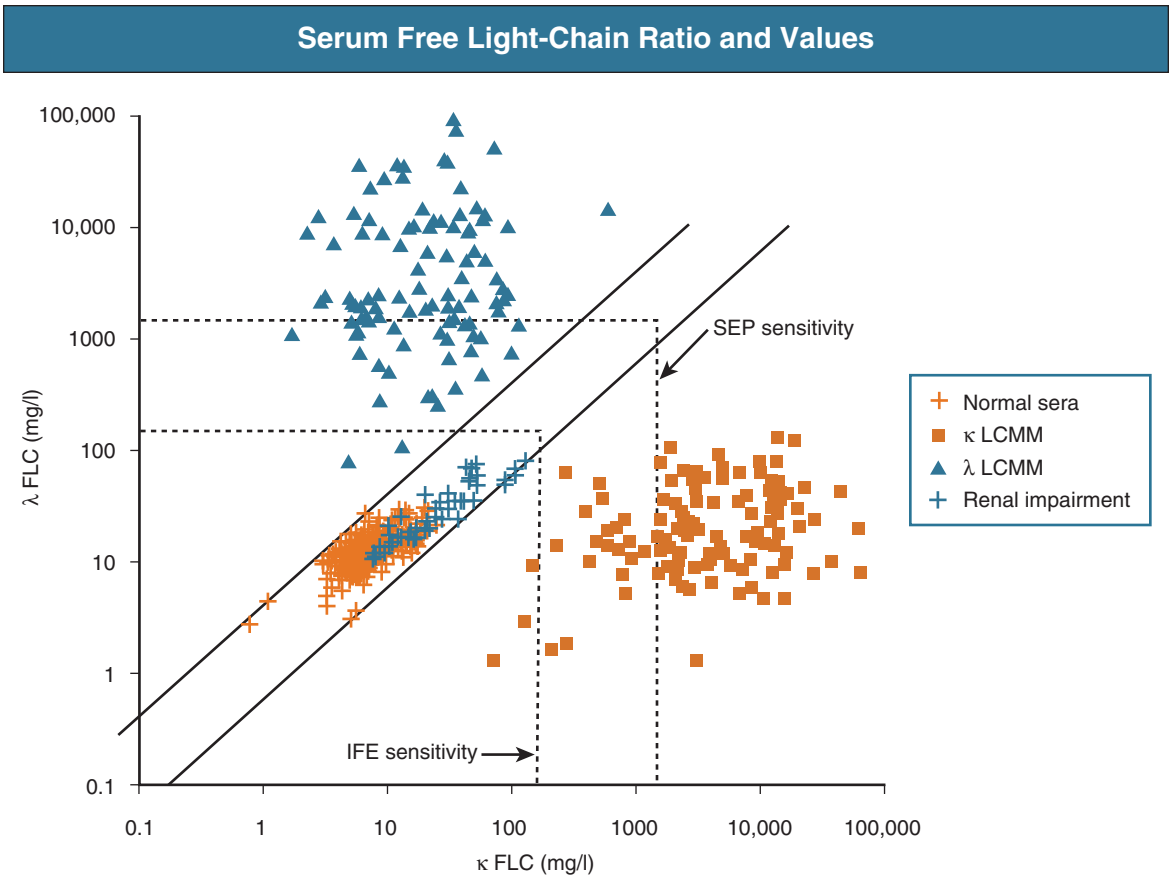

Figure 65-4 Serum free light-chain ratio and values in normal individuals, patients with renal impairment, and light-chain myeloma. *FLC,* Free light chain; *IFE,* immunofixation electrophoresis; *SEP,* serum protein electrophoresis; *LCMM,* light-chain multiple myeloma. *(Reprinted from reference 21.)*

rehydration, treatment of hypercalcemia, treatment of sepsis, and reduction in LC load with chemotherapy. Response to treatment with improvement in renal function is associated with improved clinical outcomes.[27] Reversibility occurs more frequently with lesser degrees of initial renal impairment, lower LC excretion, and hypercalcemia. Although renal function improves in the majority of patients, approximately 10% of patients with renal impairment at diagnosis may require dialysis. Patients requiring dialysis have reported rates of recovery of renal function as low as 5% to 15%, although recently these figures have increased up to 75% with the use of newer targeted LC-reduction strategies.[28-30] Sometimes this recovery occurs many months after presentation.

TREATMENT

There are three key issues in the management of MCN. The first is to suspect and diagnose myeloma in the differential diagnosis of AKI, and the inclusion of serum FLC measurement for routine evaluation of otherwise unexplained AKI in appropriate clinical circumstances is essential. This is because renal injury in myeloma is directly related to FLC excess, and the increased sensitivity and specificity of FLC measurement along with its rapid availability may implicate or refute myeloma as a likely diagnostic possibility days in advance of standard tests (SPE or IFE) or renal biopsy. Early diagnosis is crucial to allow implementation of the second strategy, which is to prevent or reverse oliguria by rapid identification and management of possible contributing factors to renal impairment, which are present in approximately 50% of patients. Hypercalcemia, sepsis, and nonsteroidal anti-inflammatory agents (NSAIDs) are the most common precipitants. Intravenous volume expansion is helpful to increase glomerular filtration, reduce single-nephron LC concentration, and increase tubular flow. The use of furosemide to promote diuresis should be minimized because it may favor cast formation by increasing distal urinary sodium concentration and urinary acidification. There is no clinical evidence of the superiority of volume expansion with sodium bicarbonate over sodium chloride, although prevention of urinary acidification is in theory desirable and in severe renal failure may be necessary for management of metabolic acidosis. The maintenance of a high fluid intake (3 l/day) with water after initial volume correction and restoration of urine output with intravenous crystalloid is recommended to maintain high urine flow rates. Hydration before the use of contrast agents for radiologic or other procedures is essential.[31,32]

The third key requirement is the rapid reduction of FLC in the serum by chemotherapy and, in patients with proven cast nephropathy, by enhanced dialysis (see later) or in some patients plasma exchange. The immediate commencement of high-dose dexamethasone 40 mg daily is recommended, because plasma cells are highly responsive to corticosteroids, which induce rapid apoptosis and lowering of LC concentration. The addition of newer chemotherapy strategies (see later) with high immediate LC-lowering effects in combination with corticosteroids is also critical to rapid response.[33-35] The routine addition of plasma exchange to conventional treatment did not improve either recovery from renal failure or patient survival.[36] The large volume of distribution of LCs (which freely cross cell membranes) is not well suited to plasma exchange; however, in some circumstances its use as an adjunct to chemotherapy may be

considered beneficial.[37] The use of a Polyflux dialysis membrane (HCO 1100, Gambro) with a high cutoff of molecular weight up to 50 kD, in conjunction with early chemotherapy, has been shown to reverse renal failure in association with the rapid reduction in circulating FLCs in patients with cast nephropathy.[29,38,39] The optimal use of this membrane is under clinical trial and may differ according to the type of LCs, response to chemotherapy, use of convective therapies, and extended duration of dialysis.[40] A suggested algorithm for management of multiple myeloma with AKI is shown in Figure 65-5.

Chemotherapy

Although myeloma is usually incurable, chemotherapy will induce clinical improvement and extended survival by control of the underlying disease in the majority of patients. The chemotherapy of myeloma is undergoing rapid evolution and has moved on from traditional chemotherapy with melphalan and prednisolone. The use of melphalan in patients with renal impairment (glomerular filtration rate [GFR] <30 ml/min) requires dose adjustment to avoid the risk of significant hematologic toxicity.[41] Bortezomib, a reversible proteasome inhibitor whose clearance is independent of renal function, has been successfully and safely used in patients with severe degrees of renal failure and myeloma without significant toxicity, and is recommended as the agent of choice for rapid reduction of LC in combination with dexamethasone and high-cutoff hemodialysis.[33,42,43] Bortezomib not only lowers the LC load by direct effects on plasma cells but may also protect renal proximal tubular cells by inhibiting activation of IL-6 and NF-κB induced by LC endocytosis.[44] Thalidomide and lenalidomide are increasingly used first-line treatment or as consolidation or maintenance therapy in conjunction

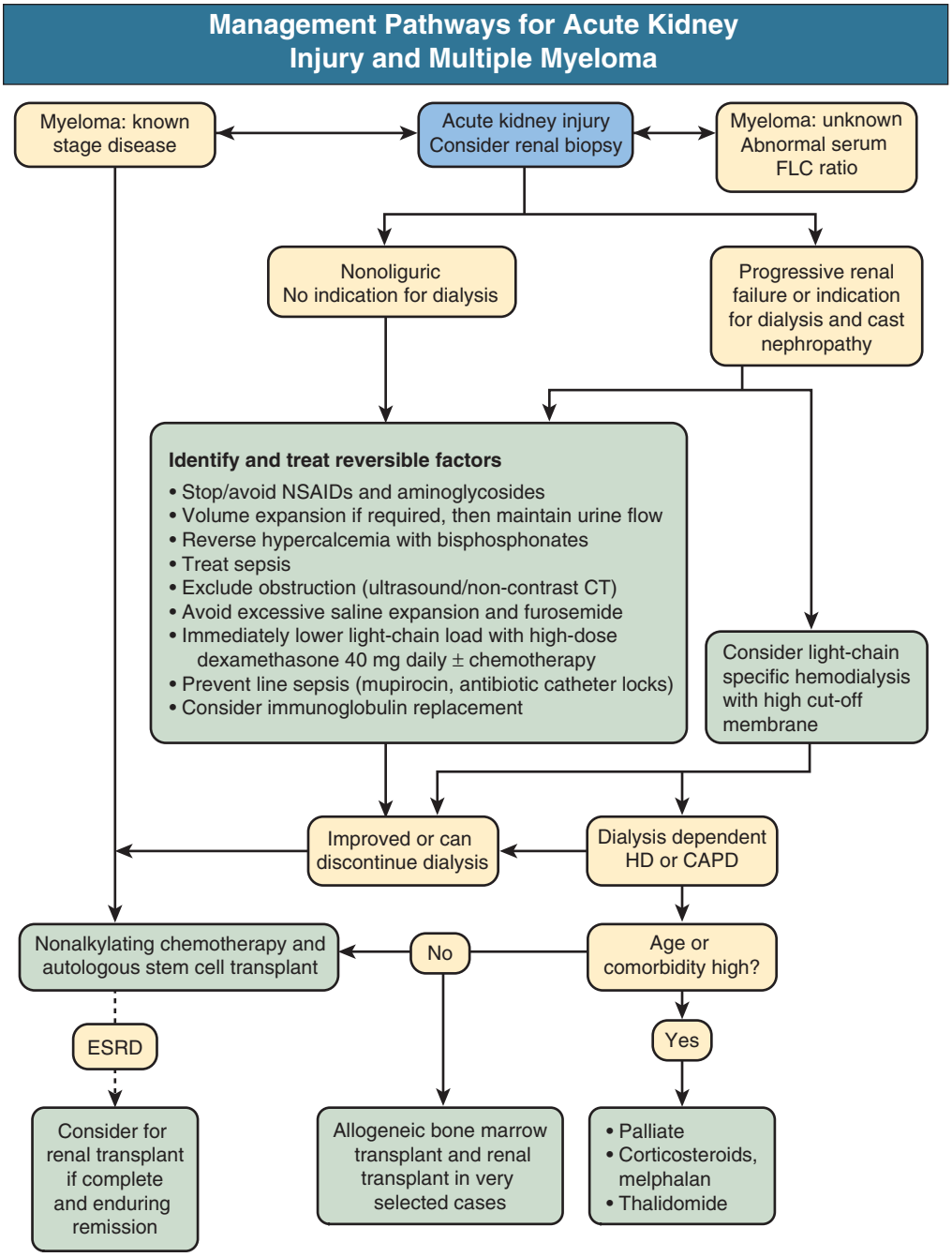

Figure 65-5 Management of multiple myeloma and acute kidney injury. *CAPD,* Continuous ambulatory peritoneal dialysis; *CT,* computed tomography; *ESRD,* end-stage renal disease; *FLC,* free light chain; *HD,* hemodialysis; *NSAIDs,* nonsteroidal anti-inflammatory drugs.

with dexamethasone. Side effects of thalidomide include peripheral neuropathy, venous thrombosis, and teratogenicity; and although thalidomide has minimal renal excretion or removal by hemodialysis, some dose reduction may be prudent.[45,46] Lenalidomide may have reduced neurotoxicity; however, its use in patients with renal failure requires dose reduction, and myelosuppression may be more common in patients with reduced GFR.[47,48] Autologous stem cell transplantation (ASCT) significantly extends survival and is now the treatment of choice for eligible patients, usually those younger than 60 years with low comorbidity and chemotherapy-responsive disease.[49] Even patients with renal impairment and on dialysis may be suitable candidates for ASCT, although increased morbidity and mortality are recognized.[50,51] For the very elderly, chemotherapy selection is dependent on comorbidity, and melphalan-prednisolone or dexamethasone-thalidomide may be useful. Close multidisciplinary management and discussion with hematologists and oncologists is required to individualize decision making because of the continuous advances in this area.[52]

Infection and progression of disease remain the major impediments to survival, especially within the higher-risk ESRD group. Median survival in recent ESRD series with conventional therapies before ASCT was only 4 to 8 months; however, survival of up to 7 years has been reported in selected cases of ESRD managed with ASCT.[43,53]

Adjunctive Therapies

Patients with CKD or ESRD and multiple myeloma respond to erythropoiesis-stimulating agents, and these should be used along with other hematopoietic agents including granulocyte colony-stimulating factor (G-CSF) as required, although early in the disease frequent transfusion may be necessary.[54] Intravenous bisphosphonates rapidly correct hypercalcemia and are preferred to furosemide (which may aggravate tubular LC injury). In the longer term, bisphosphonates may reduce bone fracture.[55] However, there have been several reports of toxicity (acute tubular necrosis, proteinuria) with high doses and/or rapid infusion of pamidronate and zoledronic acid; reduced doses (pamidronate, 30 to 60 mg; zoledronic acid, 4 mg) and slower infusion rates are recommended.[56,57] Replacement of profound immunoglobulin deficiency with regular intravenous immunoglobulin (IVIG) has been proven to reduce infectious complications in stable treated myeloma patients but is not widely adopted (although recommended).[58] Caution is required to avoid further AKI resulting from the hyperosmolarity of some IVIG preparations, because renal impairment and diabetes represent known risk factors for this complication.[59]

Dialysis and Transplantation

When renal replacement therapy is required long term, both hemodialysis and peritoneal dialysis have been successfully used, and there are no data to indicate that outcome is influenced by dialysis modality. Choice of long-term therapy requires individual assessment of patient circumstances. The majority of studies support the use of dialysis, although survival is substantially reduced and early mortality (30%) is high in this group because of the severity of tumor burden and the high rates of sepsis.[60-62] Aggressive measures to reduce risk of systemic infection via antibiotic line locking and/or mupirocin at exit sites, and the use of IVIG replacement, should be routinely considered because there is often initial dependency on central venous catheters for dialysis, plasma exchange, and chemotherapy. The timing of placement of a permanent arteriovenous fistula (AVF) requires an individualized risk assessment because it may be several months before irreversibility of renal failure and a response to chemotherapy are proven. Renal transplantation has a high risk of disease recurrence in the allograft and patient mortality and, given the incurability of the disease, has rarely been appropriate.[63] Allogeneic bone marrow and renal allograft transplant have been reported, demonstrating the ability to induce allograft tolerance in haploidentical pairs.[64] This treatment is limited in availability and suitability for the majority of patients. The role of renal transplant after successful induction therapy and ASCT is unknown, but it may be suitable for younger patients when disease remission by standard criteria and normalization of the serum FLC ratio has been achieved. ASCT itself has been associated with recovery of renal function when the duration of dialysis is less than 6 months.[53,65]

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CHAPTER 66

Thromboembolic Renovascular Disease

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Renal arterial and venous thromboembolic disease presents as a wide variety of clinical syndromes, ranging from vascular catastrophe with acute renal infarction to progressive decline in renal function as a result of chronic renal ischemia. Appropriate imaging allows accurate and timely identification of renal infarction, renal artery or venous thrombosis, and other renovascular abnormalities.

Thrombotic microangiopathies are discussed in Chapter 29, and renovascular hypertension and atherosclerotic ischemic renal disease are discussed in Chapter 39.

NORMAL ANATOMY

Renal Artery

The anatomic considerations that affect the clinical presentations and outcome of renal arterial thromboembolic events include the size of the vessel involved, from the main renal artery and the branch vessels to the arterioles and glomerular capillaries, and the condition of the collateral blood supply. In most individuals, the kidney has a single artery with a diameter of 3 to 7 mm. The main renal artery branches in either a double or a triple fork pattern or, less commonly, a ladder pattern.[1] The incidence of multiple renal arteries is about 30% with bilateral supernumerary arteries in 10%. The right renal artery usually passes posterior to the inferior vena cava (IVC), but rarely can be precaval.

The main collateral vessels to the kidney include the suprarenal, the lumbar, and the ureteral vessel complexes, which can maintain renal parenchymal viability in the face of main renal arterial occlusion. The collateral circulation to the kidney is depicted in Figure 66-1. In a study examining 301 aortograms, the adrenal arteries supplied collateral circulation to the kidney in 60% of cases, the lumbar in 55%, the ureteric in 15%, and the gonadal in 13%.[2] The factors determining the development and caliber of these vessels are poorly understood but include individual anatomy, state of the aorta, rate of progression of main renal artery narrowing, and condition of the intrarenal perforating arteries.

Renal Vein

Renal veins begin in the subcapsular region of the kidney. These stellate veins communicate with perirenal and cortical venous channels and empty into interlobular veins that drain into arcuate veins. The venae rectae drain the pyramids and join the arcuate veins. Arcuate veins leave the renal parenchyma through interlobar vessels, converging into four to six trunks near the hilum of the kidney (Fig. 66-2). Two or more renal veins have been described in up to 20% of people; this is more common on the right.[3] The main renal veins empty into the IVC; the left renal vein is three times longer than the right (7.5 cm vs. 2.5 cm). The left renal vein traverses behind the splenic vein and body of the pancreas before it crosses in front of the aorta near its termination in the IVC. Anatomic variation exists such that up to 2.3% of people have retroaortic renal veins and under 1% have circumaortic veins with branches extending both behind and in front of the aorta.[4] The left renal vein collects the flow from the left ureteral, gonadal, adrenal, and inferior phrenic veins. In Gerota's fascia, the perirenal venous network communicates with the retroperitoneal collateral veins from the lumbar, azygos, and tributaries of the portal system.[5,6]

THROMBOEMBOLIC RENOVASCULAR DISEASE

Thromboembolic renovascular disease results in disruption of normal renal blood flow, which may lead to either renal ischemia or overt infarction. The caliber and type of vessels involved (artery, arteriole, vein) as well as whether one or both kidneys are affected determine the clinical presentation (Box 66-1).

THROMBOEMBOLIC ISCHEMIC RENAL DISEASE

Ischemic renal disease caused by atherosclerotic renovascular disease (ASRVD) is discussed in Chapter 39. On occasion, thrombosis of the renal artery or branch vessels occurs acutely and without overt renal infarction, providing a clinical opportunity for renal salvage. The clinical settings in which this might occur include spontaneous thrombosis of atherosclerotic renal artery occlusive disease, spontaneous dissection of the aorta involving the origin of the renal artery, dissection of the renal artery itself, and as a consequence of aortic or renal artery interventions including endovascular stenting.

The clinical presentation of renal artery or branch vessel thrombosis without infarction often involves acceleration of hypertension because of renin release, worsening renal function, and even anuria if the entire functioning renal mass is involved. Patients may develop volume overload, pulmonary edema, and symptoms of uremia.

The clinical evaluation of the patient includes ruling out overt renal infarction and defining renal parenchymal viability despite main renal or branch vessel thrombosis. This can be achieved by demonstrating a nephrogram on delayed venous-phase imaging by conventional renal arteriography, computed tomographic angiography (CTA) or contrast-enhanced computed tomography (CT), magnetic resonance angiography (MRA) with gadolinium enhancement, or nuclear isotope scintigraphy. The diagnostic approach is complicated in the setting of reduced renal function because of the concern of nephrotoxicity from radiocontrast dye. In addition, the use of gadolinium with MRA is contraindicated if glomerular filtration rate (GFR) is below 30 ml/min because of the risk of nephrogenic systemic fibrosis.

Treatment involves assessment of the risks versus potential benefits of heroic revascularization procedures. The status of the contralateral kidney and overall residual renal function (RRF) should be weighed against the potential retrievable renal function from the

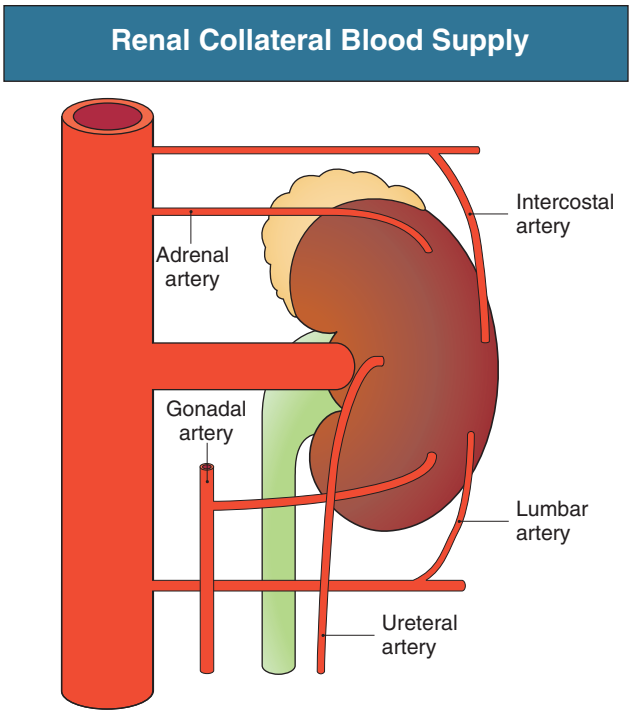

Figure 66-1 Renal collateral circulation. Diagrammatic representation of the potential collateral arterial vessels to the kidney.

underperfused kidney. The size and baseline function of the kidney before the thromboembolic event influence the potential benefits of renal revascularization. The cardiac and anesthesia risk from the intervention, such as surgical thrombectomy or bypass, has to be considered. Last, the intervention should be delayed until the clinical and renal status of the patient has recovered from any transient insults, such as acute kidney injury (AKI), decompensated congestive heart failure (CHF), myocardial infarction, and uncontrolled hypertension.

Renal artery revascularization can be achieved by endovascular thrombolysis, angioplasty, and stenting or by surgical approaches. This can be successful in restoring renal function even in patients with dialysis-dependent renal failure caused by occlusive renovascular disease.[7-9] Predictors of renal recovery are listed in Box 66-2 and include preserved renal size, evidence of a renal "blush" or nephrogram by imaging, recent decline in GFR, and recent baseline creatinine concentration below 3 mg/dl.[10] Figure 66-3 shows thrombosis of a renal artery within a stent placed 1.5 years previously for atherosclerotic renal artery stenosis in a patient with a single functioning kidney. The patient presented with anuric AKI. Percutaneous thrombolytic therapy and renal artery angioplasty restored renal perfusion and renal function.

RENAL INFARCTION

When abrupt interruption of renal blood flow occurs without adequate collateral blood supply, renal infarction may occur. Autopsy series suggest the incidence is between 0.5% and 1.5%. Renal infarction may involve the entire kidney or small areas of the cortex or medulla. Both arterial and venous thrombosis and renal artery embolism can cause renal infarction. The most common presenting symptoms of renal infarction include loin, flank, or abdominal pain with nausea and/or vomiting. Urinalysis often demonstrates microscopic hematuria and proteinuria. Transient or accelerated

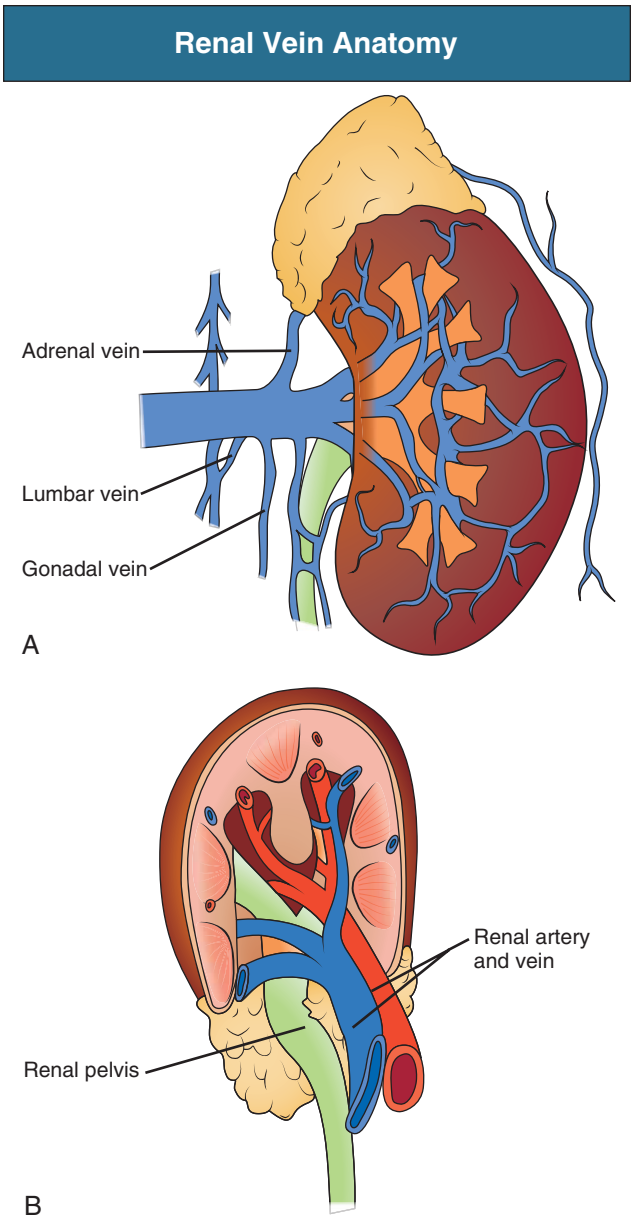

Figure 66-2 Renal vein anatomy. A, There is extensive communication between the renal venous plexus and lumbar, gonadal, and adrenal veins, which provide alternative outflow in the setting of renal vein thrombosis, particularly on the left. **B,** Transverse section of the kidney showing relative position of vascular structures in the renal pelvis. *(Redrawn from reference 11.)*

Clinical Syndromes Associated with Renal Thromboembolic Disease

- Renovascular hypertension (see also Chapter 39)
- Ischemic renal disease (see also Chapter 39)
- Renal infarction
- Atheroembolic renovascular disease
- Renal vein thrombosis
- Transplant renovascular stenosis and thrombosis

Box 66-1 Clinical syndromes associated with renal thromboembolic disease.

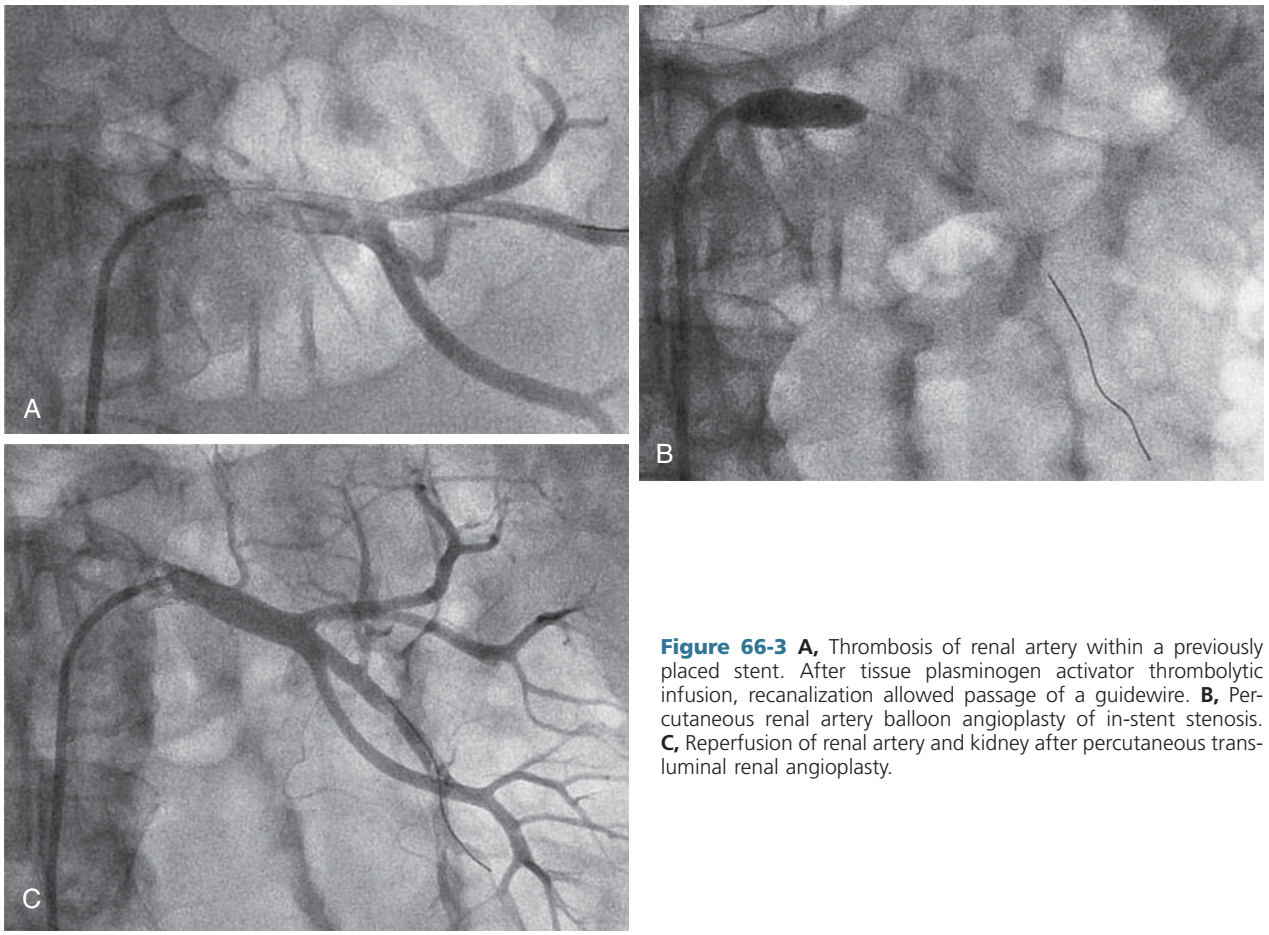

Figure 66-3 **A,** Thrombosis of renal artery within a previously placed stent. After tissue plasminogen activator thrombolytic infusion, recanalization allowed passage of a guidewire. **B,** Percutaneous renal artery balloon angioplasty of in-stent stenosis. **C,** Reperfusion of renal artery and kidney after percutaneous transluminal renal angioplasty.

Predictors of Recovery of Renal Function in Renal Artery Occlusion
Preserved renal size (>7-8 cm)
Recent baseline serum creatinine <3 mg/dl (284 μmol/l)
Recent rapid decline in glomerular filtration rate
Nephrogram visible on delayed or venous phase imaging
Distal reconstitution of occluded renal artery

Box 66-2 **Predictors of recovery of renal function in renal artery occlusion.**

hypertension may occur secondary to abrupt release of renin from the infarcted segment. Up to one quarter of cases are asymptomatic, identified only by enhancement or functional defects on renal imaging. Transient elevations in serum creatinine are not uncommon. When bilateral occlusion of both kidney arteries or infarction of a single functioning kidney occurs, the patient presents with oliguric or anuric AKI. Systemic signs of renal infarction include leukocytosis and fever. Tissue injury results in elevations of serum enzymes, most commonly lactate dehydrogenase, but transaminases, creatine kinase, and alkaline phosphatase may also be elevated.[12,13]

Diagnosis

Because the presenting symptoms are common to a number of disorders, a high clinical suspicion is required for the diagnosis of renal infarction. CT with intravenous contrast administration is the imaging modality of choice for demonstrating areas of the renal cortex that are not perfused. CT may demonstrate focal wedge-shaped areas of decreased attenuation or global infarction with or without a rim sign indicating intact collateral circulation to the renal cortex.[14] Perinephric stranding may be present as well. It is not uncommon to see simultaneous infarcts in the spleen or liver. Other potential imaging techniques include MRA with gadolinium (if GFR remains above 30 ml/min) or as time-of-flight or phase-contrast imaging, or nuclear scintigraphy with dimercaptosuccinic acid (DMSA) (Fig. 66-4). When the entire kidney is underperfused, it is often difficult to determine whether there may be salvageable renal parenchyma. Studies in experimental animals with acute renal artery occlusion have shown that the collateral circulation can maintain renal viability for up to 3 hours after occlusion.[15] In patients with underlying ASRVD, collateral vessels may be better developed and renal viability may be maintained for days to weeks. In these patients, urgent arteriography to identify the location of the arterial thrombosis or embolus may allow percutaneous or surgical revascularization.

Etiology

The most common causes of renal infarction are trauma, renal artery embolism from cardiac thrombus, and iatrogenic complications of endovascular procedures (Box 66-3). Spontaneous renal artery thrombosis or dissection is most often associated with atherosclerotic disease of the aortic or renal arteries, but other vascular causes include fibromuscular dysplasia, Takayasu arteritis, polyarteritis nodosa, Marfan syndrome, and Ehlers-Danlos syndrome with

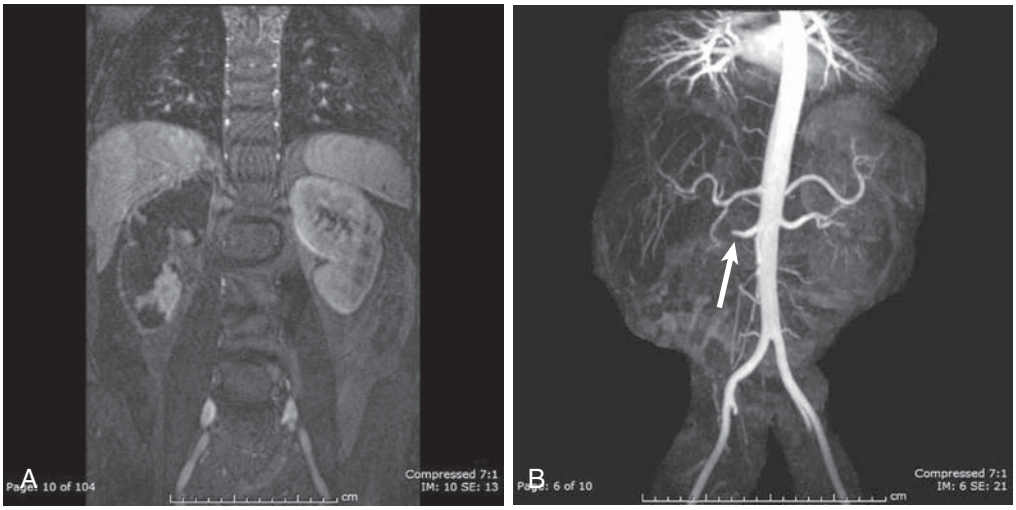

Figure 66-4 Renal infarction demonstrated by gadolinium-enhanced magnetic resonance imaging and magnetic resonance angiography (MRA) of the kidneys and renal arteries. A, Near-total infarction of the right kidney with sparing of some of the lower pole and prominent rim sign. **B,** MRA demonstrating abrupt cutoff of the right renal artery at the midvessel from either thrombosis or embolism *(arrow)*.

Causes of Renal Infarction

Renal Artery Thrombosis
Spontaneous
Renal artery atherosclerosis or fibromuscular dysplasia
Renal artery or aortic dissection
Renal or aortic aneurysms
Traumatic
Postprocedure
Endovascular stents
Renal transplantation
Hypercoagulable disorders
Malignancy
Antiphospholipid syndrome
Renal artery vasculitis
Vascular rejection
Thrombotic microangiopathies
Renal Vein Thrombosis
Nephrotic syndrome
Renal Embolism
Atrial fibrillation
Cardiac mural thrombi
Valvular heart disease
Paradoxical embolism
Tumor or fat embolism
Atheroemboli

Box 66-3 Causes of renal infarction. Bold refers to common causes.

associated dissection or aneurysms. Less common causes of infarction include hypercoagulable states, most commonly nephrotic and antiphospholipid antibody syndromes; inflammatory diseases of the retroperitoneum or aortorenal vasculature; and thrombotic microangiopathies (TMAs).

Thrombosis Caused by Trauma

Traumatic injuries to the renal arteries make up 1% to 4% of all nonpenetrating abdominal trauma. Classically, kidney trauma results from a deceleration injury, such as a fall from a great height with an upright landing on impact. This results in stretching of the renal arteries as the kidneys continue downward after the rest of the body has stopped. The subsequent stretching and recoiling of the renal arteries can result in acute thrombosis, which is typically bilateral. Direct blunt trauma to the loin or flank regions associated with motor vehicle accidents, street fights, and sports injuries can also result in renal artery thrombosis.

Evidence of lumbar vertebral injury should raise suspicion in the emergency department for renovascular trauma. Even when this injury is diagnosed early, the success rate for renal revascularization after trauma to the renal vessels remains low, between 0% and 29%.[16] The recently revised renal injury scale classification defines a class V renal injury as either main renal artery or vein laceration, avulsion, or thrombosis. In a series of 3580 traumatic renal injuries from a single institution, class V injuries had a renal salvage rate of only 4.3% and a high nephrectomy rate of 74%.[17]

Injuries to the renal pedicle that result in diminished perfusion to a single functioning kidney or to both kidneys require rapid intervention, and endovascular stabilization of renal blood flow may be helpful as a bridge to more definitive renal revascularization.

Thrombosis Caused by Hypercoagulable Disorders

Clotting disorders, such as protein C or protein S deficiency, antithrombin III deficiency, elevations in factor VIII, and rarely factor V Leiden mutations, can predispose to renal arterial thrombosis and infarction in addition to their association with renal vein thrombosis (RVT). Hypovolemia, polycythemia, and the use of oral contraceptive agents can increase the risk of thrombosis when these underlying disorders are present.

Antiphospholipid antibody syndrome is associated with both arterial and venous thrombotic events and can involve the renal circulation at any level. In patients younger than 50 years, the antiphospholipid syndrome can account for 15% to 20% of all deep venous thromboses and 30% of strokes. It is the most common cause of spontaneous arterial thrombosis. In one report of 16 cases of renal involvement with this syndrome, 15 of 16 patients had either arterial or venous thrombosis, 10 had intrarenal microangiopathy, one had suprarenal aortic occlusion, and one had main renal artery thrombosis.[18] Concomitant thromboses in the mesenteric and cerebral circulation have been reported.[19,20]

Renal Artery Embolism

The kidneys are frequently the target for emboli from thrombi originating in the heart. In one series, 1.4% of the general population had renal artery embolism at autopsy, of which only 2 of 205 cases (1%)

were diagnosed clinically.[21] The prevalences of left and right renal emboli are equal, and 12% of cases are bilateral.[22] Atrial fibrillation, cardiac thrombus after myocardial infarction, atrial myxoma or other cardiac tumors, endocarditis, paradoxical emboli, and aortic thrombus represent most of the conditions associated with renal embolism. Atrial fibrillation is the most common cause, with a rate of embolism four times higher than that of the general population; the highest risk is during the first year after the diagnosis of atrial fibrillation, when anticoagulation is subtherapeutic. When echocardiography is undertaken, cardiac thrombus is only rarely detected. Other causes of renal emboli include fiber or foam related to cardiac bypass procedures, calcium from valve annuli, and even "bullet emboli" in the setting of trauma. Aortic endovascular stenting has been associated with a 10% incidence of new renal infarcts, presumably of embolic origin.[23]

Paradoxical renal artery embolism may occur in patients with right-to-left cardiac shunts. The most common cardiac shunt is a result of atrial septal defects which are present in 9 to 35 cases per 10,000 of the population. The diagnosis of paradoxical embolism requires clinical, angiographic, or pathologic evidence of systemic embolism and the presence of venous thrombus along with an abnormal communication between the right and left circulations and a favorable pressure gradient (typically diagnosed by "bubble" echocardiography) for the passage of clot from the right to the left side of the heart.

The clinical presentations of renal artery embolism mirror those of renal infarction (Table 66-1).[22] Pain is present in more than 90% of cases confirmed by radiologic imaging techniques. It is unclear from the literature how many go undiagnosed because of lack of clinical symptoms. There is a 30-day mortality rate of 10% to 13% among patients experiencing renal embolism in the setting of atrial fibrillation.[24] Up to 40% of cases have at least transient reduction in renal function.

Although angiography is the gold standard for diagnosis of renal artery embolism, nuclear isotope scanning is also very sensitive (97%). Contrast-enhanced CT detects 80% of renal embolic events.[22] In other reports, CT or CTA has a sensitivity nearly matching that of renal angiography.

Clinical Presentation of Renal Embolism

Renal Embolism or Infarction	Atheroembolic Renal Disease
Clinical Signs and Symptoms	
Flank or loin pain (91%) Fever (49%) Nausea or vomiting (40%) Oliguria (16%) Transient hypertension (common)	Flank, abdominal, back pain (rare) Fever (common) Malaise, failure to thrive (common) Nonoliguria (common) Labile hypertension (common) Skin manifestations 60% Livedo reticularis Blue toes
Laboratory Abnormalities	
Elevated creatinine (53%) Elevated LDH (91%) Elevated CPK (rare) Leukocytosis (85%) Elevated transaminases (rare) Hematuria (72%)	Elevated creatinine (100%) Elevated ESR (97%) Elevated CPK or LDH 38% to 60% Leukocytosis (57%) Elevated amylase (57%) Eosinophilia (57%) Eosinophiluria (rare) Hematuria, transient proteinuria (common) Bland sediment (common) Hypocomplementemia 25%-70%
Diagnostic Testing	
Contrast-enhanced CT or MRI Nuclear imaging, DMSA Renal angiogram Time of flight noncontrast MRA	Tissue biopsy: skin, muscle, kidney

Table 66-1 Clinical presentation of renal embolic disease. *CPK,* Creatine phosphokinase; *CT,* computed tomography; *DMSA,* dimercaptosuccinic acid; *ESR,* erythrocyte sedimentation rate; *LDH,* lactate dehydrogenase; *MRA,* magnetic resonance angiography; *MRI,* magnetic resonance imaging. *(Modified from reference 22.)*

Aortic and Renal Artery Dissection

Aortic dissection can involve the origin of either renal artery, with the false lumen occluding the vessel and impairing renal perfusion. In this setting the predictors of renal salvage are the same as those for occlusion caused by atherosclerotic renal artery stenosis and include preserved renal size, collateral circulation permitting renal viability, and blush on imaging studies. In one report, despite renal atrophy, aortic stent graft placement allowed renal reperfusion and restoration of renal size and function.[25] Aortic dissection occurs most commonly in association with atheromatous aneurysmal vascular disease of the thoracic aorta, but it can occur in collagen disorders, such as Ehlers-Danlos type IV or Marfan syndrome, and with arteritis, such as Takayasu disease. Although MRA is nearly 100% sensitive for diagnosis of aortic dissection, CTA has a sensitivity of 93% and is more readily available, has a more rapid turnaround time, is less dependent on patient factors, and is usually the imaging modality of choice.

Dissection of the renal artery can occur after percutaneous renal angioplasty or stenting, spontaneously with ASRVD or fibromuscular dysplasia of the renal artery, or as a complication of renal artery aneurysms (Fig. 66-5). The pathogenesis is thought to be caused by penetration of blood into the arterial wall via an intimal tear or bleeding from the vasa vasorum. Risk factors for dissection include older age, hypertension, connective tissue disorders, pregnancy, bicuspid aortic valve, and coarctation of the aorta. A high index of suspicion and rapid imaging are critical to improve chances of patient and renal survival. Digital subtraction angiography is the most sensitive imaging modality because the lesion often starts in the midvessel or distal vessel and can involve branch or small polar arteries less well seen on MRA or CTA.[26] The optimal treatment of renal artery dissection is unclear. Revascularization using surgical or endovascular techniques may achieve retrieval or stability of renal function and improvement in renovascular hypertension depending on the degree of damage to the kidney beyond the dissection.

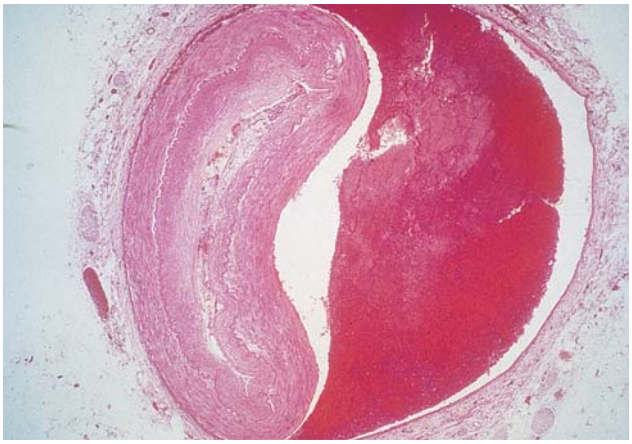

Figure 66-5 Cross section of a renal artery with dissection after renal angioplasty. Shown is the dissection with thrombus filling the false lumen. The kidney could not be salvaged.

Figure 66-6 Middle aortic syndrome. Angiogram showing typical smooth narrowing of the aorta. Bilateral stenosis of paired renal arteries is present. *(From reference 30.)*

Middle Aortic Syndrome

A rare entity, middle aortic syndrome is a diffuse narrowing of the aorta, considered a form of coarctation, causing renovascular hypertension (Fig. 66-6).[30] The cause is unknown, but associations with fibromuscular dysplasia, congenital anomalies, neurofibromatosis, Williams syndrome, and Takayasu arteritis have been reported. It can present as renal artery atresia, stenosis, or aortic thrombosis involving the renal arteries. Middle aortic syndrome usually presents as renovascular hypertension in infancy and can cause claudication of the lower extremities as well as mesenteric ischemia. Repair of middle aortic syndrome for treatment of hypertension and prevention of organ ischemia and before thrombosis is the goal. Angioplasty and stenting of stenotic segments, surgical bypass grafting, and autotransplantation of ischemic organs have been applied in the treatment of this disorder. A recently reported novel approach used tissue expanders to induce longitudinal growth of the aorta allowing for resection of the coarcted segment with end-to-end anastomosis of aortic segments of larger diameter.[27]

Thromboembolic Complication of Endovascular Interventions

Renal artery thrombosis, dissection, laceration, or embolism can occur secondary to vascular interventions, especially those involving placement of endovascular stents.[28] Occlusion of the vessel within the stent can occur many months to years after stent placement, particularly when in-stent restenosis is present. During the past decade, endovascular aortic stents have been used to treat infrarenal abdominal aortic aneurysms. When the stent crosses the orifice of the renal artery, renal perfusion is impaired, and there is a significant risk for renal artery thrombosis.[29] Renal artery stent placement may cause intimal dissection and thrombosis of the renal artery and even aortic dissection. Stent fracture or kinking can be associated with thrombosis of the lumen. Figure 66-7 demonstrates compression of a proximal renal artery stent with associated thrombotic occlusion of the vessel. Careful studies using filters to capture embolic material confirm that renal artery angioplasty with stenting of atherosclerotic renal arteries releases thousands of particles of various sizes in 70% to 100% of cases.[31] Preprocedure treatment with antiplatelet agents and intraprocedural use of embolic protection devices during renal stent implantation are under investigation as means of reducing the frequency of this underdiagnosed cause of renal infarction and chronic kidney disease (CKD).[32,33]

Renal Artery Aneurysms

Renal artery aneurysms are rare and associated most commonly with atheromatous, fibromuscular, and vasculitic disease (Fig. 66-8). They may be asymptomatic or cause renovascular hypertension, which is the presenting feature in 55% to 75% of cases. Thrombosis within an aneurysm can lead to distal thrombotic emboli and renal infarcts. Aneurysms with diameters of more than 1.5 cm have a higher risk of rupture. Elective repair of large renal aneurysms should be considered in women of childbearing age because of the risk of rupture during the third trimester of pregnancy and in patients with renovascular hypertension. Other complications of renal artery aneurysms include vessel dissection and arteriovenous fistula formation.

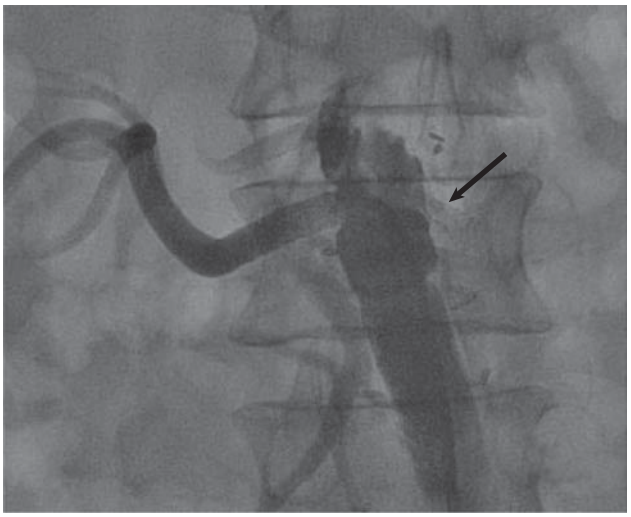

Figure 66-7 Thrombosis of renal artery complicating renal artery stenting. Right and left renal artery stents. The left renal stent *(arrow)* is triangular, indicating crimping of the proximal portion, which in this patient was associated with thrombosis of the renal artery, seen here as no contrast entering the vessel. The right renal stent is patent.

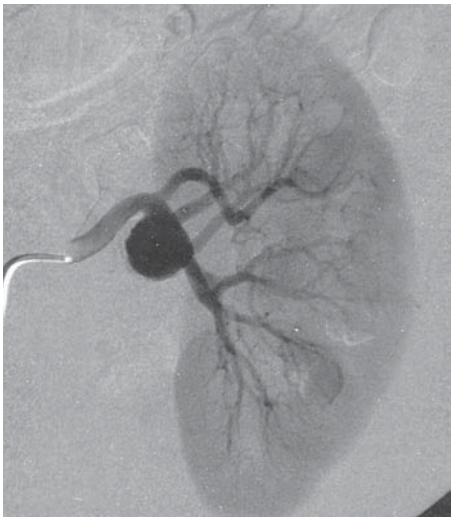

Figure 66-8 Renal artery aneurysm. Angiogram showing large renal artery aneurysm. The aneurysm is patent but is a risk factor for renal artery thrombosis.

Rare Causes of Renal Infarction

Rare causes of renal infarction include autoimmune diseases, such as Behçet syndrome, systemic lupus, and other autoimmune diseases; Henoch-Schönlein purpura (HSP); senile systemic amyloidosis; chronic Chagas disease; and drug abuse, such as intravenous injection or nasal insufflation of cocaine or even marijuana smoking. The exact mechanism involved in the pathogenesis of renal infarction in some of these conditions is unclear.

Treatment of Acute Renal Vascular Catastrophe

In the setting of renal infarction, a search for the cause of the renal vascular compromise should be undertaken to determine whether it is embolic or thrombotic. Treatment of the infarction itself is usually conservative and includes pain control and treatment of sometimes labile hypertension. If renal artery occlusion is caused by thrombosis associated with a hypercoagulable state or an embolism from a central source, systemic anticoagulation is indicated. Common sources include atrial fibrillation, atrial or mural thrombi, intracardiac mass, and valvular lesions; therefore echocardiography is indicated. Salvage of the kidney by acute thrombolytic therapy has also been attempted with limited success. There is no evidence that thrombolytic therapy can limit infarct size if it is administered in the acute setting.

Traumatic renal vascular occlusion often leads to renal infarction within 3 to 6 hours. Attempts at renal salvage under these circumstances are often unsuccessful unless the diagnosis is made immediately on presentation and immediate measures toward renal revascularization are undertaken. Renal angiography with intrarenal thrombolytic therapy and/or stenting can provide renal reperfusion in some cases even several days out from the thrombotic event.[34]

Thrombosis of atherosclerotic renal arteries, because of prior collateral development in most cases, often results in marked ischemia but not infarction of the kidney and allows consideration of optimal surgical and sometimes percutaneous endovascular revascularization to restore renal function.

ATHEROEMBOLIC RENAL DISEASE

Atheroembolic renal disease is common and may account for up to 10% of unexplained renal failure in the elderly. It most commonly occurs after arterial manipulation in arteriography, vascular surgery, angioplasty, and stent placement. In patients with extensive atherosclerosis with unstable plaques, spontaneous atheroemboli may occur, especially after the administration of oral or intravenous anticoagulants or thrombolytic agents. The incidence of atheroembolic disease after vascular interventions is unclear, but recent data suggest that it is common.[35] A study evaluated the frequency of renal perfusion defects in patients after endovascular stent repair of abdominal aortic aneurysms; 18% of the cases had identifiable renal perfusion defects, and the occurrence of these infarcts was significantly associated with atherosclerotic burden.[36] Atheroembolism may therefore be expected to occur in up to 30% of patients with extensive aortic atherosclerosis after endovascular intervention. Ipsilateral renal artery stenosis may be present in up to 80% of patients with renal cholesterol embolization. Conversely, cholesterol emboli were found in the kidneys of 36% of the patients undergoing surgical revascularization.[37] Thus, cholesterol embolization may contribute to the loss of renal function in patients with atherosclerotic ischemic renal disease.

Most patients are older than 50 years with generalized atherosclerosis and have a history of recent endovascular procedures or signs or symptoms of atherosclerotic vascular disease, such as claudication, abdominal pain, angina, myocardial infarction, transient ischemic attacks, retinal artery emboli, amaurosis fugax, stroke, abdominal aortic aneurysm, renovascular hypertension, or ischemic renal disease. Many have a history of risk factors for atherosclerosis, including hypertension, hypercholesterolemia, diabetes, and smoking.

Clinical Presentation

Acute or subacute renal impairment caused by renal microinfarctions developing as long as 6 months after the atheroembolic insult is the most common presentation leading to the diagnosis of cholesterol embolization. The clinical picture is multisystemic in nature and involves the kidneys in about 75% of patients. At autopsy, renal involvement is observed in 92% to 100%.

If a large shower of atheroemboli causes significant tubular damage, the AKI may have an oliguric phase characterized by a high fractional excretion of sodium. More often, the renal failure is nonoliguric and progressive because of ongoing embolization from a nidus of unstable ulcerative plaque. Some patients have only a moderate impairment in renal function, and others progress to end-stage renal disease (ESRD). Atheroembolic renal disease can also present as a more slowly progressive, often stair-stepping subacute renal impairment. Urinalysis findings are nonspecific but may include mild proteinuria, microhematuria, pyuria, and eosinophiluria. Renin release by ischemic zones in areas of embolization can lead to labile hypertension early in the course, sometimes associated with transient marked proteinuria. Fever, often low grade, is characteristic.

Although the kidneys are the organs most commonly involved, extrarenal cholesterol embolization will provide clues for diagnosis. Cutaneous findings in up to 60% of patients at initial presentation include blue or purple toes, mottled skin or livedo reticularis, petechiae, and purpura or necrotic ulceration in areas of skin embolization, such as the lower back, buttocks, lower abdomen, legs, feet, or digits (Fig. 66-9).

Other organs often involved include the spleen (in 55% of cases), pancreas (52%), gastrointestinal tract (31%), liver (17%), and brain (14%). This involvement can result in a number of clinical symptoms, including abdominal or muscle pain, nausea, vomiting, ileus, gastrointestinal bleeding, ischemic bowel, hepatitis, angina, and neurologic deficits. When retinal cholesterol embolization occurs, refractile yellow deposits known as Hollenhorst plaques may be seen at the bifurcation of retinal vessels on funduscopic examination (Fig. 66-10).

Figure 66-9 Livedo reticularis. The mottled skin changes associated with peripheral cholesterol embolization may be seen over the legs, buttocks, back, or flank and may be transient.

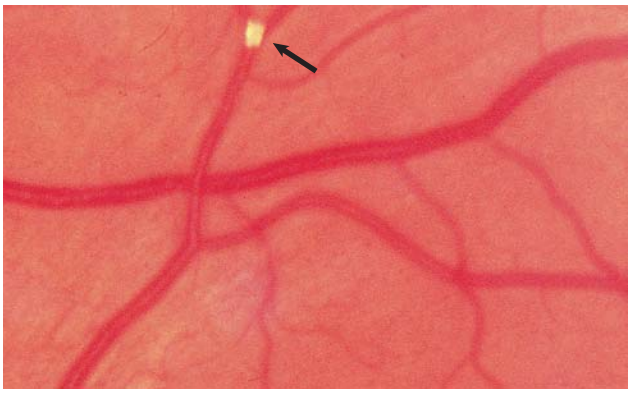

Figure 66-10 Hollenhorst bodies. Cholesterol embolus of a retinal arteriole *(arrow). (Courtesy Richard Mills, University of Washington, Seattle.)*

Diagnosis

The diagnosis of atheroembolic renal disease is suspected when subacute renal failure develops after a vascular intervention in the presence of livedo reticularis. Myriad laboratory abnormalities indicative of tissue injury are associated with cholesterol embolization, including elevated sedimentation rate (in 97% of cases), elevated serum amylase (60%), leukocytosis (57%), anemia (46%), hypocomplementemia (25% to 70%), and elevated lactate dehydrogenase and creatine kinase (38% to 60%). Eosinophilia, which may be transient, is seen in up to 57% of patients. The presence of eosinophilia should raise suspicion for atheroembolic renal disease in the appropriate clinical setting. Serum lactate is usually not elevated unless concomitant ischemic bowel is present. Definitive diagnosis is made by biopsy of an involved organ or system. A skin or muscle biopsy in an involved area may preclude the need for renal biopsy. In most circumstances, the diagnosis is made clinically.

Differential Diagnosis

Cholesterol embolization syndrome may mimic vasculitis, occult infection, neoplasm, or TMA. Contrast nephropathy with nonoliguric acute tubular necrosis (ATN) may also occur after angiography, angioplasty, or aortic vascular surgical procedures but is often more rapid as opposed to the subacute presentation of atheroemboli. Eosinophilia and eosinophiluria, rash, fever, and renal dysfunction may also be misdiagnosed as acute interstitial nephritis (AIN). Chronic cholesterol embolization syndrome may appear similar to hypertensive nephrosclerosis or ischemic renal disease. In the kidney transplant recipient, renal atheroembolism may mimic acute rejection or chronic allograft nephropathy (CAN).

Pathology and Pathophysiology

If clinical or other pathologic evidence has not secured the diagnosis, renal biopsy may be helpful. Diagnosis is based on the presence of birefringent, biconvex, elongated cholesterol crystals or biconcave clefts within the lumina of small vessels left behind in formalin-fixed tissue (Fig. 66-11). Because of the patchy nature of this disorder, open wedge renal biopsy guided by visualization of areas of ischemic infarction of the cortex has a higher likelihood of successful diagnosis than does percutaneous needle biopsy. The pathologist should be alerted by the clinician that cholesterol embolization is in the differential diagnosis before the biopsy specimen is processed. In frozen sections of tissue, the cholesterol material can be identified with polarized light microscopy. The pathologic findings may also include intimal thickening and concentric fibrosis of vessels, giant cell reaction to the cholesterol particles, vascular recanalization, endothelial proliferation, tubulointerstitial fibrosis with both eosinophil and mononuclear cell infiltrates, glomerular ischemia, and even focal segmental glomerulosclerosis (FSGS).[38] In the kidney, the most commonly affected vessels are the arcuate and interlobular arterioles, leading to patchy ischemic changes distal to these vessels.

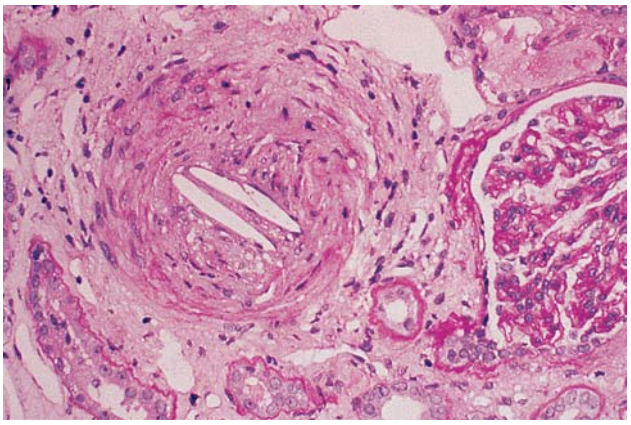

Figure 66-11 Cholesterol emboli in kidney biopsy specimen. Biconvex cholesterol clefts with giant cell reaction and recanalization of the lumen of a medium-sized renal vessel. (Periodic acid–Schiff stain.) *(Courtesy Dr. R. Horn, Vanderbilt University, Nashville, Tennessee.)*

Natural History

The natural history is determined by the extent of organ involvement and the degree of the embolization. In one series of cases, renal function declined rapidly in 29%, with a more slowly progressive course seen in 79%.[39] Among the latter group, the decline in renal function was thought to result from a combination of cholesterol embolization and ischemic renal disease. In another series, the peak serum creatinine concentration occurred within 8 weeks after an angiographic procedure.[40] Patients may also manifest acute or subacute renal impairment followed by partial recovery of renal function. Conversely, the outcome can be dismal, particularly when cerebral embolization occurs or when there is a large unstable atheromatous burden. Some patients with cholesterol embolization may develop ESRD. These patients have a mortality rate of 35% to 40% during 5 years, even when dialysis is offered.[40]

Treatment

There is no specific therapy for the cholesterol embolization syndrome. Therefore, its risk should be considered before angiographic and vascular surgical procedures are undertaken in patients with diffuse, extensive atherosclerotic disease. Because prevention is the most effective management strategy, patients with extensive aortic atherosclerosis should be considered for alternative approaches to cardiac catheterization, such as through the brachial artery. If vascular intervention is performed, signs of embolization should be sought both in the immediate postoperative period and for several months thereafter. When it is feasible, distal embolic protection devices should be used to trap embolic material for removal from the circulation to avoid end-organ damage by embolic debris.[41]

After the diagnosis of cholesterol embolization has been established, further endovascular interventions should be avoided. Poor outcomes have been reported in patients with cholesterol emboli who subsequently undergo coronary artery bypass surgery. When clinical factors dictate the need for aortic, renal, or peripheral arterial surgery, optimal timing and surgical approach are critical.

Conversely, there is a growing surgical experience with segmental aortic replacement to remove the source of emboli, particularly when atheroembolic disease occurs spontaneously. Transesophageal echocardiography is often used to identify mobile ulcerative plaque in the aorta to guide intervention.

Angiotensin-converting enzyme (ACE) inhibitors are effective in managing the labile hypertension seen early in the course of cholesterol embolization. Corticosteroids have been used with some success in patients with systemic cholesterol embolization and associated inflammatory symptoms.[42] There have also been several reports documenting improvement or stabilization of skin signs of cholesterol embolization after administration of statins,[43] which should be part of the treatment of the generalized atherosclerosis in these patients. Cholesterol embolization has also occurred after treatment with anticoagulants. Although direct causality between anticoagulants and cholesterol embolization has not been established, the proposed mechanism is that anticoagulants prevent thrombus organization over the ulcerative plaques. Therefore, anticoagulation should be avoided in the acute setting of cholesterol embolization unless a strong life-threatening indication for anticoagulation is present. This has implications for the delivery of renal replacement therapy, if indicated.

TRANSPLANT RENAL ARTERY STENOSIS AND THROMBOSIS

Epidemiology

Transplant renal artery stenosis is a common post-transplantation complication occurring most often in the period between 3 months and 2 years after transplantation. The highest reported incidence is 23% in a patient cohort screened angiographically, compared with reported incidences of 1.3% to 12% when other screening tests are used.[44] In many cases, anastomotic stenoses are not hemodynamically significant.[44] Renovascular complications, including renal artery stenosis and RVT, are more common in deceased donor than in living donor transplants and in allografts with multiple renal vessels.[45] The use of pediatric kidneys in adult recipients is associated with a higher rate of stenosis because of smaller donor vessel size, leading to greater turbulences and mismatch between donor and recipient vessels. As the transplant population ages, there has been increasing recognition of another subset of patients with pseudo–transplant renal artery stenosis, in which vascular disease proximal to the allograft artery, particularly involving the iliac vessel, results in renal ischemia.

Pathogenesis

The pathophysiologic basis for transplant renal artery stenosis is multifactorial and may include atheromatous disease in the donor artery, intimal scarring and hyperplasia in response to trauma to the vessel during harvesting, and anastomotic stenosis, which is most commonly associated with end-to-end anastomoses and may be related to suture technique. In end-to-side anastomoses, stenosis tends to develop in the postanastomotic site, suggesting that turbulence or other hemodynamic factors play a role. Immunologic causes of transplant renal artery stenosis have also been proposed on the basis of histologic similarities with chronic vascular rejection and association with prior acute rejection. Other proposed pathogenic mechanisms include calcineurin inhibitor (CNI) toxicity and cytomegalovirus (CMV) infection. Renal artery stenosis occurring many years after transplantation most often represents atherosclerotic disease in the renal artery.

Clinical Presentation

Patients typically present with new-onset hypertension or difficult-to-control blood pressure (BP) with or without graft dysfunction occurring 3 to 24 months after transplantation. Patients may also present with AKI. When the stenosis occurs in the iliac artery above the anastomosis of the transplanted renal artery (pseudo–transplant renal artery stenosis), the patient often presents with ipsilateral lower extremity claudication associated with hypertension and worsening renal function in the allograft.[46] Systolic bruits over the transplant are not diagnostic because they may represent turbulent flow in the main vessels in the absence of stenosis or biopsy-related arteriovenous fistulas. Risk factors for the development of renal artery stenosis include male gender, hyperlipidemia, and elevated serum creatinine at discharge from transplantation.

Diagnosis

Renal duplex sonography is the screening test of choice for transplant renal artery stenosis because the vessel is superficial and easy to interrogate. Peak systolic velocity of less than 180 cm/s can reliably rule out significant renal artery stenosis in the transplant vessel. The ratio of velocity in the renal and iliac vessels and the resistive index in the kidney have been shown to predict the hemodynamic response to percutaneous transluminal angioplasty. Phase-contrast MRA has an advantage over arteriography in viewing tortuous renal arteries and may provide information additional to Doppler ultrasound regarding the aorta and iliac vessels. However, with MRA, the surgical clip artifact may obscure the proximal renal artery, and it often cannot resolve peripheral renal vessels. High false-positive rates are associated with sharp anastomotic angles. CTA has the advantage over MRA from an imaging standpoint but requires a large amount of contrast material. The gold standard is selective renal angiography of the transplant and iliac artery. In situations in which the risk for contrast-induced nephrotoxicity is high, carbon dioxide angiography can be performed safely.

Treatment

Transplant renal artery stenosis causing renovascular hypertension or decline in kidney function may require intervention.[47] Angioplasty is the preferred initial approach to transplant renal artery stenosis, with initial success rates of up to 75% and patency for follow-up periods of up to 30 months. The average complication rate for angioplasty of the allograft artery is 10%. It is often unsuccessful when there is arterial kinking and is associated with a high complication rate in this setting. The reported rates of late restenosis are 10% to 33%, necessitating repeated procedures or stent placement at the site of restenosis or in the iliac artery when pseudo–transplant renal artery stenosis is caused by iliac atherosclerotic occlusive disease proximal to the takeoff of the transplant artery.[48]

Surgical revascularization is reserved for patients in whom angioplasty or stenting has been unsuccessful or complicated. Surgical renal revascularization is difficult and is associated with significant mortality in the transplantation setting. Extensive fibrosis develops around the allograft and often involves the renal vessels, making surgical access to the renal vessels risky. Complications include graft loss (in 15% to 30% of cases), ureteral injury (14%), and death (5%).

RENAL VEIN THROMBOSIS

Renal vein thrombosis is rare and primarily observed in children with severe dehydration (with an incidence in neonates of 0.26% to

0.7%) or in adults with nephrotic syndrome, renal tumors, or hypercoagulable states and after surgery or trauma to the renal vessels.[49] When it occurs in adults, the diagnosis is often never considered. Thrombosis of the longer left (7.5 cm) renal vein may also involve the ureteric, gonadal, adrenal, and phrenic branches that drain into the left vein, whereas on the right side, the adrenal and gonadal veins drain directly into the IVC. The renal veins also communicate with perirenal veins outside of the Gerota's fascia as part of the retroperitoneal collateral venous network: tributaries of the portal system, lumbar, azygos, and hemiazygos. Because of this network of venous complexes, occlusion of the left renal vein results in enlargement of the systemic collateral vessels and provides some protection against infarction.

Acute Versus Chronic Renal Vein Thrombosis

Experimentally, acute RVT is associated with immediate enlargement of the kidney with a marked increase in renal vein pressure, leading to a marked decrease in renal arterial flow. Complications include hemorrhagic infarction, kidney rupture, and retroperitoneal hemorrhage. In the dog, the kidney enlarges during the course of 1 week, then proceeds to atrophy as a result of progressive fibrosis. In contrast, slow, progressive ("chronic") thrombosis may allow collateral formation, resulting in minimal symptoms.

Clinical Presentation

Acute RVT is usually symptomatic and associated with loin, testicular, or flank pain and even the development of scrotal swelling or hydrocele; low-grade fever; and in the setting of a single kidney or renal transplant, symptoms of renal failure. Nausea and vomiting often accompany acute RVT, and symptoms might be confused with acute pyelonephritis. Leukocytosis can accompany acute thrombosis. Clinical signs include renal enlargement, which in infants manifests as a palpable abdominal mass. Hematuria is nearly universal and most often is microscopic. The high venous pressures result in a marked increase in proteinuria. Urinalysis sometimes reveals evidence of proximal tubule dysfunction, such as glycosuria. Oliguric renal failure occurs when RVT results in renal infarction of both kidneys or in patients with a single kidney. In some patients, RVT is diagnosed only after the patient has developed an acute pulmonary embolus and the source of the embolus is investigated or with worsening of renal function in the setting of proteinuric CKD.

Chronic RVT may be asymptomatic and is associated with extensive venous collaterals and minimal impairment of renal function and structure. Often, however, microhematuria, increase in proteinuria, and evidence of either reduced GFR or tubular dysfunction are present, particularly when indices of differential renal function are sought, such as with nuclear studies.

When RVT causes renal infarction, the distribution of the hypoperfused region tends to be medullary or subcortical. The renal impairment tends to be patchy and subtotal. These patients can develop severe hypertension acutely. The swollen kidney can rupture the capsule and result in massive retroperitoneal hemorrhage.

Etiology

The causes of RVT are listed in Box 66-4.

Neonatal Renal Vein Thrombosis

Renal vein thrombosis occurs in neonates in situations of dehydration and thrombophilia. The classic presentation triad includes a palpable abdominal mass, hematuria, and thrombocytopenia. Proteinuria, tubular dysfunction, reduced GFR, and hypertension may be associated. There is a greater predilection for development of RVT in male infants, with 67% of the reported cases occurring in boys.[50] Most cases are unilateral, with the left renal vein more commonly affected. Complications of neonatal RVT may include adrenal hemorrhage, renal atrophy, renal impairment, and hypertension. In neonates, the diagnosis is made by renal ultrasound and Doppler study of the renal veins. The strongest predictor of poor renal outcome is

Causes of Renal Vein Thrombosis

- **Malignancy**
  - **Direct invasion of tumor into the renal vein**
  - Retroperitoneal adenopathy, fibrosis, or tumor
  - Extension of inferior vena cava (IVC) obstruction
  - Hypercoagulable state with malignant disease
- **Nephrotic syndrome**
  - **Membranous nephropathy**
  - Lupus nephritis
- **Hypercoagulable states**
  - **Antiphospholipid antibody syndrome**
  - Factor V Leiden mutation
  - Antithrombin III deficiency
  - Protein S and C abnormalities
  - Heparin-induced thrombocytopenia
  - Birth control pills
  - Polycythemia
  - Others
- **Surgical or procedure complication**
  - **After aortic aneurysm repair or rupture**
  - After pyeloplasty
  - After partial nephrectomy
  - After anterior spinal fusion
  - After IVC filter or PICC
  - After embolization of gastric varices
- **Trauma**
- **Pregnancy complication**
- **After renal transplantation**
  - **Technical complication**
  - Acute cellular or vascular rejection
  - OKT3 and calcineurin inhibitor therapy
  - Sticky platelet syndrome
  - **Hypercoagulable state**
- **Infections**
  - **Acute pyelonephritis**
  - Pyogenic spondylitis
- **Inflammatory disorders**
  - **Pancreatitis**
  - Inflammatory bowel disease
  - Inflammatory aortic aneurysm
  - Behçet disease
  - Budd-Chiari syndrome
- **Neonatal**
  - **Dehydration**
  - Congenital

Box 66-4 Causes of renal vein thrombosis. Bold refers to common causes. *PICC,* Peripherally inserted central catheter.

marked decrease in perfusion detected on initial Doppler interrogation.[51] The optimal treatment approach to neonatal RVT is controversial. Fibrinolytic therapy may be associated with bleeding complications, including adrenal hemorrhage, and is usually not successful in restoring renal function unless it is undertaken within 24 hours of the thrombotic event.[52]

Nephrotic Syndrome

Patients with nephrotic syndrome have increased risk of venous thromboembolism; deep venous thrombosis is most commonly diagnosed (see Chapter 15).[53] The prevalence of RVT in nephrotic syndrome is unclear because it is largely undiagnosed; studies report frequencies from 5% to 62%.[49] Numerous abnormalities promoting a prothrombotic state occur secondary to heavy proteinuria. It is interesting to note that RVT appears to be more common in membranous nephropathy (MN) and lupus nephritis (LN), but RVT can complicate any cause of proteinuric renal disease. In this setting, RVT can lead to an increase in baseline proteinuria and present with AKI superimposed on chronic renal impairment.

After Renal Transplantation

Renal vein thrombosis after transplantation is rare and occurs in less than 0.5% to 4% of transplants, usually within the first week after transplantation.[54] It usually leads to graft infarction, but rupture of the allograft can also occur. Causes include technical issues related to the anastomosis, compression of the renal vein by fluid collections, volume depletion, acute rejection, and hemostatic and hypercoagulable states. Factor V Leiden mutation, which occurs in 2% to 5% of the population, is a risk factor for transplant RVT and should be sought when it occurs. Another syndrome known as *sticky platelet syndrome* can result in post-transplant RVT. There are some data supporting the protective effects of low-dose aspirin in this population. Immunosuppression with cyclosporine and OKT3 may increase the risk of RVT. Renal salvage is possible with early diagnosis, surgical exploration, and thrombectomy.[55]

Pregnancy

Pregnancy and the postpartum state are hypercoagulable states. There have been reports of spontaneous RVT in the postpartum period associated with renal infarction. RVT complicating pregnancy should be suspected when clinical clues such as flank pain and hematuria are present.

Malignant Disease

Malignant disease accounts for the greatest number of cases of RVT.[56] RVT can result from invasion of tumor of renal origin into the renal vein. About half of renal cell carcinomas are associated with RVT at autopsy. In addition, neoplasia originating in the renal vein or IVC, such as leiomyosarcoma or cavernous hemangioma, can cause RVT. Extrinsic compression of the renal vein by a tumor or retroperitoneal fibrosis may also cause this syndrome.

Diagnosis

Diagnosis of RVT requires imaging. Conventional ultrasound may demonstrate alterations in size and echogenicity. Renal duplex sonography may show increases in resistive indices, and ultrasound can directly visualize the filling defect, but this may depend on the angle of the vein, the body habitus of the patient, and the operator's experience. In neonates, renal Doppler ultrasound is the diagnostic study of choice. Sonographic findings in neonatal RVT include renal enlargement, loss of corticomedullary differentiation, and linear echogenicities radiating from the renal hilum as a result of interlobular and interlobar venous clot. Later scans may show linear, punctuate, or lace-like calcifications in these regions, representing calcified thrombi. Up to 80% of neonates with RVT have clot extending into the IVC. In patients with renal transplant RVT, the duplex waveform pattern demonstrates reversal of diastolic flow, which is not pathognomonic or specific for RVT. Imaging of the renal vein with MRA or other imaging modalities are needed to confirm transplant RVT. In adults, both CT and magnetic resonance (MR) venography have much greater sensitivity than renal vein duplex studies for the diagnosis of RVT. CT venography requires a significant contrast load, making MR venography preferable in patients with allergy to contrast agents or those at risk for contrast-associated nephrotoxicity. Figure 66-12 is a CT venogram demonstrating unilateral RVT.

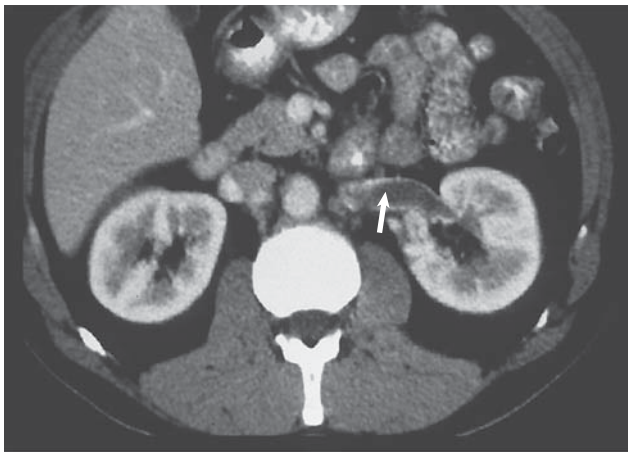

Figure 66-12 Computed tomography venogram demonstrating left renal vein thrombosis (*arrow*). *(Courtesy Dr. S. Rankin, Guy's Hospital, London.)*

Treatment

Treatment is controversial and depends on the setting, acuteness, and renal consequences. If there is no contraindication, most patients are treated with systemic anticoagulation acutely. In adults with acute RVT that is compromising renal function, catheter-directed thrombolytic therapy with urokinase or tissue plasminogen activator with or without percutaneous mechanical thrombectomy can be successful in regaining patency of the vessel and restoring renal function.[57] There are reports of successful thrombolytic therapy in pregnancy-associated RVT. The long-term benefit of this approach is unclear, and it is less successful when the thrombotic process begins in the small intrarenal venules rather than in the major veins, as is often the case when primary renal disease or a hypercoagulable state initiates the process. In neonatal RVT, which often results in renal nonfunction, thrombolytic therapy and anticoagulation have been used with variable results. In two recent reports of neonatal RVT, supportive care was recommended for unilateral RVT without extension into the IVC, whereas thrombolytics were used for bilateral cases with impending renal failure.

Surgical interventions include nephrectomy, thrombectomy, and retroperitoneal surgery for non–renal-associated abnormalities, such as tumor, retroperitoneal fibrosis, aortic aneurysm, and acute pancreatitis. Surgery tends to be reserved for situations in which the RVT results in hemorrhage from renal capsular rupture or for long-term consequences of RVT, such as hypertension or infection of a nonfunctioning kidney resulting from previous RVT.

A conservative approach may be favored when left RVT occurs because of the extensive collateral venous supply on that side,

ultimately allowing venous drainage and improvement in renal function. Systemic anticoagulation is indicated acutely to prevent extension of thrombus into the IVC and for prevention of pulmonary emboli. Anticoagulation should be continued indefinitely in patients with persistent hypercoagulable state after RVT. In addition, eventual recanalization of the venous system can result in delayed improvement in renal function as measured by nuclear medicine studies.

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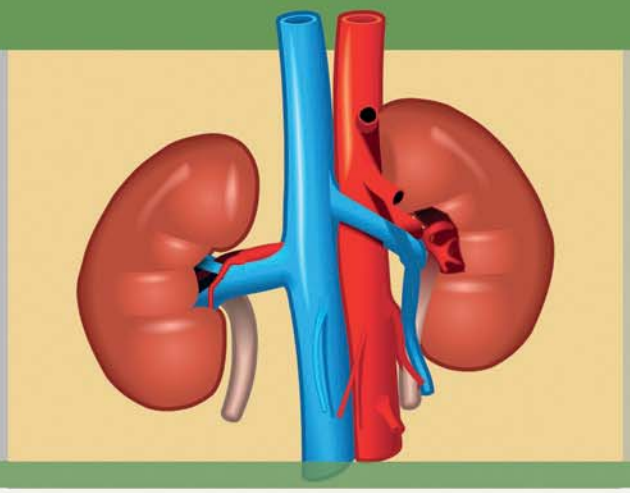

SECTION XII

Geriatric Nephrology

CHAPTER 67

Geriatric Nephrology

Mitchell H. Rosner, Edgar V. Lerma, and Sundararaman Swaminathan

Aging is associated with a decline in kidney function, which can manifest as early as the fourth decade of life and accelerates between the fifth and sixth decades. These changes affect glomerular and tubular function, systemic hemodynamics, and body homeostasis. This chapter focuses on the management of the population older than 65 to 70 years.

AGING-ASSOCIATED STRUCTURAL CHANGES

Anatomic Changes

The human kidney reaches a maximum size of approximately 400 g (12 cm in length) in the fourth decade of life. A natural decline of approximately 10% in renal mass per decade then follows. This natural decline is associated with cortical thinning and decrease in the number of functional nephrons.

Glomerular Changes

Structural glomerular changes with age include basement membrane thickening as well as development of focal and segmental or, rarely, global, glomerulosclerosis, which increases to 10% to 30%, and in some studies even exceeding 70% of glomeruli by the eighth decade (Figs. 67-1 and 67-2).[1] Preserved glomeruli often show an increase in overall tuft cross-sectional area, consistent with glomerular hypertrophy.[2] In aging mice and rats a strong relationship has been demonstrated between the glomerular hypertrophy and glomerulosclerosis, consistent with the hypothesis that glomerular hypertrophy may actually predispose to the development of glomerulosclerosis.[3] Neither kidney function nor chronic kidney disease (CKD) risk factors can explain the strong association between age and glomerulosclerosis in healthy adults.[4]

Tubular and Interstitial Changes

Tubulointerstitial injury associated with aging is most pronounced in the outer medulla, with tubular dilation and atrophy, mononuclear cell infiltration, and interstitial fibrosis. Some tubules (especially in the distal tubule and collecting duct) may develop small diverticuli; it has been suggested that these diverticuli play a role in the development of upper urinary tract infections (UTIs; pyelonephritis) by harboring bacteria, thereby predisposing to recurrent infection.[5]

Vascular Changes

Arterioles often develop hyalinosis with aging. Thickening of the arterioles with an increase in the medial thickness/lumen diameter ratio is common with aging but is observed almost exclusively in hypertensive individuals.[5] The arcuate arteries become more angulated and irregular with aging, and there is increased tortuosity and spiraling of the interlobar vessels. These changes occur independently of hypertension but are augmented in its presence. With aging, some afferent arterioles, particularly of juxtamedullary glomeruli, develop vascular shunts to the efferent arterioles, thereby bypassing glomeruli, leading to "aglomerular arterioles."[6]

AGING-ASSOCIATED CHANGES IN RENAL FUNCTION

Glomerular Filtration Rate

Inulin clearance studies document a progressive fall in glomerular filtration rate (GFR) after the age of 40 years, with a relatively greater decline in men (Fig. 67-3).[7] However, the fall in GFR is not inevitable; in as many as one third of patients who remain normotensive, there is no decrease in creatinine clearance with age.[5]

In addition to the decrease in GFR with aging, there may be a reduction in renal "reserve." Whereas some studies suggest that aging humans show a normal increase in GFR after amino acid infusion, others have shown a marked reduction in increases in renal plasma flow (RPF) and GFR in response to concurrent infusion of amino acids and dopamine in healthy elderly individuals.[8,9]

Renal Plasma Flow

Renal plasma flow also decreases from a mean of 650 ml/min in the fourth decade to 290 ml/min by the ninth decade, with increasing renal vascular resistance (Fig. 67-4).[5] The fall in RPF with age is greater in men than in women and in those who are hypertensive.[10] Because RPF decreases relatively more than GFR, filtration fraction (defined as GFR/RPF) increases with age. Studies using a xenon washout technique demonstrated that there is a true reduction in renal blood flow when it is factored for renal mass.[11] The decrease in renal blood flow especially involves the cortex, and blood flow to the medulla is relatively preserved.

Proteinuria

The prevalence of both microalbuminuria (urinary albumin levels of 30 to 300 mg/day) and albuminuria increases progressively after the age of 40 years. The increased prevalence is most marked in diabetic and hypertensive patients but is also observed in patients lacking these risk factors (Fig. 67-5).[12]

ASSESSMENT OF RENAL FUNCTION IN THE ELDERLY

Serum creatinine is a less reliable indicator of renal function in the aging population. After the age of 60 years, there is a progressive decrease in urinary creatinine excretion, which largely reflects muscle mass decreases with aging (Fig. 67-6).[13] For example, serum creatinine did not change between young patients and older patients

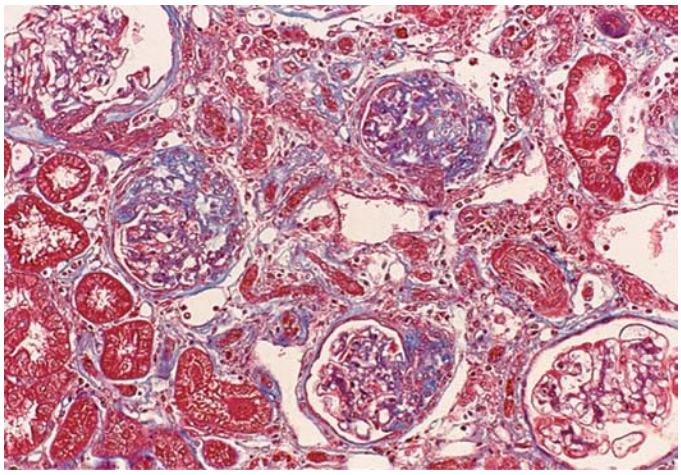

Figure 67-1 Glomerulosclerosis and tubulointerstitial fibrosis in an aging rat. Similar changes, consisting of focal segmental glomerulosclerosis, tubular atrophy, and interstitial fibrosis, occur in humans. (Trichrome stain; original magnification ×400.)

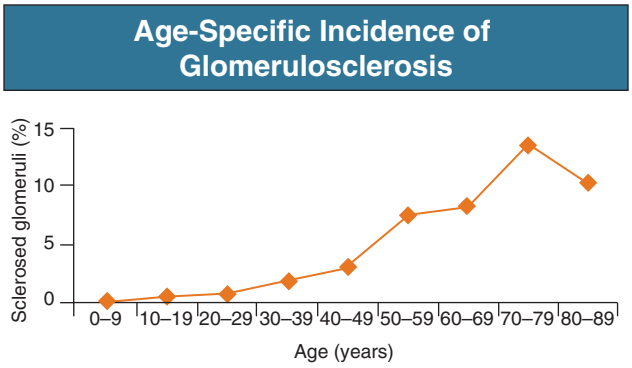

Figure 67-2 Glomerulosclerosis increases with aging. *(Modified from reference 1.)*

despite a reduction in creatinine clearances from 140 ml/min/1.73 m^2 at mean age 30 years to 97 at mean age 80 years.[14]

There is no consensus on the optimal approach to estimation of GFR in elderly people. Whereas the MDRD (Modification of Diet in Renal Disease) study equation and the Cockcroft-Gault formula for estimating GFR use age in their calculations (see Chapter 3), neither has been validated in people older than 70 years, and both underestimate true GFR in those older than 65 years with standard techniques such as isotope clearance. Although the MDRD equation may be more accurate than the Cockcroft-Gault formula,[15] serum cystatin C, which is independent of muscle mass, may be superior to both and is an independent risk factor for mortality in the elderly.[16] A new GFR-estimating equation was derived from 610 patients who were older than 70 years using iohexol clearance as the gold standard. This Berlin Initiative Study (BIS) equation worked particularly well in classifying patients with CKD stage 2 to 4 kidney function.[17] More data are needed to determine which estimated GFR equation performs the best in the elderly patient.

PREVALENCE OF CHRONIC KIDNEY DISEASE IN THE ELDERLY

According to the United States Renal Data System's 2010 and 2011 Annual Data Report as well as the National Health and Nutrition

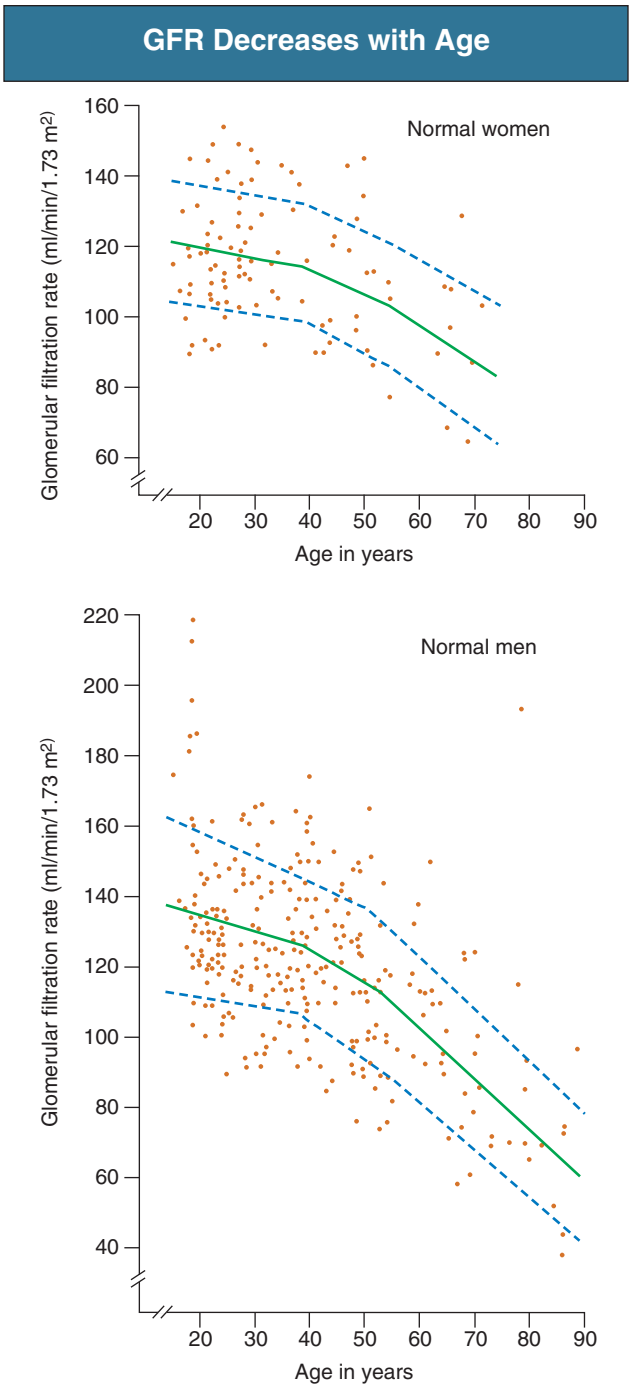

Figure 67-3 Glomerular filtration rate (GFR) decreases with age. GFR (inulin clearance) begins to fall at age 40 years, and the rate of decline is more rapid in men than in women. *(Modified from reference 7.)*

Examination Survey (NHANES) study, the incidence of CKD is increasing most rapidly in people aged 65 years and older, in whom the incidence of recognized CKD more than doubled between 2000 and 2008 (Figs. 67-7 and 67-8).[18] CKD has been associated with an overall increase in all-cause cardiovascular mortality (see Chapters 79 and 82). Nevertheless, reductions of estimated GFR (eGFR) to 50 to 59 ml/min/1.73 m^2 do not increase mortality risk among patients age 65 years or older compared with patients with eGFR of more than 60 ml/min (Fig. 67-9).[19] These observations have led to the debate regarding whether the decrease in GFR that occurs with aging should really be considered unhealthy[20] and whether the term

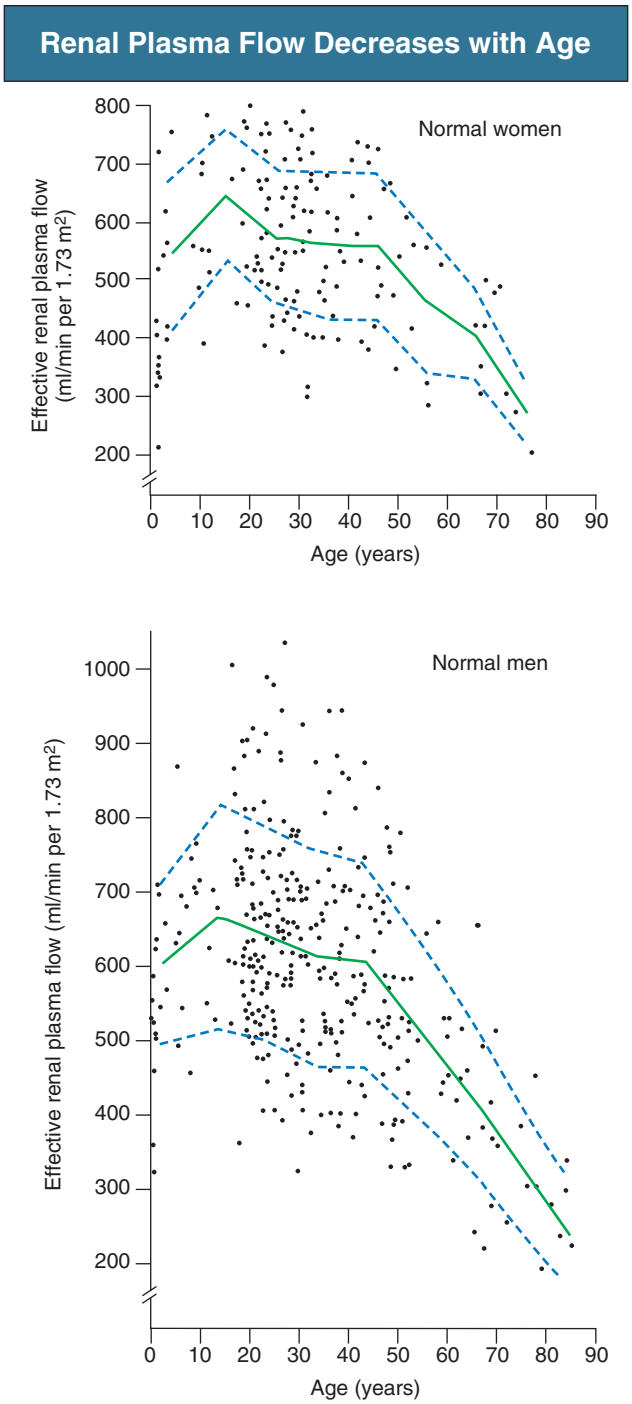

Figure 67-4 Renal plasma flow (RPF) decreases with age. RPF (*p*-aminohippurate clearance) begins to fall rapidly after the age of 50 years, and the rate of decline is more rapid in men than in women. *(Modified from reference 7.)*

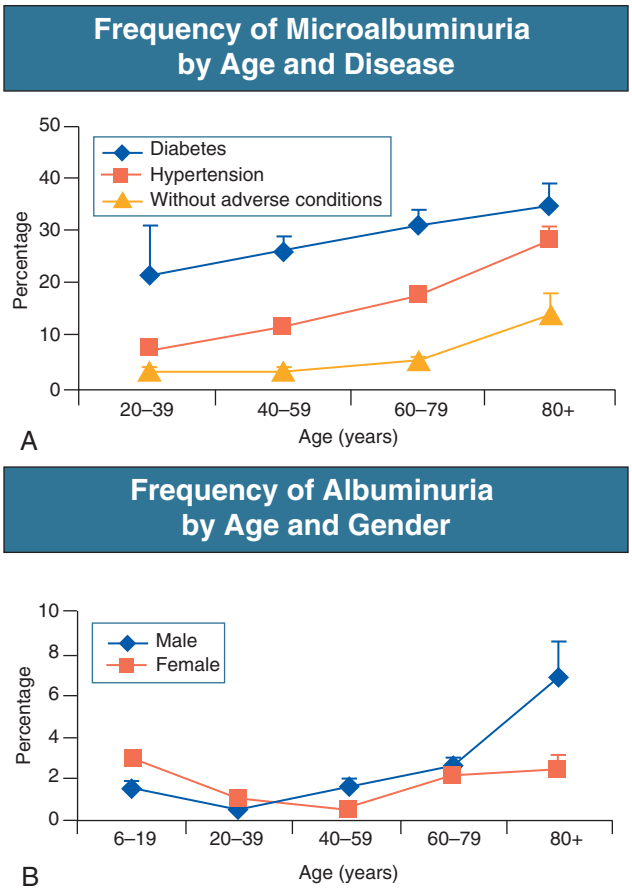

Figure 67-5 Increased proteinuria with aging. A, Microalbuminuria increases with age, with the greatest prevalence in diabetes, followed by hypertension and then the absence of either condition. **B,** Albuminuria increases with age, and the prevalence is greater in men than in women. *(Modified from reference 12.)*

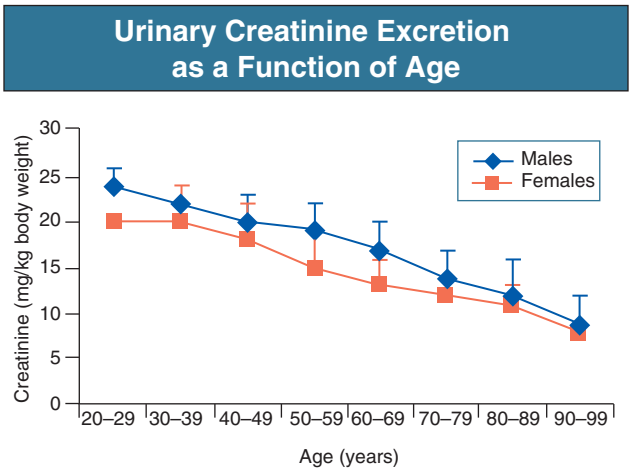

Figure 67-6 Urinary creatinine excretion (factored for body weight) decreases with age. *(Modified from reference 13.)*

"chronic kidney disease" in such cases should be replaced with "age-related reduced kidney function".[21]

RISK FACTORS FOR CHRONIC KIDNEY DISEASE IN THE ELDERLY

The variability in the severity of aging-related renal disease in humans and experimental animals has suggested that there may be specific risk factors for its development. In experimental animal models, aging-related histologic changes vary according to the genetic strain, gender, body mass index, and diet. In animal models, aging-related changes can be retarded with protein or calorie restriction or blockade of the renin-angiotensin system (RAS).[22] According to a multistage community-based survey, age, annual income, use of oral analgesics, metabolic syndrome, hyperuricemia, and hemoglobin were risk factors for CKD in both elderly and nonelderly

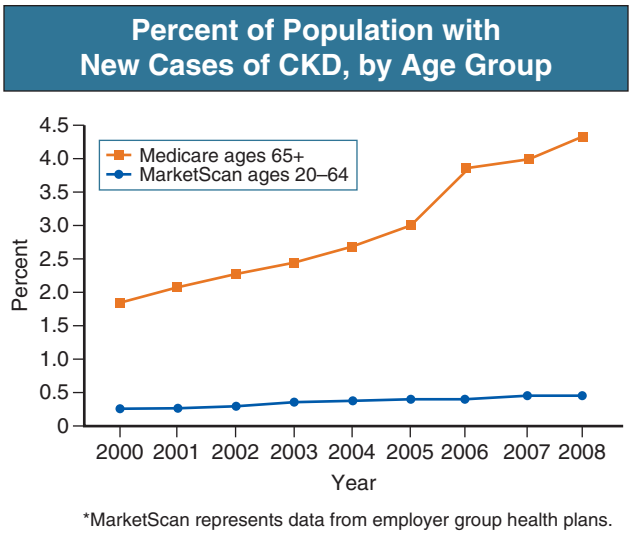

Figure 67-7 New cases of chronic kidney disease (CKD) over time stratified by age group. Medicare is a U.S. national social insurance program. MarketScan is an online health research database. *(Modified from reference 18.)*

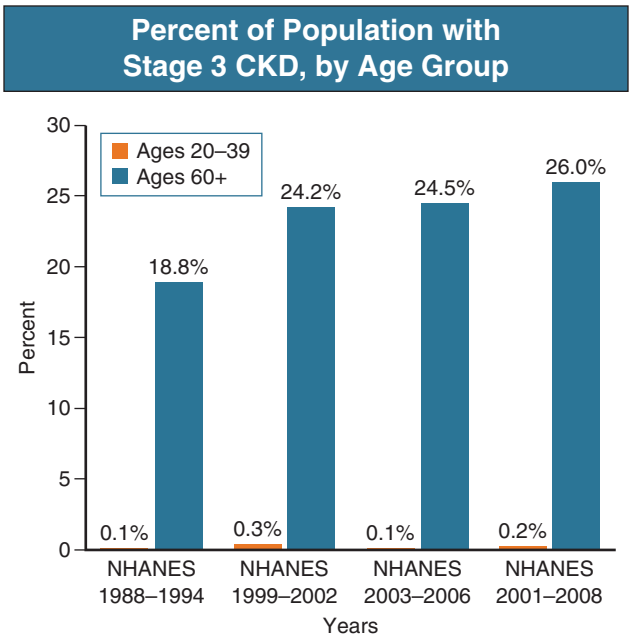

Figure 67-8 Prevalence of stage 3 chronic kidney disease (CKD) by age group over time. *NHANES,* National Health and Nutrition Examination Survey. *(Modified from reference 18.)*

patients.[23] In elderly patients, previous medical history of diabetes mellitus, CKD, stroke, and analgesic use were positively correlated with CKD.[23] In another prospective study, increased levels of physical activity correlated with a lower risk for rapid GFR decline (defined as loss greater than 3 mL/min/1.73 m^2 per year in GFR, as estimated by longitudinal measurements of cystatin C levels) in a general population of older adults.[24]

PATHOGENESIS OF AGE-RELATED CHRONIC KIDNEY DISEASE

A variety of mechanisms have been proposed for aging-related renal changes (Box 67-1).

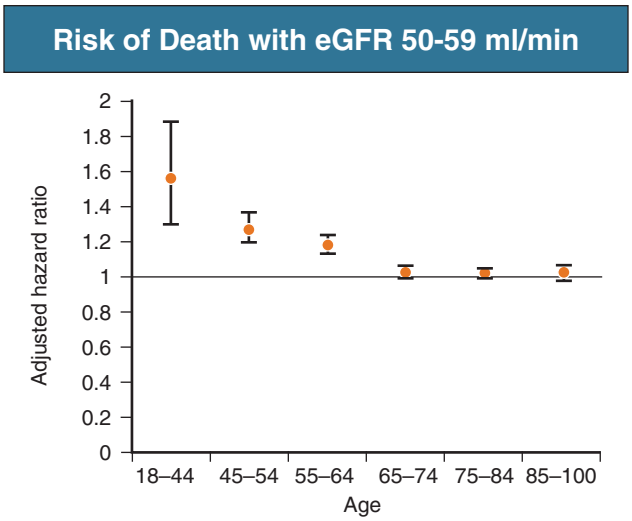

Figure 67-9 Adjusted hazard for death associated with an eGFR of 50 to 59 ml/min/1.73 m^2. *(Modified from reference 19.)*

Proposed Mechanisms for Aging-Associated Kidney Disease

- Decreased Klotho
- Oxidative stress
- Senescence (with telomere shortening and loss of mitochondria)
- Glomerular hypertension and hyperfiltration
- Intrarenal activation of the renin angiotensin system
- Decreased renalase
- Hemodynamic
  - Glomerular hypertension and hyperfiltration
  - Intra-renal activation of renin angiotensin system
  - Endothelial dysfunction (loss of nitric oxide)
  - Renal ischemia
  - Decreased renalase
- Metabolic
  - Accumulation of advanced glycation end products
  - Chronic effects of uric acid
- Cellular dysfunction
  - Oxidative stress
  - Decreased Klotho
  - Senescence (with telomere shortening and loss of mitochondria)
- Inflammation
  - Renal transformation growth factor β (TGF-β) expression
- Endothelial dysfunction (loss of nitric oxide)
- Renal ischemia
- Renal transforming growth factor β (TGF-β) expression
- Accumulation of advanced glycation end products (AGEs)
- Chronic effects of uric acid

Box 67-1 Mechanisms for aging-related kidney changes.

The kidney is the only known source of the anti-aging hormone Klotho. Mice with Klotho deficiency recapitulate features of systemic and renal aging. Klotho is synthesized by the distal nephron and is secreted as a circulating hormone.[25] Klotho is a multipotent protein and serves as a cofactor for the phosphaturic hormone fibroblast growth factor 23 (FGF-23), regulates oxidative stress, and

antagonizes transforming growth factor β (TGF-β) signaling. The mechanisms whereby Klotho regulates the aging process are being elucidated in animal models.

Additional mechanisms of renal aging may involve telomere shortening of chromosomal DNA, loss of mitochondria, and accelerated apoptosis. Increased numbers of apoptotic tubular and interstitial cells have been shown in the aging rat.[26] This process may involve oxidative stress.[27]

Aging-associated renal disease may also be mediated by activation of the RAS, which may lower renal Klotho expression. In turn, in animal models, angiotensin type I recpetor (ATI) blockade upregulates Klotho,[28] and *in vivo* Klotho gene delivery attenuated angiotensin II (Ang II)–induced renal damage.[29] Treatment of rats with angiotensin-converting enzyme (ACE) inhibitors reduces aging-associated oxidative stress and preserves mitochondria in renal proximal tubules in association with upregulation of cellular antioxidant enzymes.[30] Targeted disruption of the gene encoding for the ATIA receptor also results in marked prolongation of life span in mice.[31] The longevity in these mice was associated with a decrease in cardiac and vascular injury possibly through attenuation of oxidative stress and overexpression of prosurvival genes (also in the kidney).

A loss of nephrons results in hyperfiltration with increased glomerular hydrostatic pressure and glomerular hypertrophy, which are known risk factors for glomerular scarring.[32] Depending on the animal strain, glomerular hydrostatic pressures may be either elevated or normal with aging.[22] It is thus likely that glomerular hypertension, when it occurs with a decrease in nephron mass, is a contributor to, rather than an initiator of, the aging-associated decline in renal function.

With aging, the elastic arteries dilate and stiffen, resulting in higher pulse wave velocity with increased pressure transmission to the microvasculature.[33] Measures of large-artery stiffness are closely related to markers of renal microvascular injury, including albuminuria.[34] Aging-associated intimal hyperplasia of the interlobular arteries and disease of the afferent arteriole may also alter renal autoregulation, resulting in injury to the glomeruli.[35] Higher systemic pulse pressure, seen in aging individuals, has been associated with an accelerated decline in GFR.[36]

Endothelial function also declines with aging, particularly in men. It is associated with a progressive reduction in nitric oxide production by endothelial cells and is reflected clinically by a reduction in brachial artery reactivity.[37] Loss of normal endothelial vasodilators may account for the increased renal vasoconstrictive response observed in aging rats to agents such as Ang II and endothelin 1 and may also contribute to the development of renal microvascular disease. Endothelial dysfunction can also inhibit renal angiogenesis, resulting in progressive capillary loss and ischemia. Indeed, mice lacking endothelial nitric oxide synthase show a marked acceleration of aging-associated renal disease.

Aging is also associated with more pronounced renal hypoxia, and ambient partial pressure of oxygen (P_{O_2}) is about 20 mm Hg lower in both the renal cortex and the medulla in otherwise healthy aged individuals compared with young patients.[38] The reduced ability of the aged kidney to generate vasodilators may also contribute to renal hypoxia.[39]

Advanced glycation end products (AGEs), although typically associated with diabetes, are also present in the diet and can accumulate in aging. The content of AGEs in the diet correlates with serum AGE levels, oxidant stress, organ dysfunction, and life span in animal models.[40] Calorie restriction may extend life span in animal models in part by reducing AGE levels.[40,41] Chronic administration of aminoguanidine (an inhibitor of AGE synthesis) also reduces glomerulosclerosis in the aging rat.

FLUID AND ELECTROLYTES IN AGING

Sodium Balance and Hypertension

Aging is associated with both impaired excretion of a salt load[42] and defective conservation in the setting of sodium restriction.[43] Proximal sodium reabsorption is increased in aging, whereas distal sodium reabsorption may be reduced.[44] Studies in rats suggest that pressure natriuresis is impaired in aging.[22] Because the diet of most individuals in developed countries contains excess sodium (8 to 10 g of salt daily), there is a tendency in the elderly population for total body sodium excess.

The relative defect in sodium excretion and increased total body sodium may be predisposing factors for the development of hypertension. Blood pressure increases with age. After the age of 60 years, most people are hypertensive (Fig. 67-10).[45] Salt sensitivity occurs in more than 85% of aging people, and sodium restriction will result in

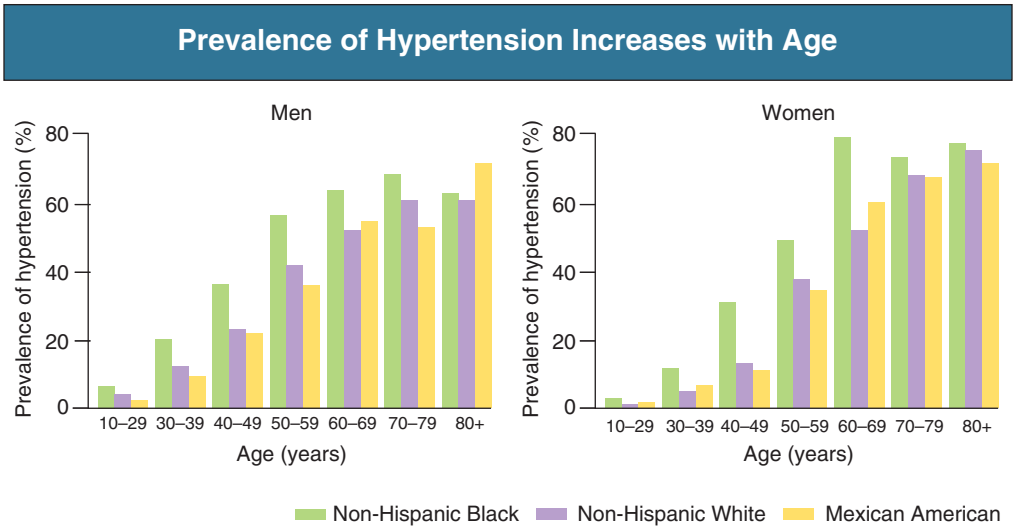

Figure 67-10 Prevalence of hypertension based on age, gender, and race. *(Modified from reference 45.)*

a significant fall (>10 mm Hg) in mean arterial pressure.[46] Populations that ingest low-sodium diets, such as the Yanomamö Indians of southern Venezuela, do not show an increase in blood pressure with age.[47] Loss of vascular compliance as a result of collagen deposition in the larger arterial vessels may also contribute to aging-associated hypertension, as may endothelial dysfunction, perhaps mediated by oxidative stress. Aging-associated renal and vascular changes may explain why correction of secondary forms of hypertension (such as primary aldosteronism, Cushing syndrome, renovascular hypertension, and hypothyroidism) is less effective at curing hypertension in older patients. In one study, diastolic blood pressure fell to below 90 mm Hg in 24 of 25 patients younger than 40 years after treatment of the mechanism responsible for the secondary hypertension but in only 38 of 61 patients older than 40 years.[48]

During hypovolemia, an inappropriate excretion of sodium is observed in the elderly that can exacerbate hypotension and increase the risk for acute kidney injury (AKI).[49]

Osmoregulation and Water Handling

The most common electrolyte abnormalities in the elderly are the dysnatremias; this results from impaired water handling with aging. Hyponatremia has been found in up to 11% of the ambulatory geriatric population and 5.3% of hospitalized elderly patients.[50] Hypernatremia is found in about 1% of patients older than 60 years admitted to the hospital.[50] Both concentration and dilution of the urine are affected by aging and account for part of the susceptibility to dysnatremias.

In the elderly, the maximal urinary osmolality and thirst response to hyperosmolality are reduced, which may predispose to dehydration and hypernatremia.[51] The impairment in urine concentrating ability results from a defect in the concentrating gradient in the medullary region and can lead to nocturia.[52] Compounding the risk for hypernatremia is that the ill elderly patient may not have ready access to water.

The elderly also have an impaired ability to dilute the urine and thus have a decreased ability to excrete a water load, leading to an increased predisposition to hyponatremia that is often compounded by the use of medications such as thiazide diuretics and selective serotonin reuptake inhibitors.[53]

Other Tubular Defects and Electrolyte Problems

Potassium excretion is impaired in the elderly, and the transtubular potassium gradient is decreased.[54] Hyperkalemia occurs more frequently in elderly patients treated with drugs that interfere with potassium excretion (such as potassium-sparing diuretics). Other factors contributing to the predisposition for hyperkalemia in the elderly include decreased GFR, lower basal levels of aldosterone, and tubulointerstitial scarring impairing the Na^+,K^+-ATPase transporters. Hypokalemia is also common because of renal or extrarenal losses.

Most elderly individuals can maintain acid-base balance under normal conditions. However, during conditions of stress when acid production is increased (sepsis or AKI), an inability to excrete an additional acid load may be uncovered. This is supported by a study demonstrating that elderly patients could not increase net acid excretion to the same level as younger adults in response to a protein meal.[55]

Hypercalcemia occurs in 1% to 3% of elderly patients. Causes include malignant tumors, hyperparathyroidism, immobilization, and use of thiazide diuretics. Hypocalcemia is less common and is observed mainly in patients with advanced CKD (in association with vitamin D deficiency and hyperphosphatemia), chronic malabsorption, and severe malnutrition. Aging is associated with increased parathyroid hormone levels (which correlate inversely with GFR) and a decrease in serum calcitriol and phosphate.

Hypomagnesemia is reported in 7% to 10% of elderly patients admitted to the hospital; most commonly, this is the result of malnutrition or laxative or diuretic use. Hypermagnesemia is less common and is found primarily in patients with CKD or who are taking large doses of magnesium-containing antacids. Gout (as well as an elevation in serum uric acid levels) is also more common in the aging population.

ENDOCRINE FUNCTION AND RENAL HORMONES

Erythropoietin (EPO) levels increase with age, probably related to a compensatory response to subclinical blood loss, increased erythrocyte turnover, and increased EPO resistance.[56] Nevertheless, EPO levels are significantly lower in the anemic elderly patient compared with the anemic younger individual, suggesting a blunted response to low hemoglobin.[57]

Elderly women with GFR below 60 ml/min have lower calcium absorption and lower 1,25-hydroxyvitamin D levels, probably because of diminished conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by the aging kidney.[58]

The kidney removes about 50% of insulin in the peripheral circulation by filtration and proximal tubular uptake and degradation. The decline of renal function in the elderly leads to a decrease in insulin clearance. This is in part offset by diminished glucose tolerance, which may relate to the increasing frequency of obesity observed in aging individuals.

CLINICAL MANIFESTATIONS

General Considerations

Aging is associated with declines in renal function that ultimately limit the ability to defend against destabilizing events. Moderate fluid loss (e.g., episode of diarrhea) and moderate fluid loading (e.g., inappropriate perioperative intravenous fluids) may be poorly tolerated and lead to hypovolemia and fluid overload, respectively. Hypovolemia in those taking multiple medications including ACE inhibitors may lead to AKI. Overzealous administration of water as 5% dextrose or 0.45% saline may result in hyponatremia especially in patients taking selective serotonin reuptake inhibitors, which may increase levels of antidiuretic hormone. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) in the elderly is associated with increased risk for hyponatremia, hyperkalemia, hypertension, and impaired renal function.

Glomerular Diseases

Elderly patients may have treatable kidney diseases identifiable on renal biopsy.[59] In a study of 235 biopsy specimens in patients older than 80 years, 67% of the patients had treatable lesions.[60] The pathologic spectrum of glomerular disease seen in elderly people is similar to that seen in the general population, although the prevalence of various pathologies differs. For example, diabetic kidney disease is seen with increasing frequency in the aging population. Among patients with the nephrotic syndrome who are older than 60 years, membranous nephropathy is the most common diagnosis (32.1% of

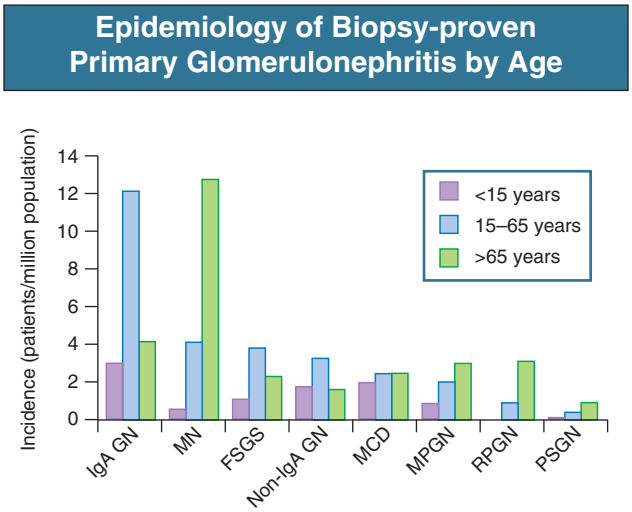

Figure 67-11 Epidemiology of biopsy-proven primary glomerulonephritis by age. Children presenting with nephrotic syndrome are often treated empirically for MCD; thus, MCD as a diagnosis is likely underrepresented in data derived from biopsy registries. *FSGS,* Focal segmental glomerulosclerosis; *IgA GN,* IgA nephropathy; *MDC,* minmal change disease; *MGN,* membranous nephropathy; *MPGN,* membranoproliferative glomerulonephritis; *non-IgA GN,* other mesangial proliferative glomerulonephritis; *PSGN,* poststreptococcal glomerulonephritis; *RPGN,* rapidly progressive glomerulonephritis. *(Modified from reference 61.)*

patients), followed by amyloidosis (typically light chain derived) and minimal change disease (Fig. 67-11).[60,61] Other important causes of AKI from glomerular disease in the elderly include rapidly progressive glomerulonephritis (GN) resulting from pauci-immune (antineutrophil cytoplasmic antibody (ANCA)–associated) GN (accounting for about 30% of elderly patients with AKI who undergo kidney biopsy).[59] In contrast, certain glomerular disorders are uncommon in elderly people, such as lupus nephritis, minimal change nephropathy, and IgA nephropathy. Only 2% of patients with systemic lupus present after the age of 60 years.[60,61] Antinuclear antibody tests performed in elderly patients are more likely to yield false-positive results.

Because of age-related declines in kidney function as well as the presence of significant comorbid medical conditions, elderly patients have a much greater risk for developing serious toxicities from immunosuppressive therapies.[62] Retrospective series examining the course of ANCA-associated GN in the elderly reveal a poorer prognosis with high rates of end-stage renal disease (ESRD), death, and treatment-related complications.[63]

Renovascular and Atheroembolic Disease

There is an increased frequency of renovascular and atheroembolic disease with aging. In several case series, AKI resulting from atheroembolic disease accounted for 4% to 7% of cases.[59] Atherosclerotic renal artery stenosis (ARAS) is estimated to be present in about 7% of patients older than age 65 years and is a major cause of secondary hypertension, ischemic nephropathy, and CKD in the elderly.[64] In elderly people with hypertension and elevated serum creatinine, especially with a history of vascular disease, a screening test for renovascular disease, such as by magnetic resonance angiography or renal artery duplex scanning, should be considered (see Chapter 39). Percutaneous transluminal renal angioplasty and renal artery stenting are of variable value in the elderly because many have significant arteriosclerosis, which may limit the benefits of intervention.[64] Thus, an individualized approach to therapy is warranted.

Acute Kidney Injury

Polypharmacy associated with aging greatly increases susceptibility to the development of AKI.[65] Whereas the causes of AKI in the elderly patient encompass the same spectrum of pre-renal, renal, and post-renal causes that are seen in other age groups, the elderly patient has a higher relative risk for developing AKI from obstructive uropathy and sepsis. Decision making regarding whether to provide active intervention such as with continuous renal replacement therapy in elderly patients with AKI and multisystem organ failure will be influenced by comorbidity and likely outcomes.

Urinary Tract Infections

There is an increased risk for asymptomatic bacteriuria and symptomatic UTIs with aging (see Chapter 53). In men, this may relate to the increased risk of prostatic hypertrophy and urinary calculi with age. In postmenopausal women, the risk is increased by the prevalence of incontinence, cystoceles, and postvoid residual urine. Chronic use of indwelling catheters in elderly patients is also associated with increased bacterial colonization rates; treatment of these UTIs should generally be based on the presence of symptoms or signs (fever, elevated white blood cell count, or dysuria). Exceptions include high-risk patients, such as those with frequent or recurrent UTIs or structural defects of the urinary tract; patients scheduled to undergo urologic surgery, particularly transurethral resection of prostate; neutropenic patients; and renal transplant recipients. Atypical presentations of UTI are common in the elderly and include presentation with lethargy, delirium, and anorexia. The treatment of catheter-associated infections is discussed in Chapter 53.

Obstructive Uropathy

Obstructive uropathy (see Chapter 60) is common in elderly men, usually a result of benign prostatic hypertrophy, prostate cancer, or urethral stricture. The incidence of obstructive uropathy in women is about one third to one half that in men, and the condition is primarily caused by malignant neoplasms of the genitourinary tract. Lower urinary tract obstruction should be excluded by measuring the postvoid residual bladder volume, either by a bedside ultrasound bladder scan or by temporary placement of a urethral catheter. Ultrasound is the most appropriate imaging study for diagnosis of upper urinary tract obstruction (see Chapter 60).

Urinary Incontinence

The lower urinary tract also undergoes significant changes with aging. Decreased bladder contractility occurs secondary to weakening and thinning of the detrusor smooth muscle. This leads to a dysfunctional pattern, eventually culminating in involuntary detrusor contractions. Bladder capacity decreases, whereas postvoid residual bladder volume increases by about 50 to 100 ml. Elderly people also have a higher frequency of nocturia, in part because of the decrease in renal concentrating capacity and perhaps also associated with disordered sleep and the increasing use of diuretics in this population.

Transient urinary incontinence is very common in the elderly and has multiple potentially treatable causes, which are best recalled by a mnemonic, DIAPPERS (Box 67-2).[66] In men, the most common cause is overflow incontinence from prostatic obstruction, whereas in women a prolapsed uterus with cystocele is frequently the cause. In the absence of an easily reversible cause, nonsurgical therapeutic options for urinary incontinence include behavioral therapy and biofeedback, pelvic floor exercises, pharmacologic therapy (e.g.,

Transient Causes of Urinary Incontinence (DIAPPERS)	
D	Delirium or confusional state
I	Infection—urinary (symptomatic)
A	Atrophic urethritis, vaginitis
P	Pharmaceuticals (e.g., diuretics)
P	Psychological, especially depression
E	Endocrine (hypercalcemia, hypokalemia, glycosuria)
R	Restricted mobility
S	Stool impaction

Box 67-2 Transient causes of urinary incontinence in the elderly (DIAPPERS). *(Modified from reference 66.)*

α-adrenergic antagonists to reduce prostatic hypertrophy), and, if it is unavoidable, long-term catheterization. Surgery may be required for large cystoceles, vaginal vault prolapse, and postprostatectomy stress incontinence.[66]

Hematuria

Benign causes of hematuria include benign prostate diseases, UTI, and cystic renal diseases. Malignant neoplasms of the urinary tract are more common in older patients. This change in epidemiology with advancing age requires that the diagnostic workup for hematuria include cystoscopy and urinary tract imaging. Bladder carcinoma is rarely observed before the age of 40 years; it increases progressively after the fourth decade. Renal cell carcinomas (RCCs) are most commonly observed in the seventh decade. RCC is more aggressive in the elderly, and treatment decisions can be difficult, especially in the setting of significant CKD where nephrectomy may lead to dialysis dependence.[67] Other causes of hematuria may need to be considered, as discussed in Chapter 61.

Nephrotoxicity and Drug Dosage

Elderly patients are prone to increased nephrotoxicity because they are often administered medicines on the assumption that a normal or nearly normal serum creatinine concentration is consistent with normal renal function. Thus, the dosage may be inappropriate; it is critical not to rely solely on serum creatinine values for determination of dosages, and eGFR should be used in this regard. Elderly patients with CKD may take multiple medications, often prescribed by multiple physicians. This creates a great risk for drug-drug interactions that can be exacerbated when renal clearance is impaired.

End-Stage Renal Disease and Renal Replacement Therapy

The mean age for a patient to initiate renal replacement therapy is currently over 60 years in the United States and in Europe. The mean age of ESRD patients requiring dialysis in most developing countries is much lower, 32 to 42 years, than that in the developed world. Recently in the United States there has been a decline in the incidence of ESRD in patients older than 65 years, with a continued high incidence in those older than 75 years (Fig. 67-12).[68] Despite the frequency of CKD among elderly patients, ESRD as an outcome is far less common than cardiovascular morbidity or mortality.[69] For example, older patients with CKD stage 3 are more likely to die and less likely to reach ESRD than are their younger counterparts.[69]

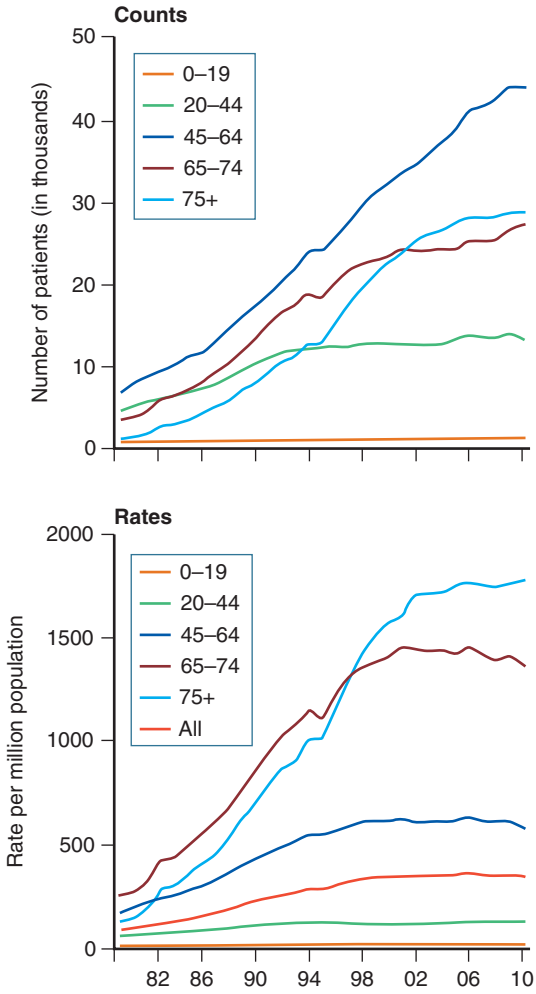

Figure 67-12 Incidence and prevalence of end-stage renal disease (ESRD) in the United States by age. Patients older than 65 years have a higher incidence and prevalence of ESRD; factored for gender and race. *(Modified from reference 68.)*

The decision to offer renal replacement therapy should not be based solely on the age of the individual. It is important to recognize that such a decision involving an elderly patient is more complex and fraught with more challenges than in younger patients and requires a multidisciplinary approach that involves family members. Nonmedical barriers may be particularly important in the elderly—for example, limited transportation, family support, and cost. Whereas the IDEAL (Initiating Dialysis Early and Late) study demonstrated no particular benefit with early initiation of renal replacement therapy,[70] another study raised the issue of potential harm of early initiation of RRT, particularly in the elderly.[71] Nursing home patients who began dialysis experienced sharp and sustained declines in their ability to perform basic daily activities.[72] A year after beginning dialysis, 58% of the patients had died, and only 13% still functioned at the same level as they had before beginning dialysis. Thus, although dialysis may be life extending, it does not lead to improvements in functional status in this patient group. Of note, the period before and after the initiation of dialysis is a time of high risk, with elderly patients having a high risk for worsening disability that is often permanent, as well as death.[73]

As with younger patients, vascular access remains the Achilles heel of hemodialysis. As with other populations, the survival of arteriovenous fistulas in elderly patients is significantly greater than that of arteriovenous grafts.[74] In fact, successful use of an arteriovenous fistula in the elderly has results similar to those in younger people, with prolonged patencies and low incidence of infections and thromboses. Similarly, use of tunneled hemodialysis catheters is also associated with increased mortality in elderly patients on hemodialysis.[74] Unfortunately, many elderly hemodialysis patients have severe widespread atherosclerosis affecting vascular beds, and catheter-based hemodialysis may be the only viable option.

Limitations of hemodialysis in the elderly may include their sensitivity to fluid shifts and the presence of significant cardiac dysfunction; hence peritoneal dialysis (PD) may theoretically offer some advantage by offering a slow, sustained degree of ultrafiltration that leads to greater hemodynamic stability. Unfortunately, inherent functional limitations and lack of social support may provide impediments to broader use of PD in the elderly.[75] Studies have demonstrated similar outcomes in elderly patients undergoing hemodialysis versus PD.[75]

Transplantation should be considered in the management of elderly patients with ESRD because studies have shown that selected elderly recipients benefit from renal transplantation by a significant reduction in mortality compared with wait-listed ESRD patients.[76] This survival benefit is most striking for patients with ESRD caused by diabetes or hypertension, but it becomes less apparent the longer the patient waits before transplantation.[76] Even when expanded-criteria donor (ECD) kidneys are used, a 25% mortality reduction has been shown in those who undergo transplantation, as compared with those who are wait-listed.[77] Overall graft survival for the elderly transplant patient is similar to that in younger patients.[78] It has been argued that lower doses of immunosuppression are sufficient in elderly renal transplant recipients.[78] However, the Eurotransplant Senior Program, allocating kidneys from donors 65 years or older to recipients 65 years or older regardless of human leukocyte antigen (HLA) matching, found 5% to 10% increased rejection rates in this "old to old" group compared with two better HLA-matched groups, the "old to any" and the "any to old," within the Eurotransplant Kidney Allocation System.[79] In a subanalysis of the Efficacy Limiting Toxicity Elimination (ELiTE)–Symphony study, a large prospective, randomized trial comparing immunosuppressive regimens in renal transplant patients, equal rates of rejection in elderly (60 years or older) versus younger (younger than 60 years) recipients were demonstrated.[80] Furthermore, this subanalysis suggested that older recipients who receive a marginal kidney from an older or expanded-criteria donor may fare worse than younger recipients, with an increased likelihood of death, delayed graft function, graft loss, treatment failure, and reduced graft function.

For those who decide not to pursue renal replacement therapy, maximum conservative management and palliative care, which focus on symptomatic therapy, are options. This concept underscores the importance of individualizing patient goals with a focus on quality of life. For those with severe functional or cognitive impairment or for whom complications of dialysis have negatively affected their quality of life, dialysis discontinuation is an important consideration. Hospice services remain underused for ESRD patients but may provide an important support mechanism for patients and their families who wish to discontinue dialysis.

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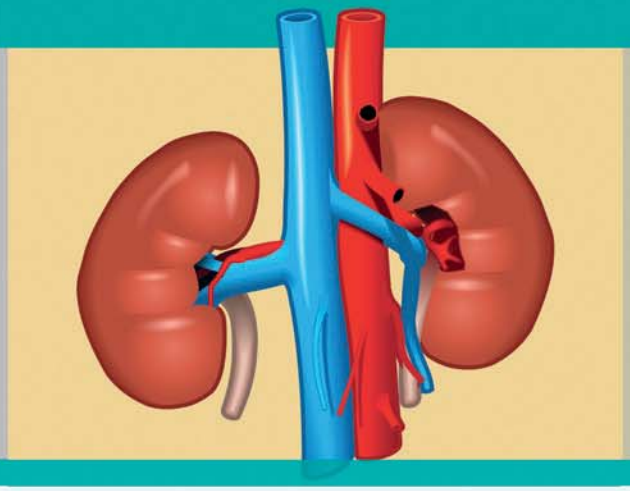

SECTION XIII

Renal Disease and Cancer

CHAPTER 68

Onconephrology: Renal Disease in Cancer Patients

Ala Abudayyeh and Abdulla Salahudeen

Renal disease is an important complicating feature of cancer, and also of its treatments and complications. Renal syndromes such as the syndrome of inappropriate antidiuretic hormone (SIADH) and tumor lysis syndrome (TLS) are commonly associated with cancer. However, cancer is also associated with other electrolyte abnormalities and renal syndromes (Box 68-1). The frequency of kidney complications in patients with cancer, and especially those undergoing treatment, is leading oncologists to include a nephrologist as part of a team approach for cancer therapy.[1] In this chapter we review the major renal syndromes associated with cancer or its treatment.

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is the most common reason why nephrologists are consulted with regard to hospitalized cancer patients and includes pre-renal, intrarenal, and post-renal AKI (see also Chapter 69). In a recent survey, the rate of AKI in patients admitted to a comprehensive cancer center was 12%, nearly threefold higher than in most noncancer settings, and AKI was also associated with poorer clinical outcomes.[2,3] AKI developed in 55% of these cancer patients after they had been in the hospital for at least 48 hours (Fig. 68-1). The significant risk factors for AKI in these patients were diabetes, hyponatremia, and the use of intravenous radiocontrast, chemotherapy, and antibiotics.[2] Identifying cancer patients who are likely to develop AKI in the hospital may allow kidney injury prevention (KIP) strategies to avert AKI and improve clinical outcomes.[2]

Pre-renal Acute Kidney Injury

Nearly one third of AKI in cancer patients is pre-renal resulting from reduced renal perfusion caused by volume depletion from chemotherapy-induced nausea, vomiting, and diarrhea. In addition, chemotherapy-associated hypoalbuminemia contributes to the reduction in effective plasma volume, adding further to the reduction in renal perfusion. Extracellular volume depletion as a result of third spacing as in malignant ascites or pleural effusion, or insensible losses from neutropenic fever can also lead to pre-renal AKI. Similarly, renal fluid loss may occur as a consequence of hypercalcemia-associated nephrogenic diabetes insipidus, which can be compounded by the renal vasoconstrictive effect of hypercalcemia (see Chapter 10).[4] In patients with pre-renal dysfunction, use of nephrotoxic agents such as intravenous radiocontrast, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, and various antibiotics and antiviral and antifungal agents may result in enhanced nephrotoxicity leading to intrarenal AKI.

Intrarenal Acute Kidney Injury

Intrarenal AKI is one of the commonest forms of renal injury in cancer patients, often preceded by pre-renal AKI. The cause is often multifactorial (see Chapter 69). Several chemotherapeutic agents as well as other medications commonly used in cancer patients can cause intrarenal AKI. AKI in this setting is referred to as toxic acute tubular necrosis (ATN), which tends to be nonoliguric and milder in severity (Table 68-1). In contrast, cancer patients with sepsis and septic shock sustain ischemic ATN, which is often oligoanuric and severe. Most of these patients with septic shock and ischemic ATN would have received chemotherapy with or without hematopoietic stem cell transplantation (HSCT) and are often neutropenic. Renal recovery is slow in ischemic ATN and often incomplete.[5] Nevertheless, the presence of cancer alone should not preclude patients from being considered for dialysis. It is our practice to provide dialysis for at least 48 hours to critically ill cancer patients with advanced renal failure so that a proper evaluation can be made for the role of continuing dialysis. The majority of cancer patients in septic shock receive large volume resuscitation, blood products, and vasopressors while oligoanuric and therefore require continuous renal replacement therapy (CRRT).[2,5] The occurrence of AKI remains an important obstacle for the effective use of chemotherapeutic agents. Conversely, high and repetitive doses of chemotherapy, concurrent with other nephrotoxic agents, render the patient vulnerable to AKI.

Post-renal Acute Kidney Injury

In patients with genitourinary cancers, obstruction of the urinary tract is a likely cause for acute (post-renal) AKI or chronic kidney disease (CKD). Cancers commonly associated with urinary tract obstructions are cancers of the bladder, prostate, cervix, and ovary. Among these, patients who have undergone pelvic irradiation or urogenital surgery with urinary diversion are more likely to have urinary obstruction. The obstruction seen in patients with cervical and ovarian cancers can be a result of metastatic spread involving the ureters or can be caused by ureteral or bladder compression from lymphadenopathy (Fig. 68-2). In HSCT recipients with BK infection, ureteral obstruction is not an uncommon cause of renal impairment. Although ultrasound (US) examination of kidney and bladder is the screening test for obstruction in these patients, occasionally the US findings may be negative if the obstruction is of short duration or when renal encasement by retroperitoneal cancer has occurred. In patients in whom the index of suspicion for obstruction is high, repeat US examination, nephrostogram, or both may become necessary.

MYELOMA AND AMYLOIDOSIS

Myeloma and amyloidosis are discussed in detail in Chapters 65 and 27, respectively. Renal involvement occurs in about 50% of patients with multiple myeloma, but the degree of renal involvement varies depending on the type of myeloma.[6,7] Myeloma with light-chain overproduction is commonly associated with renal involvement, with as many as 50% of patients requiring dialysis.[8] The type of light

Kidney Disease Associated with Common Cancers and Cancer Treatments

Leukemia

Common: AKI from sepsis, volume depletion, drug toxicity

Rare: Infiltrative disease, glomerulonephritis, AKI from TLS

Myeloma

Common: Myeloma kidney, AKI from volume depletion

Rare: Amyloidosis, LCDD, Fanconi syndrome, AKI from hypercalcemia, MPGN type I

Lymphoma

Common: AKI from TLS and volume depletion

Rare: Obstructive uropathy, infiltrative disease, minimal change disease (Hodgkin), MPGN type 1 (non-Hodgkin lymphoma)

Renal Cell Carcinoma

Common: Anti-VEGF toxicity

Rare: Obstructive uropathy, membranous nephropathy

Lung and Head and Neck Cancer

Common: Platinum toxicity

Rare: SIADH, membranous GN

Genitourinary and Gynecologic Cancers

Common: Obstructive uropathy

Rare: Platinum toxicity

Kidney Disease in Commonly Used Cancer Treatments

Common: AKI, tubulopathy, and CKD from chemotherapeutic agents (e.g., cisplatin, ifosfamide, methotrexate); complications of conditioning regimen and HSCT, and from toxicities of targeted anticancer therapies (including proteinuria, TMA, and hypertension)

Rare: Radiation nephritis, TMA, glomerulonephritis

Obstructive Uropathy

Common: Genitourinary and gynecologic cancers

Rare: Lymphoma

Box 68-1 Kidney disease associated with common cancers and cancer treatments. *AKI,* Acute kidney injury; *CKD,* chronic kidney disease; *GN,* glomerulonephritis; *HSCT,* hematopoietic stem cell transplantation; *LCDD,* light-chain deposition disease; *MPGN,* membranoproliferative glomerulonephritis; *SIADH,* syndrome of inappropriate antidiuretic hormone; *TLS,* tumor lysis syndrome; *TMA,* thrombotic microangiopathy; *VEGF,* vascular endothelial growth factor.

Timing of AKI Following Admission to a Cancer Center

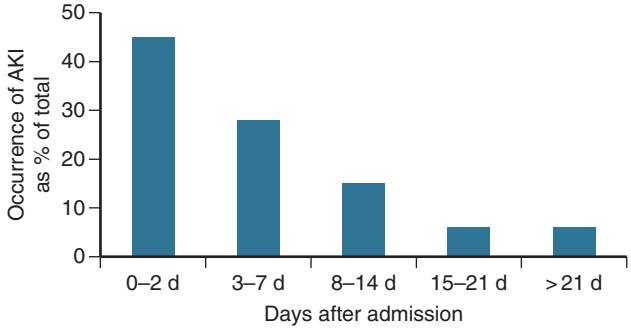

Figure 68-1 Timing of acute kidney injury (AKI) after admission to a cancer center. In 55% of patients, AKI developed after 48 hours after admission, suggesting an opportunity to undertake proactive measures to potentially prevent AKI. *(Modified from reference 2.)*

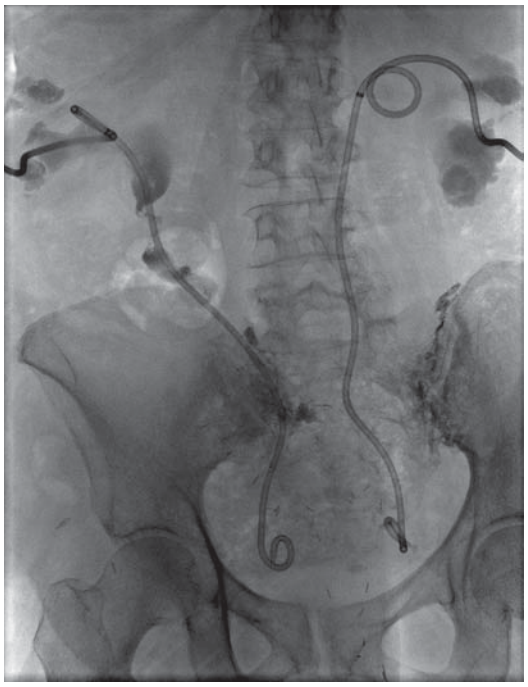

Figure 68-2 Nephrostogram showing bilateral obstructive uropathy (dilated pelvicalyceal system) in a patient with advanced rectal cancer treated with chemotherapy, radiation, and surgery. Bilateral nephroureteral catheters are in place for urine drainage. *(From the University of Texas MD Anderson Cancer Center, 2013.)*

chain is also important; cast nephropathy and renal amyloidosis are common with lambda light chains, whereas severe proximal tubular injury causing Fanconi-like syndrome and light-chain deposition disease are common with kappa light chains. Treatment of myeloma with dexamethasone, thalidomide or related compounds such as lenalidomide, or proteasome inhibitors such as bortezomib, followed by myeloablative HSCT, has substantially improved the survival of myeloma patients.[9] Although renal involvement of myeloma is associated with poorer clinical outcomes, kidney biopsies are not routinely performed in cancer centers. However, prompt institution of chemotherapy often leads to rapid renal recovery, occasionally obviating the need for dialysis. Reduction in serum light-chain levels with a combination of chemotherapy and plasma exchange or high-cutoff dialysis has also been shown to correlate with renal recovery, but currently there are no data to suggest that adding extracorporeal removal of light chains to myeloma therapy provides any added advantage.[8] The presence of renal failure or being on dialysis is no longer a contraindication to HSCT for myeloma.[10] Nevertheless, these patients require dose reduction of lenalidomide and melphalan to avoid major systemic toxicities. Unlike the initial reports that suggested that recovery of renal function after HSCT occurs in a sizable proportion of patients on dialysis because of myeloma, this seems to be the exception rather than the rule in clinical practice.[11,12]

Primary systemic (AL) amyloidosis in patients with light-chain disease is another infrequent manifestation of myeloma. When amyloidosis does complicate myeloma, it carries a grave prognosis. Large kidneys, gross proteinuria, and characteristic renal deposition of amyloid are hallmarks of renal amyloidosis and, based on autopsy studies, it occurs in about 5% to 10% of patients with myeloma.[13] The

Commonly Used Treatments in Cancer Patients that May Cause Renal Toxicity		
Tubular Injury	**Glomerular Injury**	**Renal Vascular Injury**
Acute Tubular Injury	**FSGS**	**Thrombotic Microangiopathy**
Platinums, zoledronate, ifosfamide, mithramycin, pentostatin, imatinib, diaziquone, pemetrexed	Interferon (IFN), pamidronate, zoledronate	Bevacizumab (anti-VEGF monoclonal antibody)
Tubular Syndromes	**Minimal Change Disease**	**Tyrosine Kinase Inhibitors**
Renal Tubular Acidosis	IFN, pamidronate	Sorafenib, sunitinib, imatinib
Ifosfamide, amphotericin, calcineurin inhibitors	**Proteinuria**	**Other Agents**
Fanconi-like Syndrome	Sorafenib, sunitinib, vatalanib, axitinib	Gemcitabine, mitomycin C, interferon-α (IFN-α)
Cisplatin, ifosfamide, azacitidine, diaziquone, imatinib, pemetrexed		
Salt Wasting		
Cisplatin, azacitidine		
Magnesium Wasting		
Cetuximab, cisplatin, panitumumab		
Nephrogenic Diabetes Insipidus		
Cisplatin, ifosfamide, pemetrexed		
Acute Interstitial Nephritis		
Sorafenib, sunitinib		
Crystal Nephropathy		
Methotrexate, acyclovir		
SIADH		
Cyclophosphamide, vincristine		

Table 68-1 Commonly used treatments in cancer patients that may cause renal toxicity. *FSGS,* Focal segmental glomerulosclerosis; *SIADH,* syndrome of inappropriate antidiuretic hormone.

treatment of AL amyloidosis with chemotherapy followed by HSCT has been shown to improve patient survival and reduce proteinuria.[14]

ANTI–VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY

The discovery that vascular endothelial growth factor (VEGF) is an important mediator of tumor growth and angiogenesis led to the development of drugs targeting VEGF and VEGF receptors (VEGFRs) for cancer therapy.[15] However, VEGF is also an essential growth factor to maintain glomerular endothelial health. VEGF is secreted by podocytes and traverses the basement membrane where it binds to VEGFRs on endothelial cells and maintains glomerular endothelial cell integrity and filtration barrier function (Fig. 68-3). Anti-VEGF drugs such as the monoclonal antibody bevacizumab, as well as drugs that inhibit tyrosine kinase such as sunitinib, block VEGF function. This leads to dysfunction of the glomerular endothelial cells and disruption of the filtration barrier, resulting in proteinuria, thrombotic microangiopathy (TMA), hypertension, and renal failure.[16,17] Mild and asymptomatic proteinuria is common, and heavy proteinuria occurs in less than 10% of treated patients.[18] Hypertension or aggravation of preexisting hypertension is common. The reported incidence varies from 17% to 80%.[19,20] The onset of hypertension reflects the efficacy of VEGF blockade, perhaps explaining why bevacizumab-induced hypertension correlates with clinical outcome in patients with advanced colorectal cancer.[21] Hypertension is managed with the use of standard antihypertensive medications, although the use of ACE inhibitors or ARBs is preferable in patients with proteinuria.[20] The occurrence of renal side effects with anti-VEGF therapy often necessitates a reduction in dose and possibly discontinuation of the drug.

TUMOR LYSIS SYNDROME

Patients with high-grade lymphoma, acute leukemia, and other rapidly proliferating tumors are prone to TLS, especially with the initiation of chemotherapy (see Chapters 69 and 71). Among these, patients with Burkitt lymphoma who are treated with rituximab are particularly at risk. Volume depletion, hypotension, large primary or metastatic tumor load, preexisting CKD, and concurrent exposure to potential nephrotoxic agents are common risk factors associated with TLS-induced AKI. Cell lysis leads to hyperuricemia, hyperkalemia, hyperphosphatemia, and acidosis causing AKI, primarily from the deposition of uric acid crystals in the tubules. Recent studies suggest that hyperuricemia may also play a role in TLS-associated AKI independent of crystals, possibly because of the effect of uric acid to stimulate inflammation and endothelial dysfunction.[23] Tissue deposition of calcium phosphate crystals may also occur, including in the myocardium, where it may have a role in causing severe arrhythmias. A proactive approach is adopted especially in patients with high risk for TLS, which involves hydration to maintain a high urine output (>100 ml/h) and the use of allopurinol or recombinant uricase (rasburicase) to block the increase in serum uric acid levels. Rasburicase degrades uric acid to water-soluble allantoin. Whether rasburicase, which is costly but more effective at lowering uric acid levels, is superior to allopurinol in the prevention of TLS-associated AKI is uncertain.[24] Dialysis should be considered early in

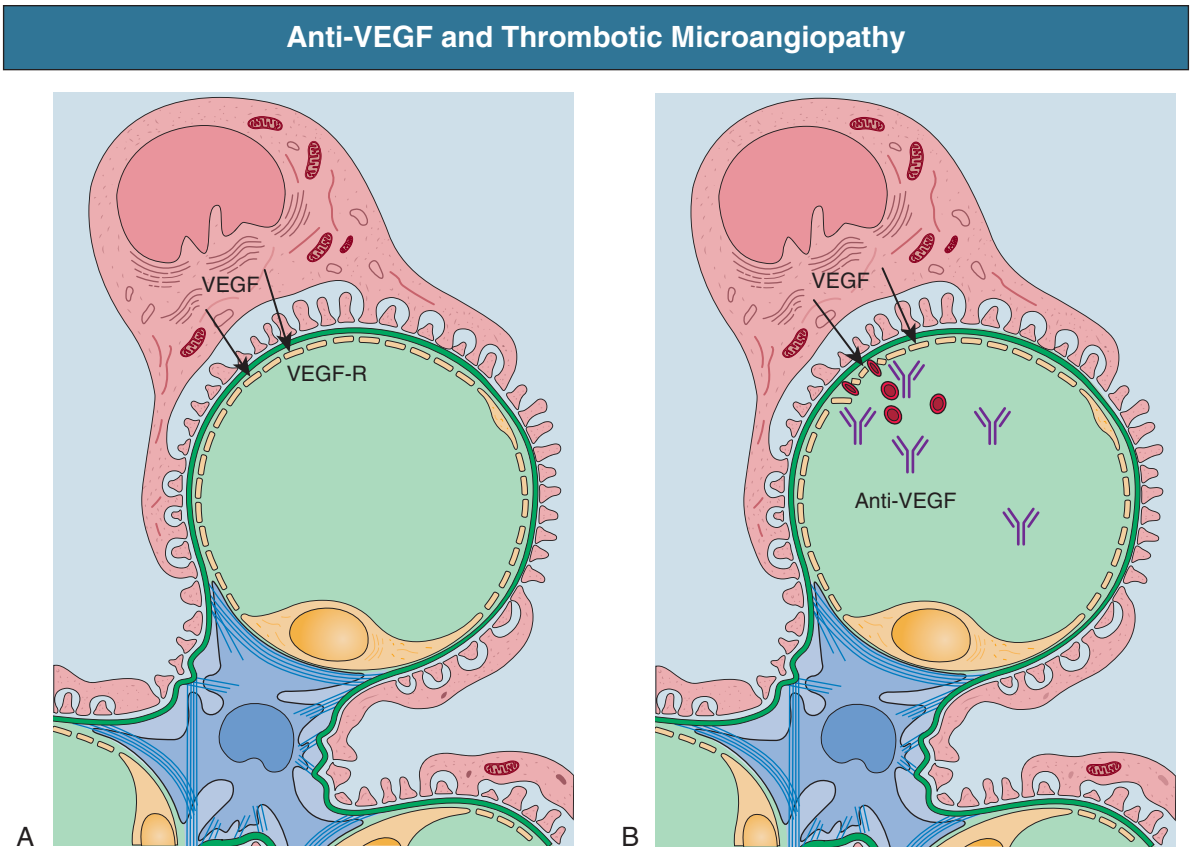

Figure 68-3 Anti–vascular endothelial growth factor (VEGF) and thrombotic microangiopathy. A, Under normal circumstances, VEGF is produced constitutively by the podocyte and crosses the glomerular basement membrane *(arrows)* to bind VEGF receptors (VEGF-Rs) on the endothelial cells, where it maintains endothelial health and integrity. **B,** When anti-VEGF antibody is administered, the antibody binds to the VEGF and blocks its binding to the endothelial cell, resulting in endothelial cell injury and thrombotic microangiopathy. Key: Platelets (red circular disks in **B**).

patients with TLS who develop signs of progressive renal failure (rising serum creatinine, e.g., over 1.5 mg/dl [130 µmol]) because even mild renal dysfunction can limit the kidneys' ability to eliminate the rapidly accumulating high levels of potassium and other tumor lysis products that occur in massive TLS. Furthermore, accumulation of tumor lysis products in turn can aggravate renal injury.[25] Patients at risk for TLS need close laboratory monitoring, and in patients with severe TLS and especially those with reduced urine output and kidney function, continuous dialysis or CRRT may be required to control hyperkalemia and persistent hyperphosphatemia (Fig. 68-4).[26] In many patients dialysis can be discontinued after 2 to 3 days provided good urine output and sufficient renal function are present.

CANCER-RELATED GLOMERULONEPHRITIS

Although the presence of cancer-related glomerulonephritis (GN) seldom changes the oncologist's approach to the underlying cancer management, this relatively rare entity is of considerable interest to nephrologists because it may provide insights into the pathophysiology of primary GN. Rarely proteinuria or nephrotic syndrome can be the presenting feature of cancer. Membranous nephropathy (MN) is the most common glomerular pathology associated with solid tumors; in the largest series of 240 patients with kidney biopsy–proven MN, a cancer diagnosis was noted in 10%, but a cancer diagnosis in many was made after the diagnosis of MN.[27] Common cancers associated with MN are lung, gastric, colon, and renal carcinomas, but several other solid tumors can also be associated—for example, prostate and breast cancers (Table 68-2).[28] In Hodgkin disease, the most common lesion is minimal change disease (MCD; see Chapter 17), possibly related to tumor-related T cell dysfunction. Chronic lymphocytic leukemia is commonly associated with membranoproliferative glomerulonephritis (MPGN; see Chapter 21), especially in the presence of cryoglobulinemia. HSCT is associated with MN, and, rarely, an MCD lesion can be a manifestation of chronic graft-versus-host disease (GVHD).[29] Use of interferon-α (IFN-α) anti-VEGF therapies, and bisphosphonates in cancer therapy have also been associated with various glomerular diseases and TMA.[28]

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Among the types of HSCT, the myeloablative allogeneic HSCT, which requires administering higher doses of irradiation, chemotherapy, or a combination, carries the highest risk for development of AKI—as high as 70%—and occurrence of AKI in any form of HSCT is associated with poor clinical outcomes including survival.[30] The causes of AKI in HSCT are multifactorial, and in addition to usual and anytime causes of AKI such as volume depletion, intravenous contrast, sepsis, and drug toxicity, HSCT can be associated with a few specific syndromes that tend to occur during certain time intervals after HSCT (Table 68-3). A rare but early form of AKI may occur within hours after HSCT and is caused by hemolysis-related

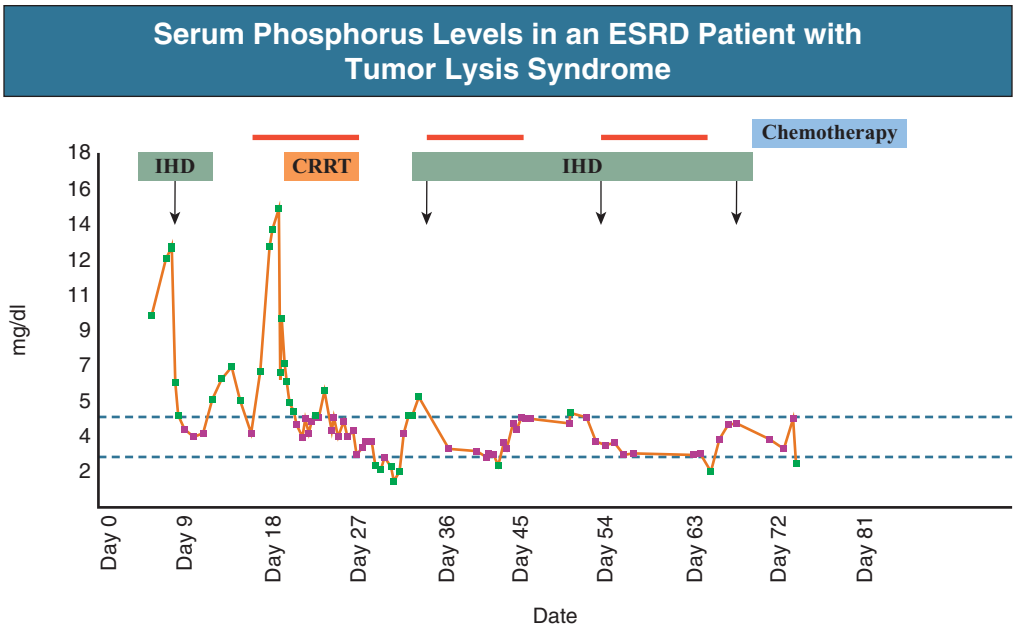

Figure 68-4 Serum phosphorus levels in an ESRD patient with tumor lysis syndrome. Shown is the effect of continuous renal replacement therapy (CRRT) or intermittent hemodialysis (IHD) *(arrows)*.

pigment nephropathy from the stem cell preservative dimethyl sulfoxide. Within days after HSCT, the rare "engraftment syndrome," consisting of fever, skin rash, and pulmonary edema, which has been ascribed to marked cytokine release related to neutrophil recovery, can lead to multiorgan failure including AKI. Within weeks to months, several syndromes may occur that can cause AKI, including veno-occlusive disease (VOD) of the liver, GVHD, TMA, and BK virus nephropathy.[31] VOD is a serious and potentially fatal complication of myeloablative HSCT that is fortunately on the decline as a result of less intensive conditioning regimens.[32] Features of VOD such as fluid retention, low urinary sodium excretion, and abnormal liver functions suggest that it is a form of hepatorenal syndrome. Severe VOD may result in multiorgan failure including AKI necessitating dialysis and is associated with a very high mortality.[25] Defibrotide is an oligonucleotide with antithrombotic and fibrinolytic activity that carries minimal hemorrhagic risk and has been shown to improve VOD outcomes, but the drug is currently awaiting U.S. Food and Drug Administration (FDA) approval.[33] Late-onset AKI (20 to 99 days) after hematopoietic cell transplantation (HCT) is usually caused by TMA as a result of renal endothelial and mesangial cell (mesangiolysis) injury secondary to irradiation used for conditioning before HSCT or as a complication of GVHD. TMA resembles hemolytic uremic syndrome in that thrombocytopenia, schistocytosis, anemia, and elevated lactate dehydrogenase (LDH) are present. Later in the course (after 3 months), use of nephrotoxic agents such as calcineurin inhibitors is common as a long-term cause of progressive renal dysfunction, especially when their doses are escalated to prevent or manage GVHD in patients who have undergone allogeneic transplants. Patients who have undergone HSCT show a decline in their estimated glomerular filtration rate (eGFR) by at least 25 mL/min/1.73 m^2, irrespective of age,[34] but patients seldom develop end-stage renal disease (ESRD) as a complication of HSCT. BK virus infection occurs in up to 70% of HSCT recipients, more often in the unrelated cord blood transplants conditioned with myeloablative regimens.[35] BK cystitis, which usually affects the bladder but may involve the kidneys and ureters, occurs early in the course of HSCT and can persist. Treatment options are limited; cidofovir is sometimes used but is marginally effective and also is associated with its own nephrotoxicity. Infection of the ureters may cause ulcerations, resulting in hematuria, ureteral stenosis, and obstruction. Temporary placement of a percutaneous nephrostomy catheter relieves obstruction and significantly improves kidney function.[36]

ELECTROLYTE ABNORMALITIES

Although electrolyte abnormalities are common in cancer patients, factitious laboratory findings are also not infrequent and should be kept in mind to avoid unnecessary admission, investigation, and potentially harmful treatment. Paraproteins, especially IgM, may cause assay interferences with several tests, mostly because of physical interferences with reagents, reactions, or both.[37] Pseudohyperkalemia may occur in patients with acute leukemia, chronic lymphocytic leukemia, and chronic myeloproliferative disorders, mostly because of cells releasing potassium during storage. When factitious values are suspected, careful collection and prompt analysis of repeat samples (often including comparison of plasma and serum drawn values) are required.

Hyponatremia is the most common true electrolyte abnormality and affects nearly 50% of hospitalized cancer patients.[38] Hyponatremia is frequently caused by SIADH and can be associated with both euvolemia and increased extracellular volume. SIADH was originally described in small cell lung cancer, but it may occur with non–small cell lung cancer, head and neck cancers, and a number of hematologic cancers.[39,40] Pain and pain medications such as morphine and its derivatives, antidepressants, and several chemotherapeutic agents may also cause hyponatremia either by increasing arginine vasopressin (AVP) secretion or by enhancing its effect at the renal tubule. Fluid restriction to correct hyponatremia is difficult in cancer patients, especially in patients receiving chemotherapy or HSCT, because these procedures are associated with high fluid intake. Oral sodium chloride and loop diuretics are only partly effective, whereas

Cancer-Associated Glomerular Diseases	
Malignancy	**Glomerular Diseases**
Lung cancer	MN, MCD, MPGN type 1, IgAN, FSGS, CGN, TMA
Colon cancer	MN, MCD, CGN
Stomach cancer	MN
Pancreas cancer	MN, MCD, IgAN
Bladder cancer	MCD
Renal cell cancer	AAA, CGN, IgAN, MCD, FSGS, MPGN
Prostate cancer	MN, CGN
Breast cancer	MN, FSGS, MPGN type 1, TMA
Esophageal cancer	MPGN type 1, FSGS
GI stromal tumor	AAA
Gastric cancer	MPGN type 1, CGN, TMA
Spleen sarcoma	AAA
Head and neck cancer	MN, IgAN
Wilms tumor	MN, MPGN type 1
Teratoma	MN
Ovarian cancer	MN, MCD
Cervical cancer	MN
Endometrial cancer	MN
Tongue cancer	IgAN
Mesothelioma	MCD
Melanoma	MN, MPGN type 1
Skin cancers (basal, squamous cell)	MN
Pheochromocytoma	MN
Thymoma	MCD, FSGS, CGN, MPGN type 1
Hodgkin disease	MCD, MN, MPGN type 1, IgAN, FSGS, CGN, AAA, anti-GBM
Non-Hodgkin disease	MN, MCD, MPGN type 1, IgAN, FSGS
CLL	MN, MCD, MPGN type 1, FSGS, CGN
AML	MN, FSGS
CML	MN, MCD, MPGN type 1
MGUS	MPGN type 1
T cell leukemia	FSGS

Table 68-2 Cancer-associated glomerular diseases. Includes small cell, non–small cell, squamous cell, and bronchogenic cancers. *AAA,* AA amyloidosis; *AML,* acute myelogenous leukemia; *CGN,* crescentic glomerulonephritis; *CLL,* chronic lymphocytic leukemia; *CML,* chronic myelogenous leukemia; *FSGS,* focal segmental glomerulosclerosis; *GBM,* glomerular basement membrane; *GI,* gastrointestinal; *IgAN,* IgA nephropathy; *MCD,* minimal change disease; *MGUS,* monoclonal gammopathy of unclear significance; *MN,* membranous nephropathy; *MPGN,* membranoproliferative glomerular nephritis; *TMA,* thrombotic microangiopathy. *(From reference 28.)*

use of V_2 receptor antagonists such as tolvaptan is very effective in correcting hyponatremia.[41] Although SIADH is common in cancer patients, in one third of patients hyponatremia may result from volume depletion. Hypovolemic hyponatremia should be correctly identified from the history, physical examination, and urinary sodium excretion (see Chapter 71). In these patients normal saline repletion promptly corrects the hyponatremia.

Causes of Acute Kidney Injury (AKI) and Other Renal Disease in Relation to the Timing of Hematopoietic Stem Cell Transplantation (HSCT)	
Peri-HSCT	Tumor lysis syndrome from conditioning regimen (rare) Systemic toxicity from conditioning regimen—for example, volume depletion (common) Dimethyl sulfoxide (DMSO)–induced hemolysis, acidosis, and pigment nephropathy (rare)
Days to weeks after HSCT	Pre-renal AKI from volume depletion, AKI from neutropenic sepsis and drug toxicity (common) AKI related to engraftment syndrome (rare)
Weeks to months after HSCT	AKI from sepsis, volume depletion, drug and radiocontrast toxicity (common) AKI from veno-occlusive disease of the liver, graft-versus-host disease (GVHD), thrombotic microangiopathy, and BK virus nephropathy (rare)
Months to years after HSCT	CKD from previous AKI, from continuous use of calcineurin inhibitors especially with GVHD, and from preexisting cancer—for example, myeloma (common)

Table 68-3 Causes of AKI and other renal disease in relation to the timing of HSCT.

Hypernatremia is much less frequent in hospitalized cancer patients compared with hyponatremia (3% vs. 47%), but it is associated with higher mortality and longer hospital stays.[42] Most hypernatremia occurs in the hospital and is observed primarily in critically ill patients with leukemia and HSCT who are receiving loop diuretics. Treatment of hypernatremia is discussed in Chapter 8.

Other electrolyte abnormalities that are common in cancer patients, especially those who are receiving chemotherapy, include hypokalemia, hypomagnesemia, and hypophosphatemia. Vomiting and diarrhea and poor nutrition from chemotherapy can account for many of these abnormalities. However, severe abnormalities are usually caused by drug-induced tubular injury resulting from an acquired form of Fanconi syndrome. Ifosfamide and cisplatin are the commonest agents, but κ light-chain myeloma can also be associated with acquired Fanconi syndrome. Cetuximab, which is often used for the treatment of colorectal cancer, can cause hypomagnesemia that occasionally can be severe. Under normal circumstances, epidermal growth factor (EGF) binds its receptor (EGFR) and stimulates magnesium reabsorption in the distal convoluted tubular cell. Cetuximab is an EGFR antibody that competes with EGF for its receptor, thereby inhibiting normal reabsorption of luminal magnesium and causing renal wasting.

When it comes to electrolyte replacement, the general principles of replacing present deficit and ongoing loss also apply in cancer patients. Patients with Fanconi-like syndrome and severe cetuximab-induced hypomagnesemia may require large amounts of parenterally administered electrolytes to correct their deficit and ongoing losses. The electrolyte requirement subsides with time, but extensive replacement may be required over weeks to months. Renal tubular acidosis (see Chapter 12) resulting from tubular bicarbonate loss is also common in patients with κ light-chain myeloma and in cancer patients treated with antineoplastic, antifungal, or calcineurin-inhibitor drugs and generally responds to oral alkali therapy.

Hypercalcemia is common in cancer patients with advanced cancer with bone metastasis and heralds a poor prognosis. Hypercalcemia is frequently associated with multiple myeloma and can

Management of Cancer-related Hypercalcemia

1. General measures: intravenous fluids followed by loop diuretics.
2. Administer calcitonin, corticosteroids, or both for acute and short-term calcium control.
3. If patient is severely symptomatic and with reduced urine output and impaired renal function, consider dialysis with low-calcium dialysate.
4. Start bisphosphonates for longer-term hypercalcemia control (adjust for renal dysfunction).
5. Treat cancer.
6. For bone resorption–associated hypercalcemia: Humanized anti-RANKL antibody (denosumab) may be more effective than bisphosphonates (under evaluation).
7. For PTHrP-related hypercalcemia: Humanized monoclonal antibody against human PTHrP may be more effective than bisphosphonates (under evaluation).

Box 68-2 Management of cancer-related hypercalcemia. *RANKL,* Receptor activator of nuclear factor κB ligand; *PTHrP,* parathyroid hormone–related protein.

be the presenting feature. Several mechanisms may underlie the tumoral hypercalcemia, such as elevated parathyroid hormone–related peptide (PTHrP) levels arising from the tumor cells as in lung cancer, ectopic vitamin D in certain lymphomas, or tumor resorption of bones as in advanced cancer (see also Chapter 10). Treatment of hypercalcemia often begins with vigorous administration of intravenous fluids (Box 68-2). Although corticosteroids and calcitonin are still useful, persistent hypercalcemia requires bisphosphonate therapy for longer-term control. Rarely dialysis with low-calcium dialysis bath can be used to reduce severe hypercalcemia in symptomatic patients, especially in the presence of renal impairment or inadequate urine output. Use of bisphosphonates, especially zoledronate and pamidronate, can be complicated by AKI and collapsing FSGS, respectively, but ibandronate, another drug in this class, is not known to be associated with renal toxicity.[43]

CANCER THERAPY IN CHRONIC KIDNEY DISEASE AND END-STAGE RENAL DISEASE PATIENTS

Patients with CKD or ESRD have a higher risk for developing cancers, especially renal cell carcinomas (see Chapter 89). Because of the renal failure, treating these patients with chemotherapeutic agents also poses several unique challenges. Pharmacokinetic modeling of chemotherapeutic agents in cancer patients on dialysis suggests that these agents in general tend to be overdosed.[44] Careful dosage and timing of dialysis are critical because overdosage can aggravate systemic toxicities with fatal consequences, whereas underdosage can lead to ineffective cancer treatment (see Chapter 77). Common risk factors for chemotherapy-induced nephrotoxicity include volume depletion, hypoalbuminemia (reduced effective plasma volume), metabolic derangements (hyperuricemia and hypercalcemia), older age, presence of diabetes and other comorbid conditions, underlying AKI or CKD, presence of sepsis, and concomitant use of other potential nephrotoxins. Therefore, optimizing the renal status of the CKD patient before chemotherapy—applying the KIP strategy—such as correcting volume status, adjusting the chemotherapeutic doses of certain drugs according to renal function, removing potential nephrotoxic agents, and taking precautionary measures against tumor lysis can reduce the chance for AKI and in turn chemotoxicity. Moreover, administration of certain chemotherapeutic agents such as platinum compounds requires dose adjustments and timing with dialysis. Other commonly used agents for cancer treatment that need consideration for dose adjustment for glomerular filtration rate and dialysis are melphalan, methotrexate, pemetrexed, capecitabine, hydroxyurea, fludarabine, etoposide, irinotecan, and lenalidomide.[45,46] When tumor lysis occurs in ESRD patients, it can be particularly challenging because of the lack of kidney function to eliminate the products of tumor lysis, and the institution of 2 to 3 days of CRRT or even continuous hemodialysis may become necessary (see Fig. 68-4). Moreover, in CKD-ESRD patients undergoing active cancer treatment, erythropoietin (EPO) should be used judiciously because several controlled trials have shown that higher doses can be associated with poorer cancer outcomes,[47] possibly as a result of stimulation of cancer growth by EPO itself. Use of EPO in this population should follow FDA guidelines and should be managed in consultation with the oncologist.

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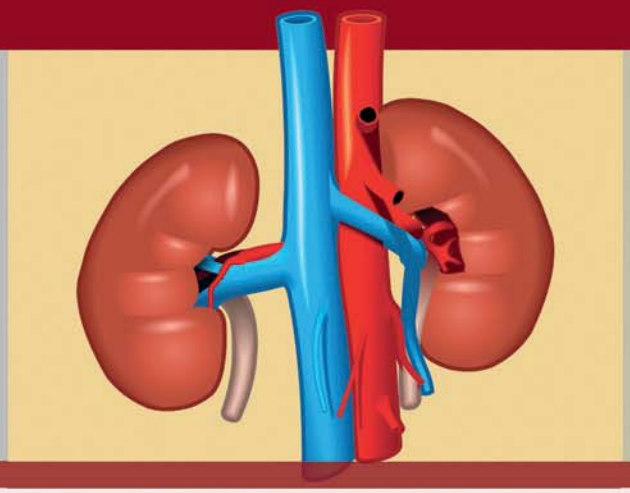

SECTION XIV

Acute Kidney Injury

CHAPTER 69

Pathophysiology and Etiology of Acute Kidney Injury

J. Ashley Jefferson, Joshua M. Thurman, and Robert W. Schrier

DEFINITION

Acute kidney injury (AKI) is a clinical syndrome denoted by an abrupt decline in glomerular filtration rate (GFR) sufficient to decrease the elimination of nitrogenous waste products (urea and creatinine) and other uremic toxins. This has traditionally been referred to as *acute renal failure* (ARF), but in recent years an effort has been made to implement the term *acute kidney injury* instead, and to develop a standardized definition of AKI. One proposed definition of AKI, for example, is a decline in kidney function over 48 hours as demonstrated by an increase in serum creatinine of greater than 0.3 mg/dl, an increase in serum creatinine of more than 50%, or the development of oliguria.[1] Staging criteria have also been developed based on the magnitude of the rise in serum creatinine and changes in the volume of urine output over 1 week,[1] and studies have validated that these staging criteria are of prognostic value (see Table 71-1).

ETIOLOGIC OVERVIEW

Although AKI is defined by a reduced GFR, the underlying cause of the renal impairment is most frequently a result of tubular and vascular factors. AKI can have a broad range of causes, and the differential diagnosis must be considered in a systematic fashion to avoid missing multiple factors that may be contributing to the condition. The traditional paradigm divides AKI into pre-renal, renal, and post-renal causes. Pre-renal uremia may be caused by hypovolemia or a decreased effective arterial volume. Post-renal obstructive renal failure is usually diagnosed by urinary tract dilation on renal ultrasound. Intrinsic renal causes of AKI should be considered under the different anatomic components of the kidney (vascular supply; glomerular, tubular, and interstitial disease; Fig. 69-1). Major extrarenal artery or venous occlusion must also be considered in the differential diagnosis (see Chapter 66). Similarly, disorders of the small intrarenal vasculature can result in AKI (e.g., vasculitis, thrombotic microangiopathy [TMA], malignant hypertension, eclampsia, postpartum states, disseminated intravascular coagulation [DIC], scleroderma; see Chapters 25, 29, 37, 44, and 64). All forms of acute glomerulonephritis (GN) can present as AKI, as can acute inflammation and space-occupying processes of the renal interstitium (e.g., drug-induced, infectious, and autoimmune disorders, leukemia, lymphoma, sarcoidosis).

In the hospital setting, pre-renal uremia and acute tubular necrosis (ATN) account for the majority of AKI cases,[2,3] often in the setting of AKI superimposed on chronic kidney disease (CKD), so-called "acute-on-chronic renal failure" (Fig. 69-2). The term *tubular necrosis* is a misnomer because the alterations are not limited to the tubular structures and true cellular necrosis in human ATN is often minimal. However, the term *acute tubular necrosis* is commonly used in the clinical setting. To make things even more confusing, the terms *acute tubular necrosis, acute renal failure,* and *acute kidney injury* are frequently used interchangeably in the literature. The term *acute tubular necrosis* should be reserved for cases of AKI in which a renal biopsy (if performed) shows the characteristic changes of tubular cell injury, and for patients with findings of tubular injury (such as renal tubular epithelial cells in the urine sediment) in an appropriate clinical setting (Fig. 69-3).

There are also significant geographic differences in the causes of AKI; the spectrum of causes in tropical countries is described in Chapter 70.

PATHOPHYSIOLOGY AND ETIOLOGY OF PRE-RENAL ACUTE KIDNEY INJURY

Impaired renal perfusion with a resultant fall in glomerular capillary filtration pressure is a common cause of AKI. In this setting, tubular function is typically normal, renal reabsorption of sodium and water is increased, and consequently urine chemistries reveal a low urine sodium (<20 mmol/l) and a concentrated urine (urine osmolality >500 mOsm/kg) as long as no loop diuretic has been administered.

A marked reduction in renal perfusion may overwhelm autoregulation and precipitate an acute fall in GFR. With lesser degrees of renal hypoperfusion, glomerular filtration pressures and GFR are maintained by afferent arteriolar vasodilation (mediated by vasodilatory eicosanoids) and efferent arteriolar vasoconstriction (mediated by angiotensin II). In this setting, AKI may be precipitated by agents that impair afferent arteriolar dilation (nonsteroidal anti-inflammatory drugs [NSAIDs]) or efferent vasoconstriction (angiotensin-converting enzyme [ACE] inhibitors and angiotensin receptor blockers [ARBs]).

Pre-renal AKI is commonly secondary to extracellular fluid volume depletion resulting from gastrointestinal losses (diarrhea, vomiting, prolonged nasogastric drainage), renal losses (diuretics, osmotic diuresis in hyperglycemia), dermal losses (burns, extensive sweating), or possibly sequestration of fluid, so-called third spacing (e.g., acute pancreatitis, muscle trauma). Renal perfusion may be impaired even in the setting of normal or even increased extracellular fluid. For example, renal perfusion may be reduced by a decreased cardiac output (heart failure) or by systemic arterial vasodilation with redistribution of cardiac output to extrarenal vascular beds (e.g., sepsis, liver cirrhosis). The presence of AKI in the setting of severe heart failure has been termed the *cardiorenal syndrome* and is often exacerbated by the use of ACE inhibitors and diuretics.

An unusual cause of pre-renal AKI is the hyperoncotic state. Infusion of large quantities of osmotically active substances such as mannitol, dextran, or protein can increase the glomerular oncotic

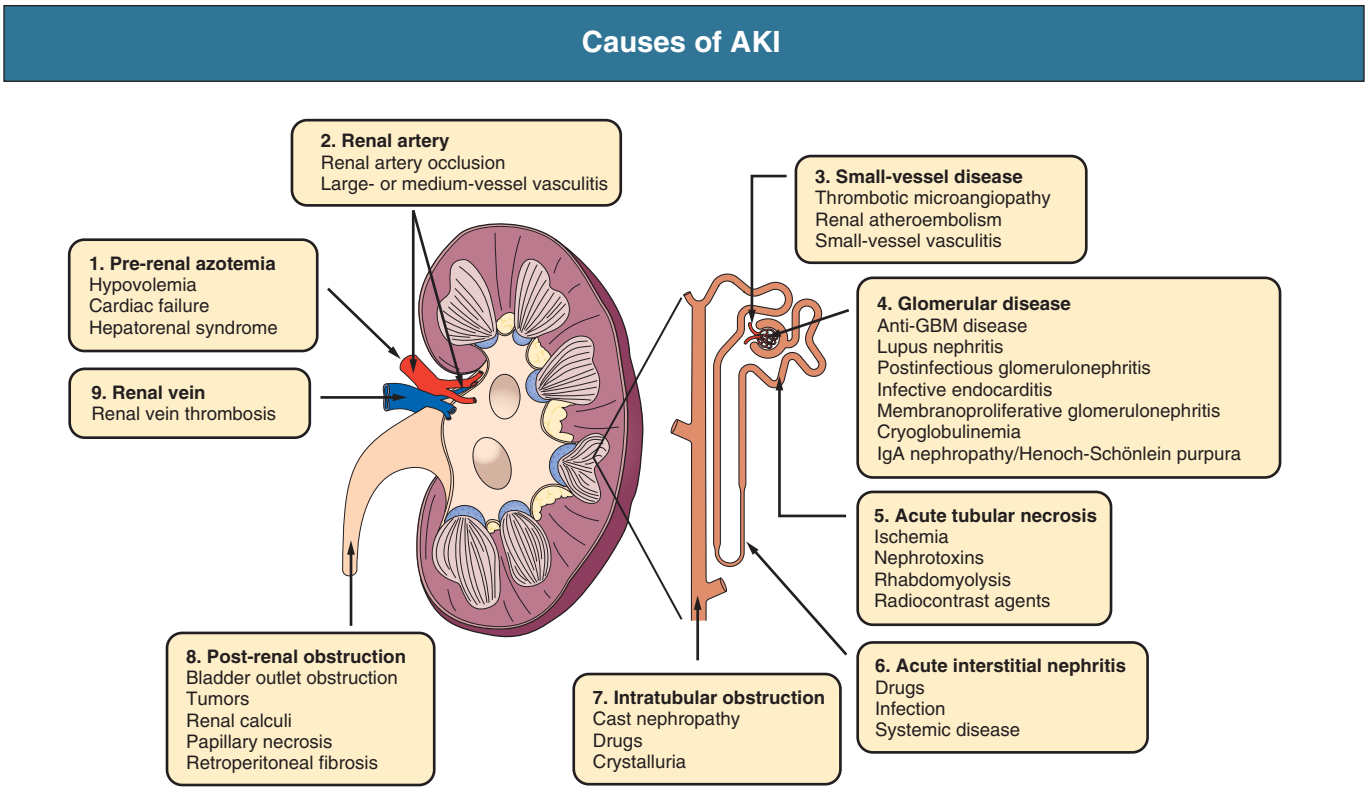

Figure 69-1 Causes of acute kidney injury (AKI). AKI is classified into pre-renal, renal, and post-renal causes. Renal causes of AKI should be considered under the different anatomic components of the kidney (vascular supply; glomerular, tubular, and interstitial disease). *GBM,* Glomerular basement membrane.

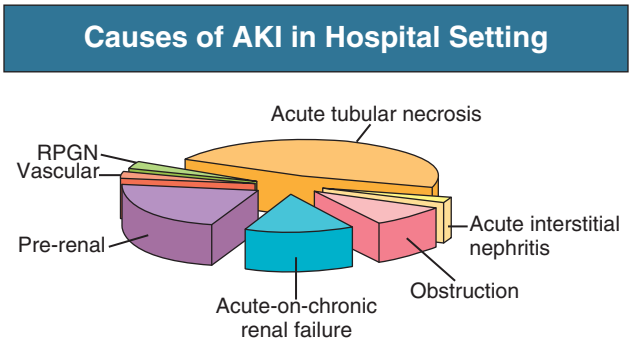

Figure 69-2 Causes of acute kidney injury (AKI) in the hospital setting. Madrid Acute Renal Failure Study (1996). *RPGN,* Rapidly progressive glomerulonephritis.

pressure enough to exceed the glomerular capillary hydrostatic pressure, which stops glomerular filtration, leading to an anuric form of AKI.

Pre-renal AKI can be corrected if the extrarenal factors causing the renal hypoperfusion are rapidly reversed. Failure to restore renal blood flow (RBF) during the functional pre-renal stage will ultimately lead to ischemic ATN and tubular cell injury.

PATHOPHYSIOLOGY AND ETIOLOGY OF POST-RENAL ACUTE KIDNEY INJURY

In any patient presenting with AKI, an obstructive cause must be excluded because prompt intervention can result in improvement or complete recovery of renal function (see Chapter 60). Post-renal forms of AKI are divided into intratubular and extrarenal. Tubular precipitation of insoluble crystals (phosphate, oxalate, uric acid, methotrexate, acyclovir, sulfonamides, indinavir, triamterene) or protein (hemoglobin, myoglobin, paraprotein) can increase intratubular pressure. If sufficiently high, this opposes glomerular filtration pressure and can decrease GFR. Similarly, obstruction of the extrarenal collecting system at any level (renal pelvis, ureters, bladder, or urethra) can lead to post-renal AKI. Obstructive uropathy is common in older men with prostatic disease and in patients with a single kidney or intra-abdominal, particularly pelvic, cancer. Severe ureteral obstruction is also seen with retroperitoneal fibrosis. Most causes of obstructive uropathy are amenable to therapy, and the prognosis is generally good, depending on the underlying disease. Obstructive uropathy is further discussed in Chapter 60.

PATHOPHYSIOLOGY OF ACUTE TUBULAR NECROSIS

Acute tubular necrosis commonly occurs in high-risk settings, which include vascular and cardiac surgery, severe burns, pancreatitis, sepsis, and chronic liver disease. ATN is responsible for most cases of hospital-acquired AKI and is usually a result of ischemic or nephrotoxic injury. In the intensive care unit, two thirds of cases of AKI are a result of the combination of impaired renal perfusion, sepsis, and nephrotoxic agents.[4]

The importance of combined injurious mechanisms is also emphasized by experimental data. In animal studies, severe and prolonged hypotension (<50 mm Hg for 2 to 3 hours in the rat) does not cause ATN. Similarly, in animal models, very high doses of single nephrotoxic agents are required to induce AKI. These features may

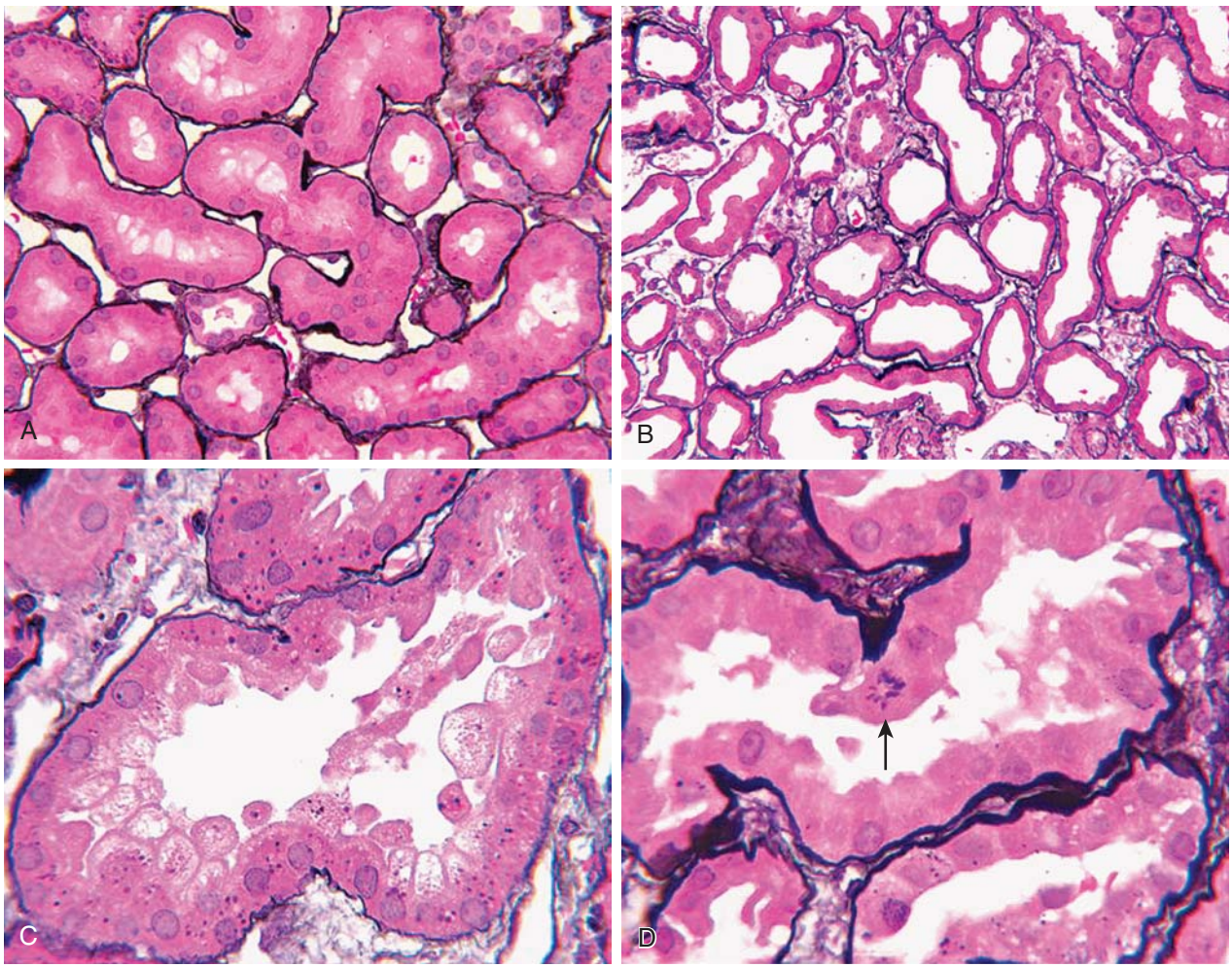

Figure 69-3 Renal pathology in acute tubular necrosis (ATN). A, Normal cortical renal tubules. **B** and **C,** ATN. Note the flattened epithelium, bare basement membranes, and intraluminal cellular debris. **D,** Recovering ATN showing a tubular epithelial cell mitotic figure *(arrow). (Courtesy Erika Bracamonte, MD, University of Arizona.)*

reflect an inherent resistance to tubular injury in animal models, but also illustrate the fact that a single insult alone is rarely sufficient to induce ATN. Fever may exacerbate ATN by increasing the renal tubular metabolic rate, thereby increasing adenosine triphosphate (ATP) consumption. In an experimental model (renal artery occlusion in the rat), renal ischemia for 40 minutes resulted in minimal renal injury at 32° C but marked renal injury at 39.4° C.

The typical course of uncomplicated ATN is recovery over 2 to 3 weeks; however, superimposed renal insults often alter this pattern. For example, episodes of hypotension induced by hemodialysis may lead to additional ischemic lesions, potentially prolonging renal functional recovery, and patients with AKI often have multiple comorbidities.

Histology

The typical features of ATN on renal biopsy include vacuolization and loss of brush border in proximal tubular cells. Sloughing of tubular cells into the lumen leads to cast obstruction, manifested by tubular dilation. Interstitial edema can produce widely spaced tubules, and a mild leukocyte infiltration may be present (see Fig. 69-3).

Despite the term *acute tubular "necrosis,"* frankly necrotic cells are not a common finding on renal biopsy, and histologic evidence of injury frequently involves only 10% to 15% of the tubules despite marked functional impairment. This implies that factors other than just tubular cell injury (such as vasoconstriction and tubular obstruction) are important in the loss of GFR.

TUBULAR INJURY IN ACUTE TUBULAR NECROSIS

The tubular damage is usually caused by a combination of ischemic injury resulting in depletion of cellular ATP and direct tubular epithelial cell injury by nephrotoxins. Most accept that the S_3 segment of the proximal tubule and the medullary thick ascending limb (mTAL) are particularly vulnerable to hypoxic injury (Fig. 69-4). There are several reasons for this vulnerability.[31]

Blood Supply

The blood flow to the kidney is not uniform, and most of it is directed to the renal cortex, where the cortical tissue partial oxygen pressure (P_{O_2}) is 50 to 100 mm Hg, for glomerular filtration. By contrast, the outer medulla and medullary rays are watershed areas receiving their blood supply from vasa recta. Countercurrent oxygen exchange occurs, leading to a progressive fall in P_{O_2} from cortex to medulla,

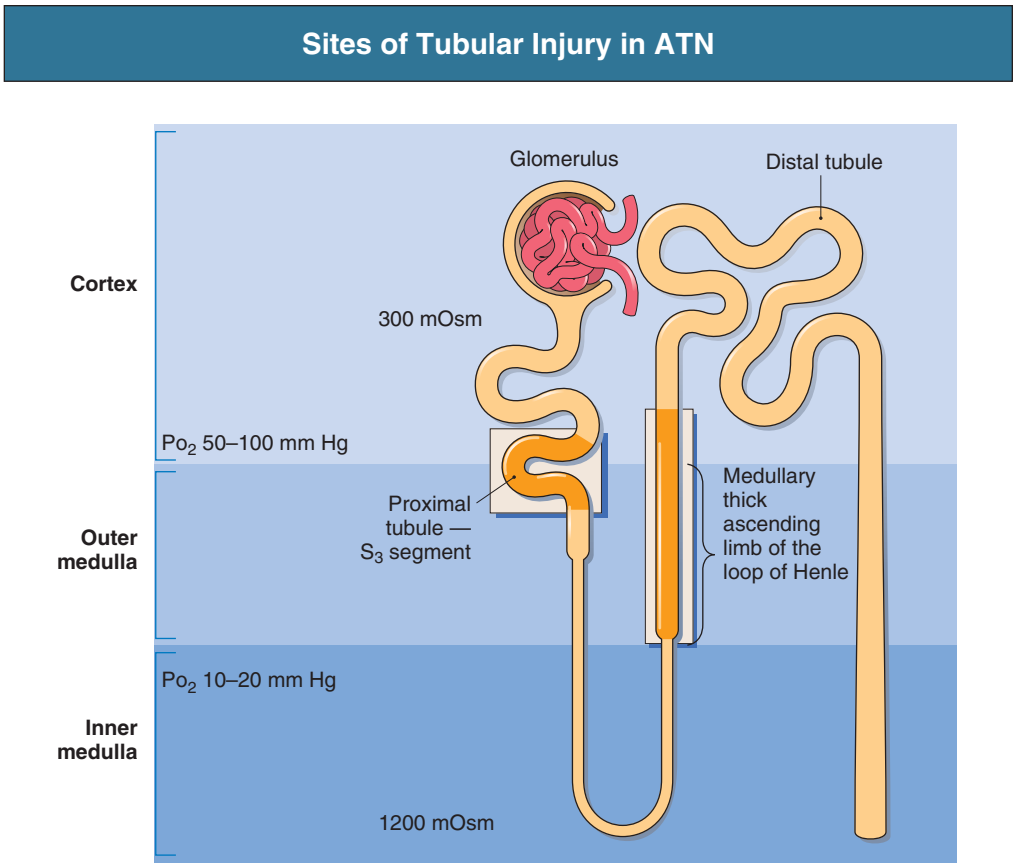

Figure 69-4 Sites of tubular injury in acute tubular necrosis (ATN). The S_3 segment of the proximal tubule and the medullary thick ascending limb are particularly vulnerable to ischemic injury because of the combination of borderline oxygen supply and high metabolic demands.

which results in medullary cells living on the "brink of hypoxia" (medullary P_{O_2} as low as 10 to 15 mm Hg). The S_3 segments of proximal tubule cells and distal mTALs are thus exposed to borderline chronic oxygen deprivation.

High Tubular Energy Requirements

The cells of the S_3 region and mTAL have high metabolic activity, principally because of sodium reabsorption driven by basolateral membrane Na^+-K^+-ATPase. Indeed, blocking sodium reabsorption in the mTAL with loop diuretics raises the medullary tissue P_{O_2} from about 15 to 35 mm Hg. Of note, the reduction of GFR in the setting of AKI may be renoprotective by diminishing sodium filtration and hence limiting ATP-dependent sodium reabsorption.

Glycolytic Ability of Tubular Cells

Proximal tubular cells have minimal glycolytic machinery and rely almost solely on oxidative phosphorylation for the generation of ATP. In contrast, mTAL cells have a large glycolytic capacity and are more resistant to hypoxic or ischemic insults.

Hemodynamic Factors in the Development of Acute Tubular Necrosis

Impaired Renal Autoregulation

Autoregulation normally occurs between systolic blood pressures of 80 and 150 mm Hg; within this range, RBF, glomerular pressures, and GFR are maintained. Below 80 mm Hg, this autoregulation fails, and ischemic injury may result. In certain conditions, such as aging or chronic renal disease, autoregulation is abnormal, and ischemic injury may occur more easily with reductions in perfusion pressure. In addition, experimental studies demonstrate impaired autoregulation in ischemic ATN. In settings of low renal perfusion (e.g., volume depletion, left ventricular failure, edematous states, renal artery stenosis), GFR may be dependent on autoregulation mediated by vasodilatory prostaglandins acting on the afferent arteriole and angiotensin II–mediated efferent arteriolar vasoconstriction to maintain glomerular pressure. Any interference with these mechanisms (e.g., administration of ACE inhibitors or acute inhibition of cyclooxygenase-1 [COX-1] or COX-2 by NSAIDs) may produce a precipitous fall in GFR.

Intrarenal Vasoconstriction

In established ATN, RBF is decreased by 30% to 50%. Indeed in AKI, rather than the normal autoregulatory renal vasodilation that occurs in response to decreased perfusion pressure, there is evidence of renal vasoconstriction. A number of vasoconstrictors have been implicated in this response, including angiotensin II, endothelin-1, adenosine, thromboxane A_2, prostaglandin H_2, leukotrienes C_4 and D_4, and sympathetic nerve stimulation (Fig. 69-5). Tubuloglomerular feedback (TGF) also contributes to this vasoconstriction. Some of these vascular abnormalities may be mediated by increased cytosolic calcium content in afferent arterioles as a result of ischemia. Disruption of the actin cytoskeleton in vascular smooth muscle cells may also impair autoregulation.

Tubuloglomerular Feedback

The role of TGF (see Chapter 2) in the setting of AKI may be partly beneficial because the resultant decrease in GFR limits sodium

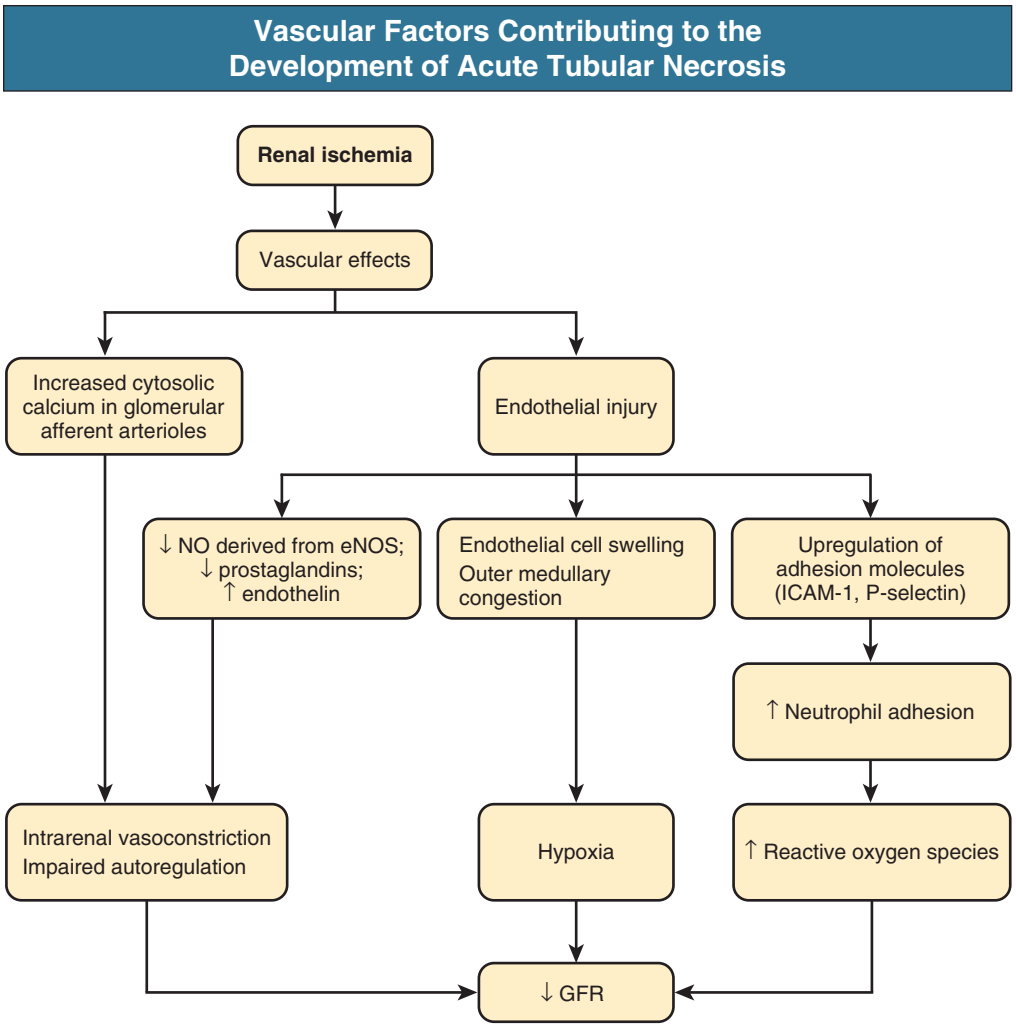

Figure 69-5 Vascular factors contributing to the development of acute tubular necrosis. *eNOS,* Endothelial nitric oxide synthase; *ICAM-1,* intercellular adhesion molecule 1; *GFR,* glomerular filtration rate; *NO,* nitric oxide.

delivery to damaged tubules and decreases ATP-dependent tubular reabsorption, protecting against intracellular ATP depletion augmenting renal injury. In this respect, adenosine A_1 receptor knockout mice with absent TGF have augmented AKI after ischemia reperfusion.

Endothelial Cell Injury and the Development of Acute Tubular Necrosis

Acute kidney injury is not limited to the tubular cell, and endothelial cell injury occurs partly as a result of acute renal ischemia and oxidant injury.[5] Endothelial injury is characterized by cell swelling, upregulation of adhesion molecules (with enhanced leukocyte–endothelial cell interactions), and impaired vasodilation (decreased endothelial nitric oxide synthase and vasodilatory prostaglandins) and may mediate some of the impaired autoregulation and intrarenal vasoconstriction described earlier. Endothelial injury within the peritubular capillaries (vasa recta) may produce congestion in the outer medulla, exacerbating hypoxic injury to the S_3 segment of the proximal tubule and the thick ascending loop of Henle.

Tubular Epithelial Cell Injury and the Development of Acute Tubular Necrosis

The tubular cell may be injured because of ischemia, with resulting depletion of cellular energy stores (ATP), or from direct cytotoxic injury. Following acute renal ischemia, tubular cell injury may also result from the restoration of RBF (reperfusion injury). Mediators of tubular cell injury include reactive oxygen species (ROSs), intracellular calcium influx, nitric oxide, phospholipase A_2, complement, and cell-mediated cytotoxicity. Mitochondrial injury can be caused by ROSs, depletion of antioxidants, and increased intracellular calcium. Disruption of mitochondrial function then exacerbates cellular injury because of disrupted energy metabolism and release of proapoptotic proteins. Autophagy is a mechanism by which cells degrade proteins, and it is a central part of the cellular response to stress and injury. Experimental work has shown that autophagy is important for removal of damaged mitochondria and recovery of tubular epithelial cells from ischemic injury. ROSs may be derived from local sources (including xanthine oxidase and COXs, and secondary to mitochondrial injury) or from infiltrating leukocytes. In models of ischemic ATN, a variety of methods that inhibit ROSs protect against renal injury.[6] Hypoxia inducible factor (HIF) and downstream mediators such as heme oxygenase 1 may protect cells against ischemic injury.[7]

Factors that affect the integrity and function of the renal tubular epithelial cells and contribute to the reduction in GFR include the following (Fig. 69-6):

Cell death—Despite the term *acute tubular necrosis,* only a small percentage of tubular cells undergo cell death, and of these, many actually die by apoptosis rather than necrosis. Indeed, recent studies in animal models have shown amelioration of renal injury

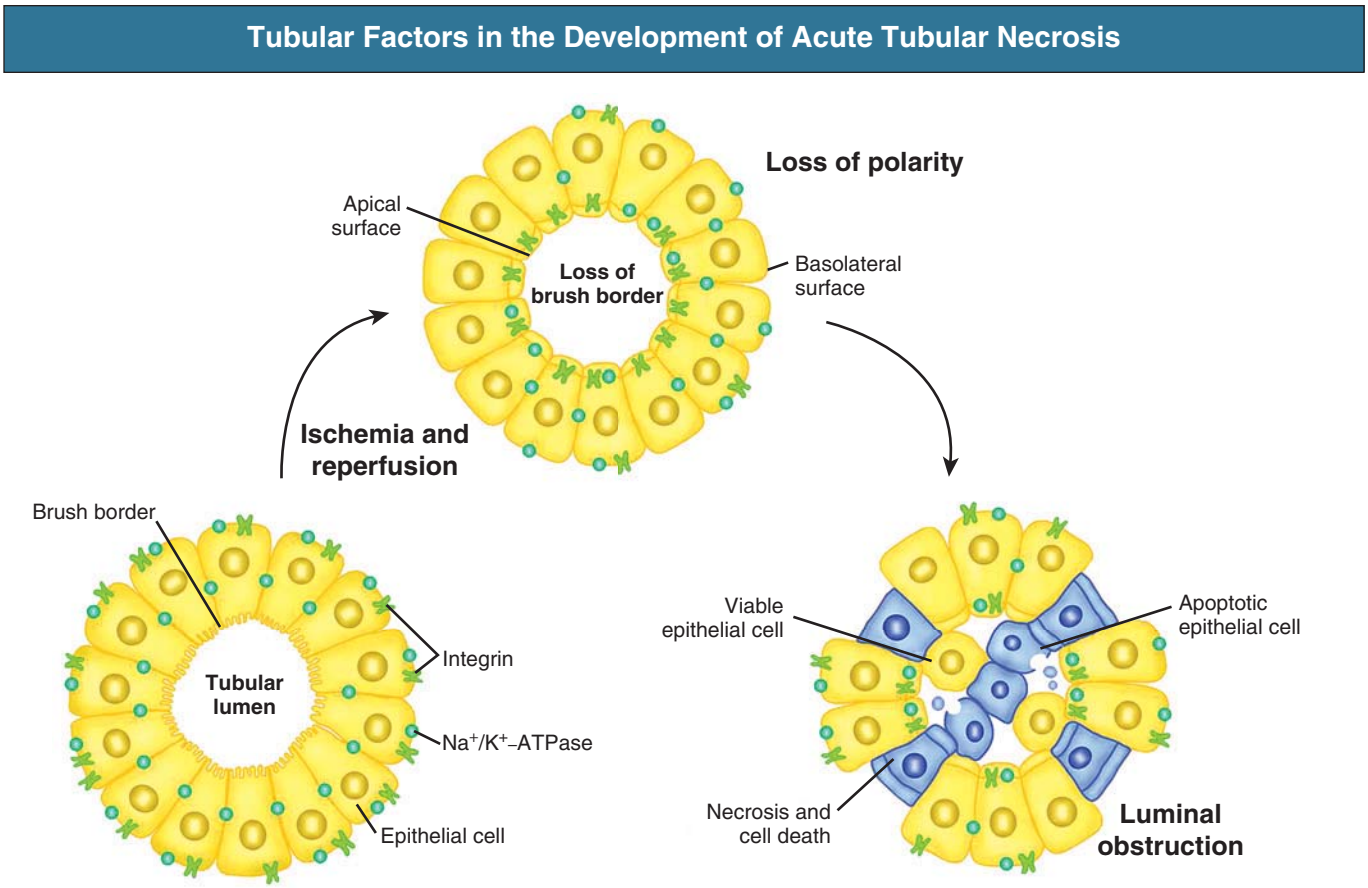

Figure 69-6 Tubular factors in the development of acute tubular necrosis. Loss of cell polarity results in weakening of cell-to-cell and cell matrix adhesion, resulting in cast obstruction and backleak of tubular fluid. *(Modified from reference 31.)*

with use of caspase inhibitors and p53 inhibitors that decrease apoptosis.[8]

Disruption of actin cytoskeleton—A characteristic feature of sublethally injured cells is the disruption of the actin cytoskeleton. Activation of the cysteine protease calpain (partly because of increased intracellular calcium) can degrade actin-binding proteins such as spectrin and ankyrin. This leads to abnormal translocation of Na^+-K^+-ATPase and other proteins from the basolateral membrane to the cytoplasm or apical membranes. In the proximal tubular cell, this loss of polarity results in impaired proximal reabsorption of filtrate with resultant increased distal NaCl delivery and activation of TGF.

Cast obstruction—Tubular cells are attached to the tubular basement membrane by $\alpha_3\beta_1$ integrins, which recognize RGD (arginine-glycine-aspartate) sequences in matrix proteins. Disruption of the actin cytoskeleton results in movement of integrins from basolateral positions to the apical membrane, leading to impaired cell matrix adhesion and cell detachment. Many of these detached cells are still viable and can be cultured from urine of patients with ATN. Sloughed proximal tubular cells can bind to RGD sequences in Tamm-Horsfall protein, resulting in cast formation and intratubular obstruction. In models of ischemic AKI, the elevation in tubular pressures may be inhibited by synthetic RGD peptides mitigating the obstructive process.

Backleak—The loss of adhesion molecules (E-cadherin) and tight junction proteins (ZO-1, occludin) results in the weakening of junctions between cells, allowing filtrate to leak back into the renal interstitium. Although this does not alter the actual GFR at the level of the glomerulus, the net effect is a reduction in the measured GFR. Earlier dextran sieving experiments suggest only a modest effect of backleak on the decrement of GFR in AKI (about 10%); however, in the renal allograft with delayed graft function because of severe ATN, backleak has been calculated to account for up to 50% of the reduction in inulin clearance.

Inflammatory Factors in the Development of Acute Tubular Necrosis

Although ischemia causes direct renal cytotoxicity, tissue inflammation during reperfusion also contributes to renal injury and may cause some of the systemic effects of AKI. Components of both the innate and the adaptive immune systems contribute to the pathogenesis of ATN.[9] The innate immune system is activated by cellular injury and certain pattern recognition molecules. Toll-like receptor 2 (TLR2) and TLR4 are upregulated within the kidney after ischemia, are activated by molecules released from injured cells, and induce renal epithelial cells to produce chemokines. The complement system is also activated within the tubulointerstitium after ischemia and reperfusion, predominantly by the alternative pathway. It can directly induce nearby epithelial cells to produce proinflammatory cytokines (such as tumor necrosis factor α [TNF-α], interleukin [IL]–6, IL-1β) and chemokines (such as monocyte chemoattractant protein 1[MCP-1], IL-8, regulated upon activation normal T cell expressed and presumably secreted [RANTES]) that promote the infiltration of the kidney by leukocytes and are also directly vasoactive.

A network of dendritic cells extends throughout the renal tubulointerstitium; these cells help shape the inflammatory response within the kidney after ischemia and reperfusion, likely through their

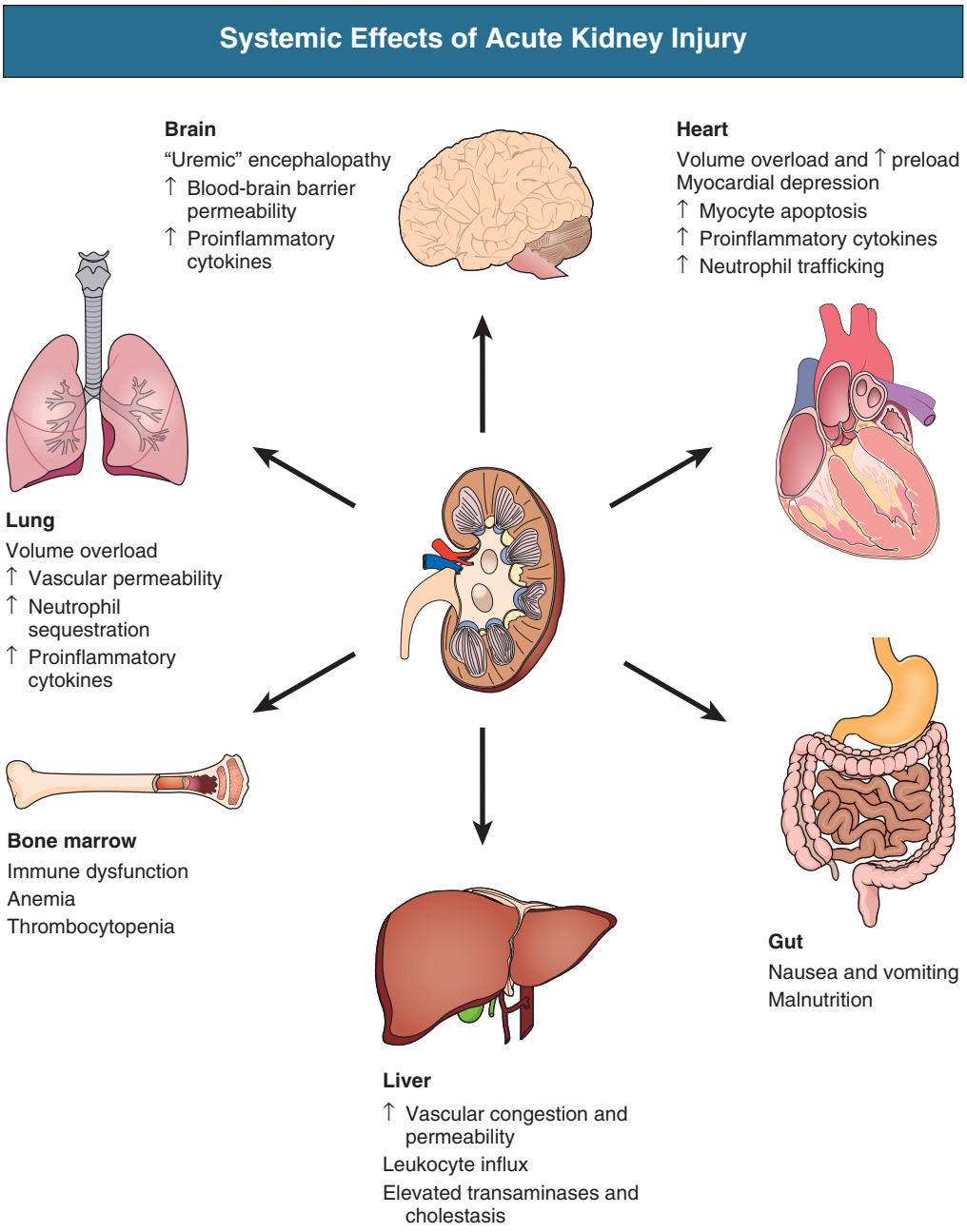

Figure 69-7 Systemic effects of acute kidney injury. Acute kidney injury (AKI) may contribute to remote organ injury, partly because of abnormalities in inflammatory and immune function from renal tubular dysfunction. *(Modified from reference 10.)*

interactions with other inflammatory cell types. Neutrophils and mononuclear cells are seen in peritubular capillaries on renal biopsy. Experimental studies have shown that neutrophil activation and the release of proteases and ROSs can exacerbate injury. By contrast, neutrophil depletion with antibody, or inhibiting neutrophil adhesion molecules (ICAM-1) with antibody or antisense oligonucleotides, ameliorates injury in ischemic ATN. ICAM-1 knockout mice are similarly protected. Monocytes infiltrate the reperfused kidney and differentiate into the M1, or inflammatory, type. M1 macrophages seem to exacerbate renal injury after ischemia, but studies have demonstrated that macrophages may later convert to the M2 "anti-inflammatory" type and promote repair of the kidney.

A number of studies have also demonstrated that cells of the adaptive immune system, including T and B lymphocytes, contribute to renal injury in models of ATN. Experimental ischemic reperfusion injury may be ameliorated by T cell or B cell deficiency. It is not known whether these responses are antigen specific. Furthermore, some B and T cell subsets, such as T regulatory cells, help limit renal injury.

We should also recognize that AKI may have systemic effects on other organ systems.[10] The injured kidney may prime and activate leukocytes, with the production of proinflammatory cytokines, which can mediate remote organ injury (Fig. 69-7). The lungs may be particularly vulnerable from the combined effects of volume overload, increased vascular permeability, and the proinflammatory environment. These distant organ effects may partly account for the increased mortality in patients with AKI (Chapter 72).

RECOVERY PHASE

Recovery from ATN requires the restoration of tubular cell number and coverage of denuded tubular basement membrane. A marked increase in cell proliferation occurs in recovering human ATN, and

mitotic figures may be seen by light microscopy (see Fig. 69-3). There has been some debate about the origin of the restored tubular cells. Some studies have suggested that mesenchymal stem cells locate to areas of tubular injury and transform into proximal tubular cells. Indeed, in experimental models, ischemia reperfusion injury may be ameliorated by infusions of mesenchymal stem cells. More recent evidence, however, suggests that the restoration of tubular cell number is a result of the dedifferentiation and proliferation of surviving tubular cells.[11] A number of growth factors have been implicated in the proliferative response, including insulin-like growth factor 1 (IGF-1) and hepatocyte growth factor (HGF); however, a therapeutic trial of subcutaneous recombinant IGF-1 in critically ill patients failed to show an acceleration in renal functional recovery.[12] After tubular epithelial cell proliferation, the dedifferentiated cells must migrate to areas of denuded tubular basement membrane, attach to the basement membrane, and differentiate into mature polar tubular epithelial cells.

NEPHROTOXIC AGENTS AND MECHANISMS OF TOXICITY

The identification and avoidance of nephrotoxic agents in AKI is critical in the management of this condition because AKI may be rapidly reversible on removal of the offending agent. The mechanisms of nephrotoxicity are very broad and include alterations in renal hemodynamics, induction of direct tubular injury, generation of allergic reactions resulting in interstitial nephritis, and intratubular obstruction. The list is extensive, but the more common agents are presented in Figure 69-8.

Nonsteroidal Anti-inflammatory Drugs

The NSAIDs are a common cause of AKI in the community because of the large amounts of these drugs either prescribed or bought over the counter.[13] The newer COX-2–specific NSAIDs have similar effects on renal function as the nonselective NSAIDs and thus are not safer with respect to AKI.

This type of NSAID-related AKI may be caused by a hemodynamically mediated reduction in GFR in particular clinical situations, such as atherosclerotic cardiovascular disease in elderly patients, preexisting CKD, states of renal hypoperfusion (including sodium depletion, diuretic use, hypotension), and sodium-avid states such as cirrhosis, nephrotic syndrome, and congestive heart failure. There is little evidence that NSAIDs impair renal function in otherwise healthy individuals. This form of AKI is usually reversible in 2 to 7 days after discontinuation of the drug.

Less frequently, NSAIDs induce ATN or, even more rarely, papillary necrosis.[13] NSAIDs, including the COX-2–specific NSAIDs, may also cause an acute interstitial nephritis, often with significant proteinuria (see Chapter 62). Other renal side effects of NSAIDs include fluid and electrolyte disturbances such as sodium retention exacerbating hypertension and congestive heart failure, hyponatremia, and hyperkalemia.

Angiotensin-converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Angiotensin-converting enzyme inhibitors and ARBs may also cause hemodynamically induced AKI in the setting of reduced renal perfusion resulting from impaired vasoconstriction of the efferent arteriole. They can also directly impair renal perfusion by their antihypertensive effects. Patients in whom renal perfusion is compromised because of dehydration, renovascular disease, or functionally impaired autoregulation are at risk for developing AKI after initiation of therapy with ACE inhibitors or ARBs.

Patients chronically treated with ACE inhibitors have an increased risk for postoperative renal dysfunction, probably as a consequence of intraoperative hypotensive episodes.

Aminoglycosides

Aminoglycosides are excreted by glomerular filtration, and toxicity may occur if the dose is not adjusted for underlying renal impairment. Cationic amino groups (NH_3^+) on the drugs bind to anionic megalin on the brush border of proximal tubular epithelial cells, and the drugs are then internalized by endocytosis. Aminoglycosides accumulate in proximal tubular cell lysosomes and can reach 100 to 1000 times their serum concentration. The drug interferes with cellular energetics, impairs intracellular phospholipases, and induces oxidative stress; however, the exact pathways culminating in tubular necrosis remain unclear.[14]

Nonoliguric AKI usually occurs after 5 to 10 days of treatment with gentamicin. Involvement of distal tubular segments may produce polyuria, potassium, and magnesium wasting. The risk for AKI correlates with the accumulation of gentamicin in proximal tubular cells and is related to the daily dose and duration of therapy. Prolonged accumulation in proximal tubular cells may allow development of AKI even after the drug has been discontinued. Additional risk factors for gentamicin toxicity include increasing age, preexisting renal disease, hypotension, concurrent liver disease, sepsis syndrome, and concurrent nephrotoxins.

Aminoglycoside serum levels should be followed to minimize nephrotoxicity. When possible, the drug may be administered in a single daily total dose, which leads to lower renal proximal tubular cell accumulation. Gentamicin, tobramycin, and netilmicin appear to have similar nephrotoxic effects. Amikacin, which has fewer amino groups per molecule, may be less nephrotoxic. Ototoxicity, and possibly nephrotoxicity, might be ameliorated by *N*-acetylcysteine.

The macrolide antibiotic vancomycin has rarely been associated with AKI when used as monotherapy, typically with very high serum drug levels. However, when used with gentamicin, it may increase the risk for aminoglycoside-induced AKI.

Amphotericin

The polyene macrolide antibiotic amphotericin binds to sterols in the cell membranes of both fungal walls (ergosterol) and mammalian (cholesterol) cell membranes, resulting in the formation of aqueous pores, which increase membrane permeability. The increased sodium influx leads to increased Na^+-K^+-ATPase activity and depletion of cellular energy stores.[15] In addition, the standard amphotericin formulation is suspended in the bile salt deoxycholate, which has a detergent effect on cell membranes. Nephrotoxicity relates to cumulative dosage, usually occurring after administration of 2 to 3 g.

Early signs of nephrotoxicity include a loss of urine-concentrating ability, followed by a decrease in GFR. Hypokalemia and hypomagnesemia from distal tubular toxicity are common. A distal renal tubular acidosis may be present because of proton backleak in the cortical collecting duct.

Prevention of nephrotoxicity requires the maintenance of high urine flow rates by saline loading during amphotericin administration. The more expensive liposomal amphotericin preparations reduce the incidence of AKI by 50%. The binding of amphotericin to ergosterol is more avid than to cholesterol, and by delivering

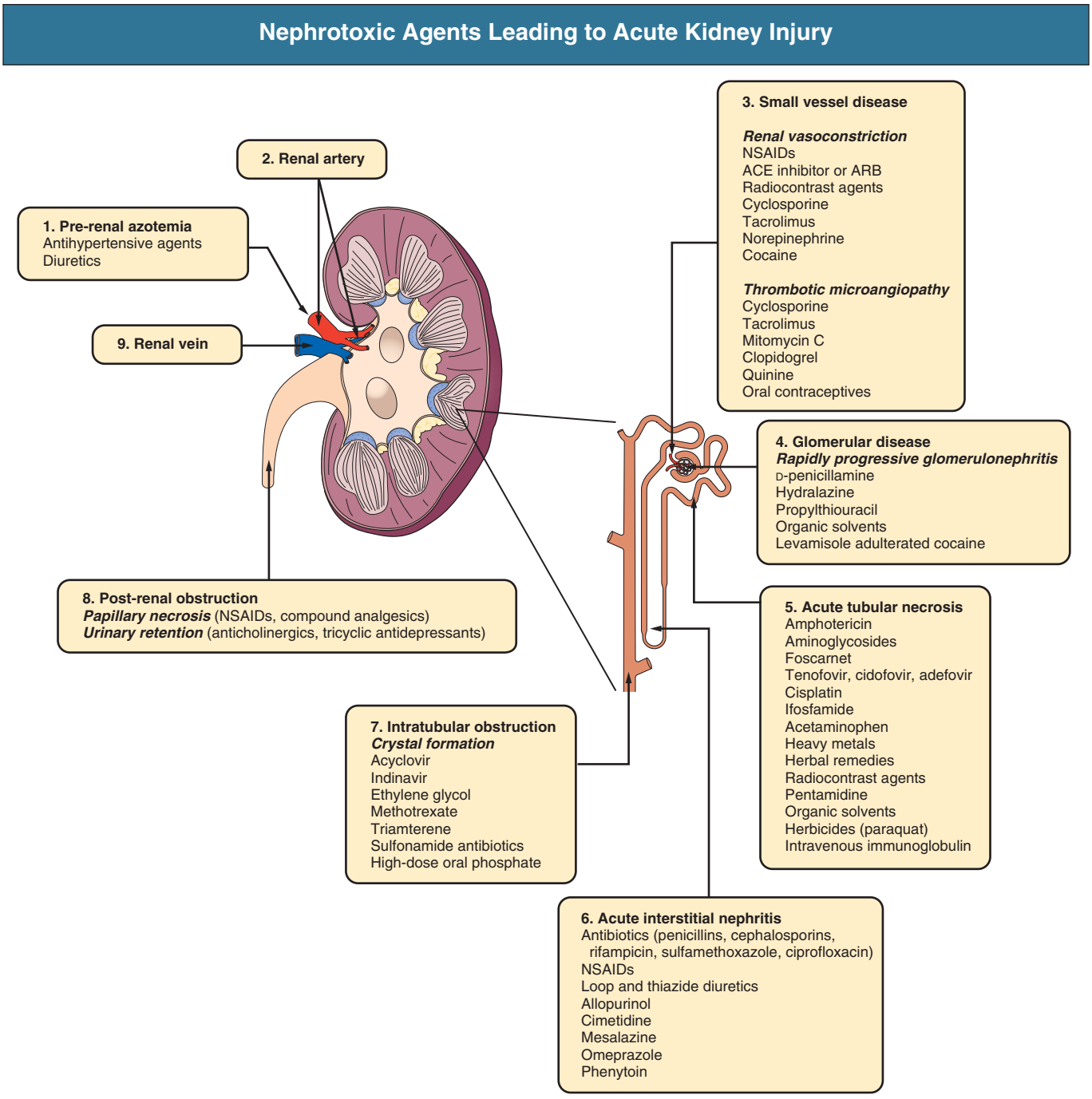

Figure 69-8 Common nephrotoxic agents leading to acute tubular necrosis. *ACE,* Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *NSAIDs,* nonsteroidal anti-inflammatory drugs.

the drug as a cholesterol liposome, diminished binding to tubular epithelial cell membranes results without altering fungal binding. In addition, liposomal preparations do not contain deoxycholate. Amphotericin-induced AKI is usually reversible with discontinuation of treatment with the drug, although distal tubular injury as manifested by magnesium wasting may persist.

Antiviral Therapy

Acyclovir

Nephrotoxicity is typically seen after intravenous acyclovir administration and may be a result of direct tubular cell toxicity and the formation of intratubular acyclovir crystals. The latter appear as birefringent needle-shaped crystals on urine microscopy. However, crystals may also be seen in patients without AKI, and renal biopsy data suggest that acute interstitial nephritis may be the predominant mechanism of toxicity. Ceftriaxone appears to increase the risk for acyclovir nephrotoxicity. In contrast, ganciclovir has little nephrotoxicity.

Oliguric AKI typically occurs within a few days of treatment and may be associated with abdominal or loin pain. High serum levels of acyclovir resulting from decreased renal clearance may produce neurologic toxicity. The AKI is usually mild and recovers on stopping the drug.

Foscarnet

Foscarnet is a phosphate analogue used in the treatment of severe cytomegalovirus infection but also inhibits proximal tubule sodium-phosphate cotransport. AKI occurs in 10% to 20% of treated patients and may be caused by ATN or intratubular crystal obstruction and acute interstitial nephritis. The AKI is usually nonoliguric and associated with mild proteinuria (<1 g) and a benign urine sediment. Hypocalcemia caused by chelation of calcium may be present. The renal failure is usually reversible, although recovery may take several months. Prehydration markedly decreases the incidence of AKI.

Cidofovir and Adefovir

The nucleotide analogues cidofovir and adefovir have been associated with AKI secondary to proximal tubular injury in 12% to 24% of patients. These agents are transported into the proximal tubule by the human organic anion transporter (hOAT), and nephrotoxicity may be reduced by volume expansion and by concurrent use of probenecid, which blocks hOAT.

Other Antiviral Agents

Most other antiviral agents are not nephrotoxic. In the treatment of hepatitis C virus (HCV), there have been rare reports of ATN secondary to interferon-α.

Immunosuppressive Agents

Calcineurin Inhibitors

Cyclosporine and tacrolimus may cause acute renal impairment as a result of afferent arteriolar vasoconstriction partly mediated by endothelin. This is usually reversible on dose reduction. Persistent injury may lead to chronic interstitial fibrosis in a striped pattern along medullary rays, reflecting the ischemic nature of the insult as well as the development of arteriolar hyalinosis. Associated clinical features include hypertension, hyperkalemia, hyperuricemia, and wasting of phosphate and magnesium from tubular injury. Calcineurin inhibitors also cause reversible tubular dysfunction, and they are associated with the development of TMA, likely because of their effects on the endothelium (see Chapters 29 and 101).

Other Immunosuppressive Agents

The monoclonal anti-CD3 antibody (OKT3) or polyclonal antilymphocyte and antithymocyte preparations (ALG, ATG) may cause a first-dose cytokine release syndrome and pre-renal AKI secondary to capillary leak. OKT3 has rarely been associated with a hemolytic uremic syndrome (HUS). Intravenous immunoglobulin (IVIG) can cause AKI, which may be partly mediated by the high sucrose concentration in these products. Tubular uptake of sucrose may result in osmotic cell swelling and injury. Methotrexate is toxic to proximal tubular epithelial cells and rarely may cause intratubular crystal obstruction. Although it is not known to cause AKI, sirolimus delays the recovery of AKI in animal models and in kidney transplant patients with delayed graft function.

Acetaminophen (Paracetamol)

Isolated ATN with acetaminophen may occur in rare patients, but renal injury is more typically associated with acute hepatitis. Renal and liver toxicity usually occur when more than 15 g have been taken, but in alcoholics, normal doses may be toxic. Acetaminophen is conjugated in the liver and undergoes renal excretion. Less than 5% undergoes metabolism by P-450 (CYP2E1) enzymes to form a toxic metabolite, *N*-acetylimidoquinone, which is inactivated by the thiol group of glutathione. With high levels of acetaminophen, glutathione becomes depleted, and *N*-acetylimidoquinone can bind to thiol groups on intracellular proteins, resulting in cell injury. Because glutathione is a major intracellular antioxidant, its loss may predispose to oxidative injury of the tubular cells.

Clinically, acute hepatitis and ATN begin only when glutathione levels are depleted, and clinical manifestations usually present 3 to 4 days after ingestion. *N*-acetylcysteine can be protective, if administered early, because it provides a free thiol group, substituting for glutathione.

Ethylene Glycol

Ethylene glycol, found in antifreeze, remains a cause of both deliberate and accidental injury. It is rapidly metabolized by alcohol dehydrogenase to glycoaldehyde and glyoxylate, which are toxic to tubular cells. Further metabolism generates oxalic acid, which can precipitate in renal tubules, leading to intratubular obstruction.

The diagnosis is suggested by the presence of a severe anion gap metabolic acidosis and a serum osmolal gap. Oxalate crystals are typically, but not always, seen on urine microscopy (see Chapter 4, Fig. 4-4). Management includes inhibition of alcohol dehydrogenase with intravenous ethanol (aiming for blood levels of 100 mg/dl [22 mmol/l]) or preferably the specific alcohol dehydrogenase inhibitor fomepizole. Hemodialysis should be performed to remove the ethylene glycol and metabolites when the level is higher than 20 mg/dl and continued until it is below 5 mg/dl. Methanol intoxication may present with similar metabolic abnormalities, but rarely causes AKI (see Chapter 12).

Warfarin Nephropathy

Acute kidney injury has been described in patients taking warfarin who develop an acute rise in the international normalized ratio (INR), usually to greater than 3. This occurs mostly in patients with underlying CKD, and biopsy studies have suggested this may be a result of increased glomerular hematuria with obstruction of renal tubules by red blood cell casts.

Illicit Drug Use

Acute kidney injury is a common condition in those who abuse drugs and may be a result of nephrotoxicity of the drug, coexistent viral infection (human immunodeficiency virus [HIV], HCV), sepsis, infective endocarditis, rhabdomyolysis, or alcohol abuse.

Cocaine induces intense vasoconstriction, which may lead to severe hypertension and rhabdomyolysis.[16] Mechanisms for rhabdomyolysis include coma and pressure necrosis; vasospasm leading to ischemic muscle injury; and adrenergic stimulation and hyperpyrexia leading to increased cellular metabolism. It typically occurs in those who inject cocaine, and the patient often presents with fever, hypertension, tachycardia, and a decreased mental state.

Other illicit drugs associated with AKI include opiates (coma-associated, pressure-induced rhabdomyolysis); phencyclidine (rhabdomyolysis secondary to hyperpyrexia and vasoconstriction); heroin (rhabdomyolysis); and amphetamines (AKI secondary to rhabdomyolysis, acute interstitial nephritis, or acute necrotizing angiitis).

Bisphosphonates

Acute kidney injury resulting from tubular injury has been described with intravenous but not oral bisphosphonates (especially zoledronate and pamidronate). This typically occurs after several months of treatment.

Acute Phosphate Nephropathy

Oral sodium phosphate has been widely used as a bowel preparation for colonoscopic procedures, but recent cases of AKI have limited the use of this purgative.[17] AKI associated with oral sodium phosphate is believed to be caused by phosphaturia and acute calcium-phosphate deposition within the renal tubules. This occurs most frequently in patients with CKD, older-age patients, and those with volume depletion.

Occupational Toxins

Heavy Metals

Lead intoxication usually causes chronic nephropathy (see Chapter 64). Rarely, acute tubular injury occurs that may be associated with Fanconi syndrome. ATN may also occur in cadmium and mercury poisoning.

Organic Solvents

Organic solvents may cause acute tubular injury because of peroxidation of membrane lipids. A subacute renal failure resulting from anti–glomerular basement membrane (anti-GBM) antibody disease has also been reported with exposure to halogenated hydrocarbons.

Herbal Remedies

Specific herbs used in traditional African medicine (e.g., Cape aloes, *Callilepis laureola*) are common causes of AKI in parts of Africa. A subacute form of renal failure caused by aristolochic acid found in certain herbs used in traditional Chinese medicine has also been described (see Chapters 64 and 78).

Radiocontrast-induced Nephropathy

Acute kidney injury secondary to contrast nephrotoxicity typically occurs in patients with underlying renal impairment and is rarely seen in patients with normal renal function.[18] It may occur with both intravenous and intra-arterial contrast, but not with oral contrast (assuming the bowel is intact). The incidence of contrast nephropathy (as defined by an increase in serum creatinine of more than 0.5 mg/dl [44 µmol/l]) is about 20% in patients with serum creatinine levels exceeding 2 mg/dl (176 µmol/l) and 50% when levels exceed 5 mg/dl (440 µmol/l). Other risk factors for the development of this condition include diabetic nephropathy, advanced age (older than 75 years), congestive heart failure, volume depletion, and high or repetitive doses of radiocontrast agent. High osmolar contrast is more nephrotoxic than low or iso-osmolar contrast agents. Concurrent use of NSAIDs, ACE inhibitors, or diuretics may increase the risk.

Pathogenesis

Medullary hypoxia and direct tubular epithelial cell toxicity are the main factors in the pathogenesis of contrast nephrotoxicity. Typically, a biphasic hemodynamic response is seen. An initial vasodilation (lasting a few seconds to minutes) is followed by a more prolonged renal vasoconstriction. The consequent medullary hypoxia may be exacerbated by the osmotic diuresis, leading to increased sodium delivery to the medullary thick ascending loop and requiring greater oxygen consumption for reabsorption.

Radiocontrast agents also cause direct tubular epithelial cell injury and induce apoptosis of these cells. Human studies have demonstrated low-molecular-weight proteinuria, suggestive of proximal tubular injury, partly mediated by ROSs. Increased markers of lipid peroxidation have been described, and the administration of antioxidants ameliorates contrast nephrotoxicity in animals. Clinical features, prevention, and therapy are described in Chapter 73.

OTHER SPECIFIC CAUSES OF ACUTE KIDNEY INJURY

Heme Pigment Nephropathy

Heme pigment nephropathy is a common cause of AKI and usually secondary to the breakdown of muscle fibers (rhabdomyolysis), which release potentially nephrotoxic intracellular contents (particularly myoglobin) into the systemic circulation. Less commonly, heme pigment nephropathy may occur as a result of massive intravascular hemolysis. Prevention and therapy of heme pigment nephropathy are discussed in Chapter 73.

Causes of Rhabdomyolysis

Muscle trauma is the most common cause of rhabdomyolysis. The initial description was by Bywaters and Beall during the bombing of London in World War II.[19] Other common causes of muscle injury include marked exercise, seizures, pressure necrosis secondary to coma, alcohol abuse, and limb ischemia (Table 69-1). In skeletal muscles confined to rigid compartments, cell swelling after injury may result in increased intracompartmental pressures impairing local microvascular circulation, leading to compartment syndrome (Fig. 69-9). In the patient with alcohol abuse, rhabdomyolysis is often multifactorial. Contributing causes include pressure necrosis from coma ("found down"), direct myotoxicity from ethanol, seizures, and electrolyte abnormalities (hypokalemia and hypophosphatemia). Therapy with statins may be associated with rhabdomyolysis. The risk is increased by concomitant therapy with fibrates, cyclosporine, or erythromycin. Familial myopathies such as McArdle syndrome and carnitine palmitoyl transferase deficiency should be suspected in patients with a history of recurrent episodes of rhabdomyolysis associated with muscle pain, positive family history, onset in childhood, and the absence of other identifiable causes. In developing countries, ingestion of hair dye containing paraphenylenediamine as a means of self-harm may cause AKI secondary to rhabdomyolysis. Snake and spider bites, bee stings, and venomous caterpillar bites may all cause rhabdomyolysis (see Chapter 70).

Causes of Rhabdomyolysis

Muscle injury, ischemia	Trauma, pressure necrosis, electric shock, burns, acute vascular disease
Myofiber exhaustion	Seizures, excessive exercise, heat exhaustion
Toxins	Alcohol, cocaine, heroin, amphetamines, ecstasy, phencyclidine, snakebite
Drugs	Statins, fibrates, zidovudine, neuroleptic malignant syndrome, azathioprine, theophylline, lithium, diuretics
Electrolyte disorders	Hypophosphatemia, hypokalemia, excess water shifts (hyperosmolarity)
Infections	Viral (influenza, human immunodeficiency virus [HIV], Coxsackievirus, Epstein-Barr virus), bacterial *(Legionella, Francisella, Streptococcus pneumoniae, Salmonella, Staphylococcus aureus)*
Familial	McArdle disease, carnitine palmitoyl transferase deficiency, malignant hyperthermia
Other	Hypothyroidism, polymyositis, dermatomyositis

Table 69-1 Causes of rhabdomyolysis.

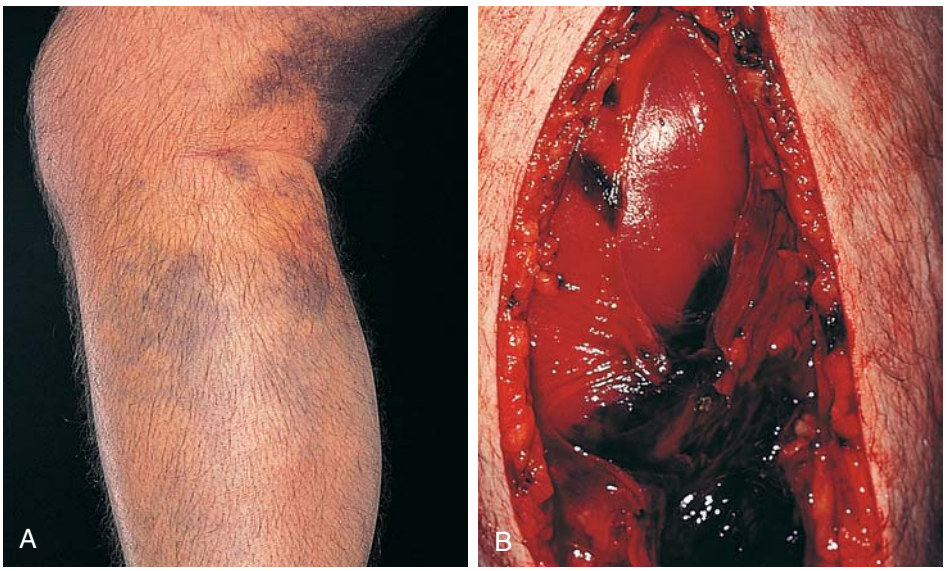

Figure 69-9 Compartment syndrome. A, Severe calf swelling caused by anterior and posterior compartment syndromes after ischemia and reperfusion. **B,** Appearance after emergency fasciotomy; note edematous muscle and hematoma. *(Courtesy Michael J. Allen, FRCS, Leicester, United Kingdom.)*

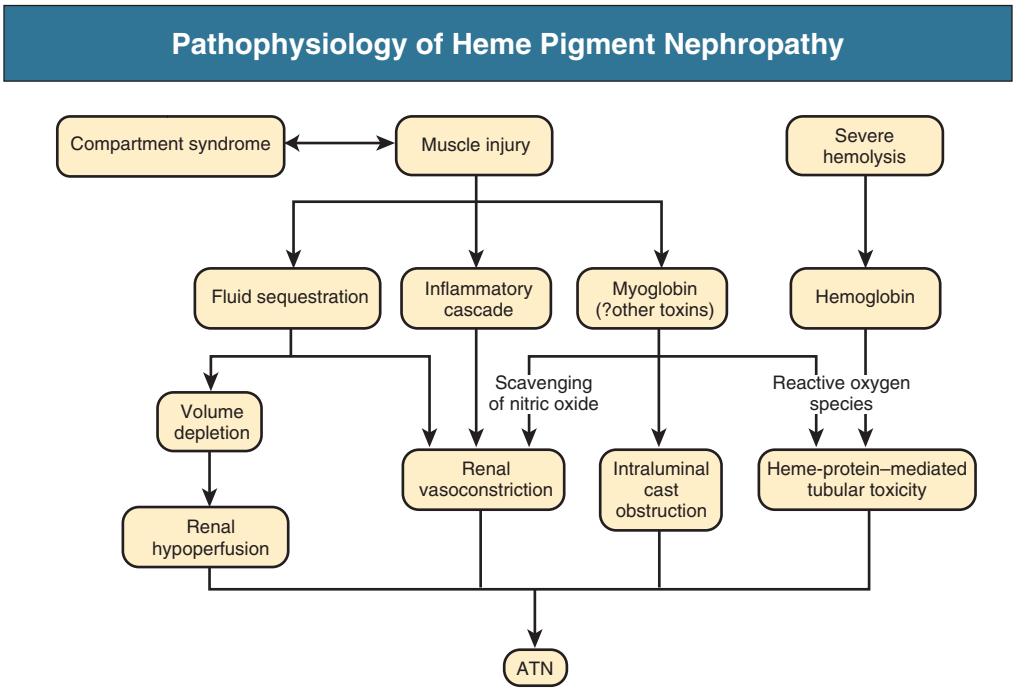

Figure 69-10 Pathophysiology of heme pigment nephropathy. *ATN,* Acute tubular necrosis.

Causes of Hemoglobinuria

Intravascular hemolysis results in circulating free hemoglobin. If the hemolysis is mild, the released hemoglobin is bound by circulating haptoglobin. With massive hemolysis, however, haptoglobin becomes exhausted. Hemoglobin (69 kd) then dissociates into α-β dimers (34 kd) which are small enough to be filtered, resulting in hemoglobinuria, hemoglobin cast formation, and heme uptake by proximal tubular cells. Like myoglobin, these processes can result in ATN and filtration failure. Causes of hemoglobinuric AKI include incompatible blood transfusion, autoimmune hemolytic anemia, malaria (blackwater fever), glucose-6-phosphate dehydrogenase deficiency, paroxysmal nocturnal hemoglobinuria, march hemoglobinuria, and toxins (dapsone, venoms).

Pathogenesis of Heme Pigment Nephropathy

The renal injury is caused by a combination of factors, including volume depletion, renal vasoconstriction, direct heme-protein–mediated cytotoxicity, and intraluminal cast formation (Fig. 69-10). Volume depletion is often prominent in patients with rhabdomyolysis because of the sequestration of large amounts of fluid (up to 15 to 20 liters) in injured muscle. Volume depletion activates the sympathetic nervous system and renin-angiotensin system, resulting in renal vasoconstriction. This may be exacerbated by the scavenging of nitric oxide by circulating heme proteins. Myoglobin (17 kd) is freely filtered at the glomerulus and is toxic to tubular epithelial cells. The heme center of myoglobin may directly induce lipid peroxidation and renal injury,[20] and liberated free iron catalyzes the formation

of hydroxyl radical through the Fenton reaction, inducing free radical–mediated injury. Renoprotection has been demonstrated in animal models with free iron scavengers and various antioxidants. Finally, the precipitation of myoglobin with Tamm-Horsfall protein and sloughed proximal tubular cells may result in obstructing casts in the distal nephron. This is enhanced by increased concentrations of tubular heme protein resulting from volume depletion with low tubular fluid flow rates. The binding of myoglobin to Tamm-Horsfall protein is enhanced in acidic urine.

Clinical features, prevention, and therapy are described in Chapter 73.

Atheroembolic Renal Disease

Atheroembolic renal disease, an under-recognized condition, occurs predominantly in older patients with atherosclerotic vascular disease, either spontaneously or, more frequently, precipitated by arteriography, vascular surgery, thrombolysis (streptokinase and tissue plasminogen activator), or anticoagulation. Destabilization of atherosclerotic plaques primarily in the aorta above the level of the renal arteries results in showers of cholesterol that lodge in small arteries in the kidneys (see Fig. 66-11) and the lower extremities (see Fig. 66-9). Characteristic needle-shaped clefts may be seen on renal or skin biopsy, denoting the localization of cholesterol plaques before dissolution with tissue fixation (see Fig. 66-11). The cholesterol emboli produce a marked and progressive inflammatory reaction, resulting in occlusion of the involved vasculature. (Renal atheroembolism is discussed further in Chapter 66.)

Renal Artery Occlusion

Acute kidney injury caused by renal artery occlusion occurs when the occlusion is bilateral or, in the case of unilateral acute occlusion, with a single nonfunctioning kidney. Thrombosis or embolization (noncholesterol) of the renal artery or its intrarenal branches is more common in elderly patients. An important risk factor for renal emboli is the presence of atrial fibrillation. Aortic dissection may also progress to occlude the renal arteries.

Renal vein thrombosis most commonly occurs in the setting of nephrotic syndrome and rarely may cause AKI if bilateral (see Chapter 66).

Acute Interstitial Nephritis

Acute interstitial nephritis is most commonly a drug-induced phenomenon and is an important differential diagnosis in AKI because removal of the offending agent can result in reversal of the condition. Less commonly, it may be caused by infection or immune-mediated diseases. Acute interstitial nephritis is discussed further in Chapter 62.

Thrombotic Microangiopathy

Thrombotic microangiopathy constitutes a wide range of conditions that should be considered when a patient presents with AKI and thrombocytopenia, although the condition may occur in the absence of a low platelet count. Endothelial activation is followed by the formation of platelet thrombi that occlude small vessels and lead to downstream ischemic injury. Endothelial injury may be triggered by infections (such as with *Escherichia coli*), drugs, or immune complexes. Thrombotic thrombocytopenic purpura is associated with reduced von Willebrand factor protease (ADAMTS13) activity, and atypical HUS is associated with genetic and acquired defects of the complement system. These entities can be difficult to distinguish clinically, and all forms of TMA can present with AKI. TMA is discussed further in Chapter 29.

Glomerular Disease

All forms of glomerular disease may present with AKI, but it is more commonly seen with forms of acute GN such as postinfectious GN, antineutrophil cytoplasmic antibody (ANCA)–associated small vessel vasculitis, anti-GBM disease, lupus nephritis, and IgA nephropathy. The term *rapidly progressive glomerulonephritis* has been used in this setting and may be associated with glomerular crescents on renal biopsy. Glomerular disease associated with a nephrotic presentation is less likely to present as AKI, but may occur as a result of volume depletion from diuretic use, superimposed ATN, or renal vein thrombosis, and rarely from a superimposed acute GN (e.g., anti-GBM disease in membranous nephropathy). Minimal change disease in adults is the most common nephrotic disorder associated with AKI. Glomerular disease is discussed further in Section IV.

SPECIFIC CLINICAL SITUATIONS

Determining the cause of AKI is often aided by recognizing common patterns of presentation and determining the likely causes arising in each of these situations.

Acute Kidney Injury in the Patient with Multiorgan Failure

About 20% of patients with sepsis and 50% of those with septic shock develop AKI. This significantly worsens the prognosis, and when dialysis is required, intensive care unit mortality increases to 45% to 80%. Sepsis is classically associated with infection. A similar condition, termed the *systemic inflammatory response syndrome* (SIRS), may occur secondary to noninfectious insults such as acute pancreatitis, major trauma, or ischemia reperfusion. Activation of the innate immune system may be caused by a number of bacterial products (lipopolysaccharide, flagellin, lipoteichoic acid, others) with pattern recognition receptors (such as Toll-like receptors) on immune cells. This leads to the activation of a wide range of cellular and humoral mediator systems, including the cytokine cascade (TNF-α, IL-1β, IL-6); the complement, coagulation, and fibrinolytic systems; and the release of mediators such as eicosanoids, platelet-activating factor, endothelin-1, and nitric oxide. Widespread endothelial injury results, leading to peripheral vasodilation, increased vascular permeability, and leukocyte infiltration. Peripheral vasodilation causes hypotension, with consequent activation of the renin angiotensin system, increased vasopressin, and increased cardiac output to maintain organ perfusion. This neurohormonal activation may constrict the afferent arterioles of the kidney and further impair renal perfusion. The causes of the AKI in this setting are typically multifactorial, resulting from a combination of hypotension, impaired renal perfusion, inflammatory mediators, and nephrotoxic agents.[21-23]

Acute Kidney Injury in the Postoperative Patient

Acute kidney injury in the postoperative period is commonly a result of problems with fluid balance, perioperative hemodynamic instability, or nephrotoxic agents. The critically ill postoperative patient may

develop SIRS. AKI may be particularly common after vascular, cardiac, and hepatobiliary surgery.

There is evidence that anesthetic agents may impair renal function. This may occur partly because of their hypotensive effects, but the metabolism of fluorinated agents can lead to the production of potentially nephrotoxic fluoride ions. Modern inhaled agents (e.g., isoflurane, halothane, enflurane) all cause a transient decrease in GFR, and the use of methoxyflurane had to be discontinued because of nephrotoxicity.

After Vascular Surgery

In patients with peripheral vascular disease, prior ischemic renal disease is often present, and preoperative diminished renal function is the strongest predictor of the risk for postoperative AKI. In aortic aneurysm surgery, most aneurysms are infrarenal; however, surgery that directly involves the renal arteries or aortic cross-clamping above the renal arteries can result in severe renal ischemia. Furthermore, aortic manipulation may dislodge atherosclerotic plaque, resulting in renal atheroembolism. Peripheral limb surgery may be complicated by rhabdomyolysis, and radiocontrast is frequently used for diagnostic purposes.

After Cardiac Surgery

Risk factors for postoperative AKI include duration of cardiac bypass, preoperative renal function, hyperuricemia, age, diabetes, valvular surgery, blood transfusions, and poor cardiac function.[24] The surgery is often performed with the patient cooled to below 30° C to protect cells against ischemic injury; however, systemic hypothermia may cause intravascular coagulation. Aortic instrumentation and clamping may lead to renal atheroembolism. Cardiac bypass causes exposure of blood to a nonendothelialized surface, resulting in activation of neutrophils, platelets, complement, and fibrinolytic systems. Significant hemolysis may also occur, potentially resulting in hemoglobinuria. Perioperative myocardial infarction or left ventricular dysfunction may impair renal perfusion postoperatively, although the low cardiac output is often transient and recovers within 24 to 48 hours. Atrial fibrillation is a common complication and may be associated with peripheral embolization. Studies have suggested that off-pump coronary artery bypass operations have a lower risk of AKI than surgeries in which patients are put on cardiopulmonary bypass.

After Hepatobiliary Surgery

Surgery to relieve obstructive jaundice is more commonly associated with AKI than other forms of abdominal surgery. This may be a result of the absence of bile salts in the gut lumen, which normally break down lipopolysaccharide endotoxin, preventing absorption. One study suggested a decreased incidence of postoperative endotoxemia when patients were treated with oral bile salts. Other factors may include direct nephrotoxic effects of bile salts on renal tubular cells and an increased incidence of biliary sepsis.

Abdominal Compartment Syndrome

Markedly raised intra-abdominal pressures (above 20 mm Hg) may occur after trauma, after abdominal surgery, or secondary to massive fluid resuscitation and can cause AKI.[25] The mechanism remains unclear, but it may be related to increased renal venous pressure and vascular resistance. Intra-abdominal pressures are poorly assessed by examination and are best estimated by measurement of intravesical (bladder) pressures. Efforts to reduce intra-abdominal pressures, including paracentesis, nasogastric suction, ultrafiltration, or surgical decompression, may occasionally improve renal function.

Causes of Pulmonary-Renal Syndrome	
Systemic vasculitis	Anti-GBM disease (Goodpasture) ANCA associated Granulomatosis with polyangiitis (Wegener) Microscopic polyangiitis Churg-Strauss syndrome Drugs (penicillamine, hydralazine, propylthiouracil) Immune complex disease Lupus erythematosus Henoch-Schönlein purpura Mixed cryoglobulinemia Rheumatoid vasculitis
Infection	Severe bacterial pneumonia; postinfectious glomerulonephritis; *Legionella;* hantavirus; opportunistic infection in immunocompromised patients; infective endocarditis
Pulmonary edema and AKI	Volume overload; severe left ventricular failure
Multiorgan failure	Acute respiratory distress syndrome and AKI
Other	Paraquat poisoning; renal vein or IVC thrombosis with pulmonary emboli

Table 69-2 Causes of pulmonary-renal syndrome. *AKI,* Acute kidney injury; *ANCA,* antineutrophil cytoplasmic antibody; *GBM,* glomerular basement membrane; *IVC,* inferior vena cava.

Pulmonary-Renal Syndromes

The term *pulmonary-renal syndrome* usually describes the presence of pulmonary hemorrhage in a patient with AKI. It can be caused by anti-GBM disease (Goodpasture syndrome), systemic vasculitis, or systemic lupus erythematosus (Table 69-2; see Chapters 24, 25, and 26). Given the fulminant course of these diseases, patients with pulmonary-renal syndrome require urgent evaluation, and specific testing for these diseases should be pursued.

A similar clinical presentation may occur with infection and AKI, or as a result of pulmonary edema secondary to volume overload in AKI. Other conditions that may masquerade as a pulmonary-renal syndrome include upper respiratory infection triggering a flare of IgA nephropathy; severe bacterial pneumonia complicated by ATN or postinfectious GN; *Legionella* species infection causing a severe atypical pneumonia; and acute interstitial nephritis or rhabdomyolysis.

Acute Kidney Injury and Liver Disease

The patient with liver cirrhosis is predisposed to the development of AKI, and the differential diagnosis typically includes pre-renal AKI, hepatorenal syndrome, and ATN.[26] In patients with cirrhosis, bacterial translocation from the gut lumen may trigger the release of vasoactive and inflammatory mediators. Arterial underfilling also induces the release of vasoconstrictive agents, impairing renal perfusion, even in patients who clinically appear volume overloaded. Assessment of intravascular volume status can be difficult, and a therapeutic trial of volume replacement is typically undertaken. Impaired renal perfusion and hyperbilirubinemia are predisposing risk factors. Alternatively, the same causative agent may be responsible for both the liver and renal injuries. This occurs with certain infections (e.g., leptospirosis, hantavirus) and nephrotoxic agents (Table 69-3). Rarely, hyperbilirubinemia from hemolysis may cause jaundice in the absence of liver disease. AKI in patients with liver disease is discussed further in Chapter 76.

Causes of Acute Kidney Injury and Liver Disease	
Pre-renal uremia	Diuretic use, gastrointestinal loss, peritoneal aspiration, hypoalbuminemia
Hepatorenal syndrome	
Acute tubular necrosis	Hyperbilirubinemia, sepsis, toxic shock syndrome
Drugs	Acetaminophen (paracetamol), NSAIDs, tetracycline, rifampin, isoniazid, anesthetic agents, sulfonamides, allopurinol, methotrexate
Infections	Hepatitis C and cryoglobulinemia, hepatitis B and polyarteritis nodosa, leptospirosis, hantavirus, Epstein-Barr virus, gram-negative sepsis, spontaneous bacterial peritonitis
Other	Papillary necrosis and obstruction, inhalation of chlorinated hydrocarbons, mushroom poisoning *(Amanita phalloides)*

Table 69-3 Causes of acute kidney injury and liver disease. *NSAIDs,* Nonsteroidal anti-inflammatory drugs.

Acute Kidney Injury in Heart Failure (Cardiorenal Syndrome)

The development of AKI in patients with decompensated heart failure is a common finding and is associated with a poor prognosis. Reduced renal perfusion secondary to decreased cardiac output has long been considered the primary cause; however, there are important contributions from right ventricular dysfunction leading to renal venous hypertension, and activation of the renin-angiotensin and sympathetic nervous systems.[27]

Acute Kidney Injury in the Cancer Patient

Patients with cancer are prone to AKI as a consequence of both their underlying disease and its treatment, and AKI may occur in up to 50% of critically ill cancer patients.[28] There is also a high incidence of pre-renal AKI in this patient group because of the high frequency of nausea, vomiting, and diarrhea (Table 69-4). More specific causes of AKI are noted in the following sections.

Tumor Lysis Syndrome

Necrosis of tumor cells, typically following chemotherapy, may release large amounts of nephrotoxic intracellular contents (uric acid, phosphate, xanthine) into the circulation.[29] This usually occurs after treatment of lymphomas (particularly Burkitt) and leukemias but may occur with solid tumors. Rarely, a spontaneous form of tumor lysis syndrome occurs in rapidly growing tumors that outstrip their blood supply. Hyperuricemia can cause acute uric acid nephropathy in patients with tumor lysis syndrome as a result of intratubular crystal obstruction and interstitial nephritis, although this is usually prevented by prophylactic use of allopurinol before chemotherapy. The release of other intracellular components can also cause tubular injury. For example, the release of intracellular phosphate can promote the precipitation of calcium phosphate in the tubules. The AKI is typically oligoanuric, and the condition should be suspected in patients with high lactate dehydrogenase levels suggestive of massive cell lysis. Markedly elevated phosphate and uric acid levels may be found. Hyperkalemia may be prominent and life-threatening.

Causes of Acute Kidney Injury in Patients with Cancer	
Pre-renal	Nausea and vomiting, hypercalcemia, cardiomyopathy secondary to chemotherapy
Vascular	Thrombotic microangiopathy (adenocarcinoma of stomach, pancreas, prostate; radiation nephropathy), renal vein thrombosis secondary to hypercoagulability, disseminated intravascular coagulation (acute promyelocytic leukemia)
Glomerular	Rapidly progressive glomerulonephritis
Acute tubular necrosis	Sepsis and antibiotic nephrotoxicity, hypercalcemia
Malignant infiltration	Lymphoma, acute lymphoblastic leukemia
Intraluminal obstruction	Tumor lysis syndrome, cast nephropathy
Post-renal obstruction	Transitional cell carcinoma of the ureters and bladder, extrinsic ureteral compression (tumor, nodes, retroperitoneal fibrosis)
Chemotherapeutic agents	
Tubular toxicity	Cisplatin, ifosfamide, plicamycin (mithramycin); 5-fluorouracil, thioguanine (6-thioguanine), cytarabine
Thrombotic microangiopathy	Mitomycin C, bleomycin, cisplatin, calcineurin inhibitors
Other mechanisms	Capillary leak syndrome (IL-2 therapy), acute interstitial nephritis (interferon-α), intraluminal obstruction (methotrexate)

Table 69-4 Causes of acute kidney injury in patients with cancer. *IL-2,* Interleukin-2.

Preventive measures include the use of high-dose allopurinol (100 mg/m^2 given orally every 8 hours [maximum, 800 mg per day]) started 2 to 3 days before chemotherapy, and either oral or intravenous fluid loading to ensure a urine output exceeding 2.5 l/day. Urine alkalinization is of less benefit than merely maintaining a high urine flow with saline, and it may promote tubular calcium phosphate deposition. However, it should be considered when serum uric acid levels are elevated (>12 mg/dl [714 µmol/l]) or urinary uric acid crystals are present. Recombinant uricase (rasburicase) is very effective in lowering serum uric acid levels (to <1 mg/dl in 24 hours) and should be considered for prophylaxis in high-risk patients.

Once the patient has developed AKI with hyperuricemia, rasburicase, which lowers uric acid much more effectively than dialysis, should be considered. It can lower uric acid levels within hours and is effective even in patients with impaired renal function. If this is not available or the patient is markedly hyperphosphatemic, early dialysis should be considered to remove these potential causes of further renal damage. Because phosphate is less well removed by dialysis than uric acid, frequent (every 12 to 24 hours) or prolonged treatments should be considered.

Hypercalcemia

Volume depletion secondary to hypercalcemia-induced nausea and vomiting may cause AKI, which may be exacerbated by hypercalcemia-induced nephrogenic diabetes insipidus. Other hypercalcemia-associated factors that may contribute to AKI include direct intrarenal vasoconstriction, acute interstitial nephritis, and intratubular obstruction.

Chemotherapeutic Agents

Cisplatin is commonly associated with a nonoliguric renal impairment.[30] Nephrotoxic injury affects both the proximal and distal nephron and clinically may be associated with magnesium wasting, impaired urinary concentration, and rarely salt wasting with volume depletion. Chloride ions in the *cis* position on the molecule may be replaced by water, releasing toxic hydroxyl radicals. Prophylaxis against nephrotoxicity includes volume loading and reducing the dose when possible. The alternative agent carboplatin appears to be less nephrotoxic. Once renal impairment is present, recovery may be poor and magnesium wasting may persist.

Ifosfamide is a cyclophosphamide analogue with a nephrotoxic metabolite, chloroacetaldehyde. AKI is usually mild, although proximal tubular dysfunction (Fanconi syndrome) and hypokalemia may be prominent.

High-dose intravenous methotrexate is also nephrotoxic, possibly because of precipitation of the drug within the renal tubules and direct toxicity to the renal epithelial cells.

Cytosine arabinoside and 5-fluorouracil may increase the likelihood of AKI when included in multidrug regimens. Both agents, for example, are associated with AKI when given in combination with cisplatin.

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CHAPTER 70

Acute Kidney Injury in the Tropics

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Acute kidney injury (AKI) in the tropics is heavily influenced by the local disease burden, which is dominated by particular infections, consumption of unsafe drinking water, use of natural medicines, exposure to environmental toxins, and envenomation by snakes or arthropods. Poverty, malnutrition, lack of an adequate sanitary infrastructure and public health system, and uncontrolled and unplanned urbanization are frequent problems that add significantly to the observed disease burden. In fact, the rupture of the ecologic balance by humans has induced particular causes of renal injury in the tropics, such as accidents involving Africanized bees or *Lonomia* genus caterpillars.[1,2]

Acute kidney injury epidemiology in the tropical area has a peculiar, bimodal pattern. Most patients are encountered in the community, and previously healthy, young individuals are frequently affected. In contrast, the epidemiology of hospital-acquired AKI in large cities and tertiary hospitals is similar to that seen in nontropical countries.[1-4]

The uniqueness of the tropical environment has a direct influence on water quality and pattern of disease. A strong seasonal variation in the incidence of AKI is noted in the tropics, with a spike during and immediately after the rainy seasons. Heavy precipitation leads to soil erosion, leaching of minerals and organic compounds, and waterlogging, conditions favorable to survival of organisms causing or transmitting infectious diseases such as leptospirosis, dengue, and malaria.[5-7] Tropical rains force venomous snakes to come out of the flooded burrows in the fields, making accidents more likely to occur.

The importance of the different causes of AKI in the tropics varies from region to region. Malaria, leptospirosis, typhus, diarrheal diseases, and envenomation are the common causes of AKI in South Asia; malaria, diarrheal diseases, obstetric accidents, and indigenous herbal remedies are frequent causes of AKI in Africa; and leptospirosis, dengue fever, envenomation, and obstetric complications are important causes of AKI in Latin American countries.[8] In addition, classical AKI caused by rhabdomyolysis from heat stroke or overexertion may also occur (see Chapter 69).

SNAKEBITES

Snakebite is an occupational hazard in the rural tropics and subtropical regions. Data based on 2005 Global Burden of Disease study suggest that globally at least 421,000 envenomations and 20,000 deaths occur each year as a result of snakebite, with the highest burden in South Asia, Southeast Asia, and sub-Saharan Africa.[9] Renal injury may develop following bites by hemotoxic or myotoxic snakes belonging to the Viperidae and Elapidae families, such as the Russell viper, saw-scaled viper, puff adder, rattlesnake, tiger snake, and green pit viper, *Bothrops* species, *Lachesis* species, *Crotalus* species, the boomslang, gwardar, and dugite, *Hypnale* species, *Cryptophis* species, and sea snakes. AKI is more frequent following Russell viper, *Bothrops,* or *Crotalus* bites, with incidences ranging from 10% to 32% (Fig. 70-1).[1,2,10-12] The prevalence is higher in children, probably because of the higher venom dose in relation to the body size.[12]

Clinical Features

Manifestations depend on the nature and injected venom dose. Local pain, swelling, blistering, ecchymosis, and tissue necrosis are frequent in Russell viper and *Bothrops* bites (Figs. 70-2 and 70-3). The commonest systemic manifestation in accidents involving these snakes is coagulation abnormalities leading to bleeding diathesis (see Fig. 70-3). Muscle paralysis and rhabdomyolysis may occur following bites by sea snakes and *Crotalus* snakes. AKI develops within a few hours to as late as 96 hours after the bite. Cola-colored urine is noted in patients with hemolysis or rhabdomyolysis. AKI is usually oliguric and catabolic, with rapidly rising levels of blood urea nitrogen (BUN), serum creatinine, and potassium. Oliguria generally lasts for 1 to 2 weeks, and its persistence suggests the likelihood of acute cortical necrosis.[1,2,10-12] Significant proteinuria and hematuria have been described in some studies and may reflect differences in venom composition.[10,13]

Laboratory investigation may show hemolysis (elevated free plasma hemoglobin and lactate dehydrogenase [LDH] and reduced haptoglobin) along with hypofibrinogenemia; reduced factors V, X, and XIIIa, protein C, and antithrombin III; and elevated fibrin degradation products. Rhabdomyolysis may be indicated by raised creatinine phosphokinase. Other findings include leukocytosis and elevated hematocrit resulting from hemoconcentration.[1,2,10-12]

Pathology

Grossly, the kidneys may show petechial hemorrhages. Light microscopy usually discloses acute tubular cell injury ranging from mild changes to overt tubular necrosis, with hyaline or pigment casts, variable degree of interstitial edema and infiltration, and scattered hemorrhages. Mesangiolysis may occur (especially with crotalid envenomation), and blood vessels may show fibrin thrombi. Electron microscopic findings include dense intracytoplasmic bodies representing degenerated organelles in the proximal tubules and electron-dense mesangial deposits. Less common findings are acute interstitial nephritis, necrotizing vasculitis, and proliferative and crescentic immune-complex glomerulonephritis (GN). Acute cortical necrosis is seen in about 20% to 25% of patients who have sustained Russell viper and *Echis carinatus* bites and has been described after *Bothrops* accidents.[1,2,10-12]

Pathogenesis

Snake venom is a complex mixture of enzymes, toxins, and peptides. Kidney injury may develop as a result of direct nephrotoxicity, renal vasoconstriction, hypovolemia, hypotension, depression of the medullary vasomotor center or the myocardium, hemolysis, altered

Figure 70-1 Russell viper. This large snake is an important cause of venomous snakebite–induced acute kidney injury in Asia.

Figure 70-2 Necrotic finger injury after *Bothrops* snakebite. *(Courtesy Carlos A. C. Mendes, São José do Rio Preto, Brazil.)*

Figure 70-3 Hemorrhagic blister developing a few hours after Bothrops snakebite. *(Courtesy Carlos A. C. Mendes, São José do Rio Preto, Brazil.)*

fibrinolysis, myoglobinuria, or disseminated intravascular coagulation.[1,2,10-12] Experimental studies have shown evidence of tubular injury manifested by increased excretion of tubular enzymes, altered fractional sodium excretion, and acute tubular necrosis.[1,2,10-12,14] Other changes including mesangiolysis, disrupted integrity of the cellular junctions, proteolysis of extracellular matrix, lysis of vessel walls (leading to mesangiolysis), and alterations in function of enzymes vital to cellular integrity have been noted. [1,2,10-12] Recently, intense inflammatory mediator release, induction of oxidative stress, and release of mitochondrial alarmins have been evoked as possible pathogenic factors in snake venom–induced AKI.[15-17]

Management

The basic therapeutic approach is the same as that for AKI from any cause (see Chapters 73 and 74). Key steps for reducing morbidity and mortality include early administration of specific monovalent antivenom, appropriate volume replacement, maintenance of good urine flow, urinary alkalization in patients with rhabdomyolysis, correction of electrolyte imbalance, administration of tetanus immunoglobulin, and treatment of infections.[1,2,10-12,14] Locally available polyvalent antivenom is effective against envenomation by multiple snakes or an unknown type of snake.[18] Unavailability of antivenom in rural hospitals and poor infrastructure that hampers transportation to health centers are major factors that delay administration of antivenom and contribute to high mortality,[19] which may reach 30%.[1,2,10-12] Recent studies suggest that up to 40% of affected patients may be found to have developed chronic kidney disease (CKD) on long-term follow-up after snakebite-induced AKI.[20,21]

ARTHROPODS

Poisonous arthropods such as bees, wasps, caterpillars, and spiders may cause AKI. Patients who have sustained hundreds of simultaneous bee stings frequently develop a multifaceted clinical picture, which includes intravascular hemolysis; rhabdomyolysis; low platelet count; coagulation disorders and bleeding; cardiovascular, hepatic, and pulmonary injury; and AKI, with mortality up to 16%.[1,22,23] In the same way, AKI can follow incidents involving multiple wasp, yellow jacket, or hornet stings.[22] The mechanisms leading to kidney injury are direct venom nephrotoxicity, intrarenal vasoconstriction, hemoglobinuria, myoglobinuria, hypotension, thrombotic microangiopathy,[24] and activation of inflammatory and oxidative stress pathways.[25] Renal histology usually shows acute tubular necrosis.[1,22,24]

Accidents involving caterpillars of the genus *Lonomia* produce severe hemorrhagic disorders. The venom induces a complex hemorrhagic diathesis with both fibrinolytic and disseminated intravascular coagulation–like activity.[22,26] Severe and prolonged AKI with renal histology suggesting ischemic injury, which evolves to CKD in some patients, has been reported after *Lonomia obliqua* accidents (Fig. 70-4).[22,27,28] Availability of *Lonomia* antivenom has led to an apparent decrease in the number of severe cases in Brazil.[27] The pathogenesis of the kidney injury might be associated with glomerular deposition of fibrin microthrombi, intravascular hemolysis, kidney tissue deposition, and direct venom nephrotoxicity and activation of the endothelial cell inflammatory pathway.[22,29-31]

Spiders of the genus *Loxosceles* may induce local necrosis at the bite site, intravascular hemolysis, rhabdomyolysis, coagulation system changes, and AKI (Figs. 70-5 and 70-6).[22,32] Even patients with mild cutaneous lesions may develop severe hemolysis and AKI, which is the main cause of death after these accidents. The pathogenesis of the kidney injury has been related to massive

intravascular hemolysis, renal vasoconstriction, direct nephrotoxicity, and rhabdomyolysis.[22,32-34]

NATURAL MEDICINES

Herbs and indigenous remedies are used extensively in poor societies living in the tropics. About 80% of the population in Africa depends on traditional medicine prepared by herbalists and faith healers using unknown ingredients. Poisoning with traditional medicines is an important cause of renal injury and mortality in sub-Saharan Africa.[35-37] AKI has been described in association with several natural remedies. An accurate assessment of their contribution to AKI is

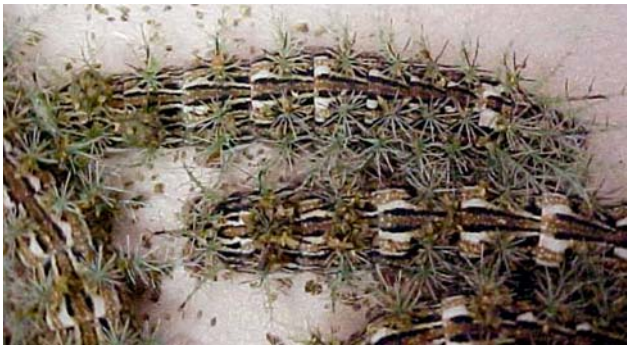

Figure 70-4 *Lonomia obliqua* caterpillars. Each hair works as a miniature hypodermic needle to inject the hemolymph, which contains powerful venom that is able to induce severe coagulation system changes. *(Courtesy Elvino J. G. Barros, Porto Alegre, Brazil.)*

Figure 70-5 *Loxosceles* species (brown recluse spider). *(Courtesy Katia C. Barbaro, São Paulo, Brazil.)*

Figure 70-6 Local necrotic injury in the left leg of a female patient after *Loxosceles* bite. A, At 4 days after the bite. **B,** At 60 days after the bite. **C,** At 3 months after the bite. *(Courtesy Carlos A. C. Mendes, São José do Rio Preto, Brazil.)*

Herbal Causes of Acute Kidney Injury in Tropical Countries

Plant (Common or Local Name)	Country	Active Molecule	Renal Manifestations	Other Manifestations
Averrhoa bilimbi (irumban puli)	South India	Oxalic acid	Intratubular obstruction	
Callilepis laureola (impila)	Sub-Saharan Africa	Atractyloside	Acute tubular necrosis	Abdominal pain, diarrhea, vomiting, jaundice, seizures, and coma
Catha edulis (khat leaf)	East Africa, Arabian peninsula	*S*-cathinone and ephedrine	Acute tubular necrosis	Hepatotoxic effects
Cleistanthus collinus (oduvan)	India	Cleistanthin A and B, collinusin, and diphyllin	AKI	Hypotension, hypokalemia, arrhythmia
Colchicum autumnale (autumn crocus)	Turkey	Colchicine	Acute tubular necrosis	Hemorrhagic gastroenteritis, muscle paralysis, respiratory failure
Crotalaria laburnifolia (bird flower)	Zimbabwe, Sri Lanka	Pyrrolizidine alkaloids	Acute tubular necrosis and hepatorenal syndrome	Hepatic veno-occlusive disease, pulmonary injury, thrombocytopenia
Dioscorea quartiniana (yam)	Africa, Asia	Dioscorine and dioscin	Acute tubular necrosis	Convulsions
Pithecellobium lobatum and *Pithecellobium jiringa* (djenkol beans)	South East Asia	Djenkolic acid	Intratubular obstruction and acute tubular necrosis	Lumbar and lower abdominal pain, hypertension
Dodonaea angustifolia (sand olive)	South Africa	Unknown	Acute interstitial nephritis	Pulmonary embolism
Euphorbia metabelensis (spurge)	Zimbabwe	Irritant chemicals in plant latex	Acute tubular necrosis	Thrombocytopenia
Larrea tridentate (chaparral)	Chile, South Africa	Nordihydroguaiaretic acid and S-quinone	Renal cysts, renal cell carcinoma	Hepatic failure
Propolis resin	Brazil	Unknown	Acute interstitial nephritis	Contact dermatitis
Rhizoma rhei (rhubarb)	Hong Kong	Anthraquinones (emodin, aloe-emodin)	Acute interstitial nephritis	None
Securidaca longepedunculata (violet tree or wild wisteria)	Congo, Zambia, and Zimbabwe	Methylsalicylate, securinine, saponins	Acute tubular necrosis	Vomiting, diarrhea
Sutherlandia frutescens (cancer brush)	South Africa	Unknown	Acute interstitial nephritis	Pulmonary embolism
Takaout roumia	Morocco, Sudan	Paraphenylenediamine	Acute tubular necrosis	Rhabdomyolysis
Semecarpus anacardium (marking nut)	India	Unknown	Acute tubular necrosis and acute cortical necrosis	Corrosive blisters in pharynx, gastrointestinal irritation, shock, coma
Taxus celebica (Chinese yew)	Asia	Flavonoid	Acute tubular necrosis and acute interstitial nephritis	Hepatitis, hemolysis, DIC
Thevetia peruviana (yellow oleander)	India, Sri Lanka	Cardiac glycosides	Acute tubular necrosis	Liver failure, cardiac arrhythmias
Tripterygium wilfordii (thunder god vine)	Taiwan	Triptolide	Acute tubular necrosis	Diarrhea, shock
Uncaria tomentosa (cat's claw)	Peru	Alkaloids and flavonols	Acute tubular necrosis	Diarrhea, hypotension, bruising, bleeding gums

Table 70-1 Herbal causes of acute kidney injury (AKI) in tropical countries. *DIC,* Disseminated intravascular coagulation. *(From reference 8.)*

rendered difficult by the failure to elicit a history as a result of the physicians' ignorance or denial or the patients' fear of stigmatization or social pressure. Often it is difficult to discount the contribution of the original illness to the AKI.[8,35-37]

About 25% to 35% of all AKI from medical causes in African hospitals are related to herbal remedies. The plant sources more frequently associated with AKI are impila *(Callilepis laureola),* djenkol beans *(Pithecellobium),* irumban puli (*Averrhoa bilimbi*), mushrooms (genera *Amanita, Galerina, Cortinarius,* and *Inocybe),* cape aloe, and raw carp bile.[8,36,37] In addition, single case reports of other natural medicines inducing AKI have been described (Table 70-1).[8,36,37]

Kidney injury may be either the sole manifestation or part of a multisystem and metabolic involvement. Management of AKI is usually supportive and includes volume replacement and correction of metabolic abnormalities. Dialytic support is given for usual indications. About 60% all patients with herbal remedy–related AKI need dialysis, with 25% to 75% mortality. Charcoal hemoperfusion is effective in clearing α-amanitin from circulation in those with poisoning from *Amanita* mushrooms.[37]

Pathogenesis of Natural Medicine–Induced Acute Kidney Injury

Several factors affect the toxicity and likelihood of kidney injury. Incorrect identification by inexperienced personnel may lead to substitution of a medicinal plant with a toxic one. An example is the substitution of *Takaout el badia*, a hair dye made from *Tamarix orientalis* seeds, with the toxic *Takaout roumia* (paraphenylenediamine), which causes AKI on accidental or intentional digestion. Incorrect methods of preparation or use can lead to nephrotoxicity, such as consumption of improperly cooked djenkol beans, intake of large quantities of star fruit or yam, and failure to ingest *impila* in the prescribed way (with sufficient water, followed by regurgitation soon after consumption). Finally, potentially nephrotoxic exogenous substances such as paint thinners, turpentine, chloroxylenol, ginger, pepper, soap, vinegar, copper sulfate, and potassium permanganate are often added to the plant extracts. The mechanisms that cause AKI are variable. Djenkol beans, star fruit juice, and *Averrhoa bilimbi* juice may induce intratubular precipitation of djenkolic acid or oxalate crystals. Raw bile of the grass carp, poisonous mushrooms, and cottonseed oil are directly toxic to renal tubules. Indirect mechanisms include interaction with metabolism of conventional drugs. St John's wort *(Hypericum perforatum)* decreases plasma levels of drugs that are metabolized by cytochrome P450 enzyme system. In kidney transplant recipients, this interaction can lower levels of calcineurin inhibitors and precipitate AKI from allograft rejection. Concomitant administration of other nephrotoxic substances can also potentiate herbal nephrotoxicity.[8,37]

AKI caused by herbal medicines is also discussed in Chapter 78.

MALARIA

Malaria is caused by five species of malarial *Plasmodium* parasites: *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale,* and *Plasmodium knowlesi.* The World Health Organization (WHO) estimated that globally malaria affects more than 200 million patients annually with nearly 1 million deaths, mostly of children with *P. falciparum* infection. There has been an increasing incidence of *P. knowlesi* infection in Southeast Asia, predominantly in Sarawak, Malaysia.[38] The contribution of malaria as the cause of AKI among different geographic areas ranges from 2% to 39%. The incidence of AKI in *P. falciparum* malaria can be as high as 60% and in *P. vivax* malaria varies from 10% to 19%. *P. malariae*–, *P. knowlesi*–, and *P. ovale*–induced AKI are less common but may be observed in patients with complicated cases.[39] In this chapter, we focus on *P. falciparum* malaria–associated AKI, which is a classical model of malaria-induced AKI. Glomerular disease associated with malarial infection is discussed in Chapter 57.

Pathophysiology

The inherent characteristics of each species of malarial parasite are important determinants in malaria pathogenesis. *P. vivax*, *P. ovale,* and *P. knowlesi* infect young erythrocytes, and *P. malariae* infects aging cells. *P. falciparum* infects erythrocytes of all ages, producing a higher number of merozoites (Fig. 70-7). Heavy parasitemia is therefore commonly observed in *P. falciparum* malaria, creating adverse effects on the microcirculation. The pathophysiologic process of malaria involves membrane changes, inflammation, and hemodynamic alterations. *Plasmodium* parasites primarily infect erythrocytes with secondary effects on the microcirculation and immune system. Parasitized erythrocytes are integral to the pathophysiologic process of the disease through decreased erythrocyte deformability and sequestration, knob and rosette formation, cytoadherence, and changes in membrane transport and permeability. It is interesting to note that nonparasitized erythrocytes also have decreased deformability. Knobs on parasitized erythrocyte membranes and cytoadherence between parasitized erythrocytes and vascular endothelial cells are characteristic of *P. falciparum* malaria; other forms of *Plasmodium* do not have this property. Recently, it has been reported that mature *P. vivax*–parasitized erythrocytes can cytoadhere to vascular endothelial cells through binding of ICAM-1 (intercellular adhesion molecule 1) and chondroitin sulfate A receptors. This cytoadherence is lower than that of *P. falciparum*–infected erythrocytes.[40] Similarly to other infectious diseases, several proinflammatory cytokines and vasoactive mediators are released. Hemodynamic changes in malaria are similar to those of bacterial sepsis, including decreased systemic vascular resistance, increased cardiac output, and increased renal vascular resistance. The initial hypervolemia is followed by hypovolemia and decreased cardiac output, with renal blood flow and glomerular filtration rate decrease. Increased blood viscosity, intravascular coagulation, hemolysis, rhabdomyolysis, jaundice, fever, lactic acidosis, complement activation, and reactive oxygen species further compromise renal blood flow. Activation of poly (ADP-ribose) polymerase by peroxynitrite and free radicals decreases oxygen usage. AKI in malaria is therefore ischemic and hypoxic in origin and usually occurs in the patient with heavy parasitemia, intravascular coagulation, or intravascular hemolysis or rhabdomyolysis.[39]

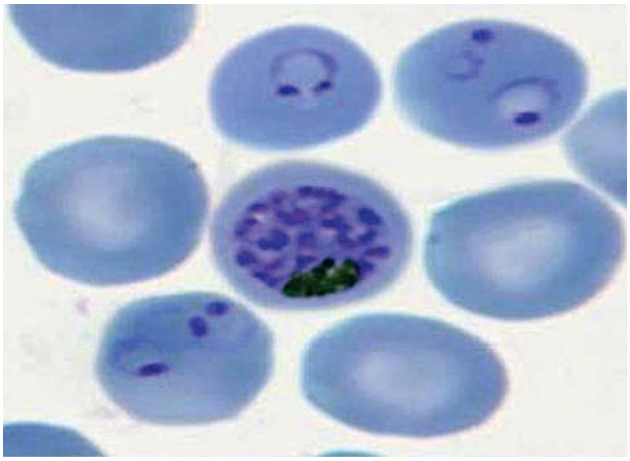

Figure 70-7 Ring form and merozoites of *Plasmodium falciparum* in infected erythrocytes.

Immune responses in malaria involve Th1 and Th2 activation. Immune complex GN is usually observed, with granular deposition of C3, IgM, and malarial antigen in the mesangial area and *in situ* immune complex deposition. Tubular changes vary from cloudy swelling to tubular degeneration with tubulorrhexis in the patient with AKI (Fig. 70-8). Bile and hemoglobin casts and Tamm-Horsfall protein (uromodulin) are present in the tubular lumen. Interstitial mononuclear infiltration and edema can be observed. Thrombotic microangiopathy has been reported.[41] Malarial antigens are occasionally seen along the glomerular endothelium and medullary capillaries. Adhesion molecules and proinflammatory cytokines are overexpressed in the vascular endothelium and proximal tubules.[39]

Clinical Manifestations

Malarial AKI affects predominantly nonimmune adults, mostly infected by *P. falciparum.* The increasing reports of severe AKI in

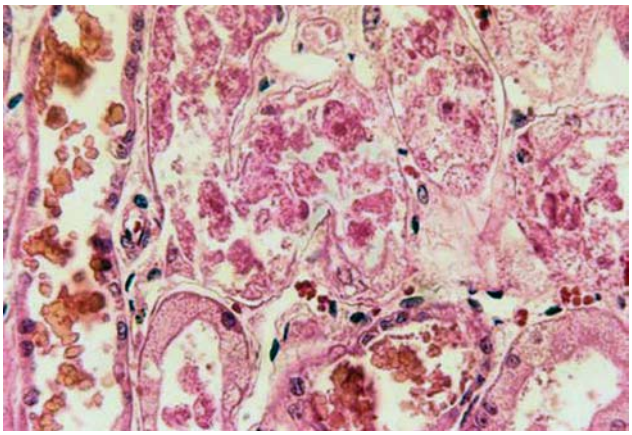

Figure 70-8 **Acute tubular necrosis in *P. falciparum* malaria.**

P. vivax infection with thrombotic microangiopathy are of interest. Mixed plasmodium infections and comorbidities resulting from sepsis are likely important contributing factors. Constitutional symptoms include fever, chills, headache, and prostration. Jaundice may be present. The urinalysis usually shows few erythrocytes, leukocytes, and granular casts and mild proteinuria (often less than 1 g/24 h). Hemoglobinuria is noted in the patient with intravascular hemolysis, frequently associated with glucose-6-phosphate dehydrogenase deficiency. Rhabdomyolysis with myoglobinuria has been observed. Fluid and electrolyte changes are common in malaria.[39,42] Hyponatremia, usually asymptomatic, is observed in 67% of patients and is related to the severity of malaria. Decreased response to water load is seen in 20% of hyponatremic patients. Fluid should be administered cautiously in hyponatremic patients to avoid fluid overload. Hyponatremia resolves within a few days after antimalarial treatment. The causes of hyponatremia are multiple, including increased antidiuretic hormone with water retention, intracellular shift of sodium caused by decreased Na^+,K^+-ATPase activity, and sodium depletion. Hypernatremia is uncommon and when present indicates hypothalamic lesions with diabetes insipidus, associated with an unfavorable prognosis. Hypokalemia caused by respiratory alkalosis occurs in 20% to 40% of the patients. Hyperkalemia is observed in patients with intravascular hemolysis, rhabdomyolysis, or AKI. Hypocalcemia with prolonged QTc intervals occurs in 45% of patients with severe malaria, is transient, and resolves when infection is controlled.[42] Decreased activities of Na^+,K^+-ATPase, Ca^{2+}-ATPase, and parathyroid hormone are considered the main causes for hypocalcemia. Hypophosphatemia secondary to respiratory alkalosis is observed in 6% to 30% of the patients. The clinical significance of both hypocalcemia and hypophosphatemia is unknown. Hypomagnesemia is seen in 30% of patients.[42] Downregulation of epithelial sodium channels (ENaCs) on the apical membrane of alveolar epithelial cells and increased vascular permeability account for the development of pulmonary edema and acute respiratory distress syndrome.[43]

Malarial AKI is characterized by a rapid increase in BUN and serum creatinine and is often associated with cholestatic jaundice. Hepatocellular jaundice may be observed with hypotension and secondary hepatic injury. Hemolytic uremic syndrome (HUS) has been described. Severe acidosis, hypoglycemia, and central nervous system symptoms can be observed. The duration of AKI ranges from one to several weeks, and the condition is oliguric in 60% of the patients. Quinine and artesunate are the antimalarial agents of choice. Early and frequent renal replacement therapy (hemodialysis or peritoneal dialysis) is lifesaving.[39] Continuous veno-venous hemofiltration (CVVH) yields good results in patients with multiorgan involvement, especially those with pulmonary edema or acute respiratory distress syndrome.[39] Exchange blood transfusion and erythrocytapheresis are adjunctive for the patient with heavy parasitemia.[43] The mortality rate of malarial AKI ranges from 10% to 50%. Multiple organ involvement carries a poor prognosis. The use of dopamine with furosemide has been successful in attenuating the progress of mild uncomplicated malarial renal injury. This is in contrast to the experience in other causes of AKI and requires larger randomized controlled studies for validation.

LEPTOSPIROSIS

Leptospirosis, a worldwide distributed zoonosis, is caused by *Leptospira* genus spirochetes. There are more than 200 pathogenic serovars of *Leptospira,* occurring in tropical and subtropical areas, which makes this infection a major public health burden. In fact, the WHO included leptospirosis as a reemerging infectious disease in both developed and developing areas, and cases have been increasingly reported in developed countries.[44,45] Wild and domestic mammals such as rodents, dogs, pigs, cattle, and horses are the typical vectors for leptospirosis. The infection is transmitted to humans through animal urine.[1,2,8,46]

Human leptospirosis is endemic in many tropical countries and usually reaches epidemic levels after either higher rainfall periods with flooding, or natural disasters such as hurricanes. Human cases range from 10 to 100 per 100,000 population per year in the humid tropics. These figures rise during outbreaks and in high-risk groups. Epidemic leptospirosis was reported in Nicaragua and Puerto Rico after hurricane strikes and in Brazil after summer floods. Some studies showed a high seroprevalence of anti-*Leptospira* antibodies in the general asymptomatic population, ranging from 18% to 33%. Indeed, leptospirosis is considered to be one of the candidates responsible for the epidemic of CKD occurring in the agricultural communities of Central America (Mesoamerican nephropathy; see Chapter 64). With use of polymerase chain reaction assay, 29% of wild small animals in the Peruvian Amazon were found to be infected with leptospirae.[1,2,8,46]

Leptospira interrogans, the only parasitic species, is mobile, aerobic, and unstained by the Gram method. Its endotoxins affect the tubulointerstitial cells. Glomerular changes are usually not relevant. The bacterial outer membrane contains lipopolysaccharide (LPS), cytotoxic glycolipoprotein (GLP) and lipoprotein (LipL), especially LipL32, which is immunogenic. As leptospirae have special tropism for kidneys, the effect of GLPs on tubular Na^+,K^+-ATPase activity is potentially involved in AKI cellular pathophysiology,[47] in the urinary concentrating defects, and in the paradoxical hypokalemia frequently seen in these patients.[1,2,8,46-49] High serum free fatty acids, mainly oleic acids (C18:1), are also potentially implicated in pulmonary hemorrhagic manifestations of the acute respiratory distress syndrome associated with this disease.[50]

Kidney involvement is almost universal in leptospirosis but becomes relevant in Weil disease, the most severe form of leptospirosis. Weil disease is characterized by multiorgan involvement, with diffuse alveolar hemorrhage, pulmonary edema, acute respiratory distress syndrome, or a combination of these features, accompanied by AKI; the disease has an elevated mortality rate.[46,48] The incidence of leptospirosis-associated AKI varies from less than 10% to more than 80%, and its severity is associated with increasing mortality.[51-54] AKI is typically nonoliguric and associated with hypokalemia.[1,2,8,46] Oliguria, jaundice, and arrhythmias have been shown to be predictors of AKI development.[51] Tubular changes characterized by high urinary fractional excretion of sodium and potassium precede

glomerular filtration rate decrease, which could explain the high prevalence of hypokalemia.[48] Antibiotic treatment is considered efficient in the disease early and in the late and severe phases, but a recent study failed to show a decrease in mortality in leptospirotic patients receiving antibiotics.[46,55] Treatment recommendations include a high dialysis dose, conservative fluid intake, and approaches to minimize lung injury, such as low tidal volume and high positive end-expiratory pressure, when artificial ventilation is required. [46,56]

HEMORRHAGIC FEVERS

Viral hemorrhagic fevers (VHFs) are caused by RNA viruses of four different families (Flaviviridae, Arenaviridae, Bunyaviridae, and Filoviridae). They can be acquired through infected arthropod bites (dengue, Rift Valley yellow fever, and Crimean-Congo virus) or by inhalation of infected rodent excreta particles (Lassa virus, Junin virus, Machupo virus, and Hantavirus). The clinical picture of VHF is characterized by fever, malaise, increased vascular permeability, and coagulation abnormalities that may lead to bleeding. AKI is an unusual complication of these diseases but has been reported in association with several forms of VHF.[1,2,8,57] Dengue and yellow fever are the most prevalent forms of VHF in tropical regions.[57]

Dengue Fever

Dengue is an acute febrile disease caused by an arbovirus, transmitted primarily by mosquitoes, with a benign evolution in most patients. The main dengue vector is the *Aedes aegypti* female mosquito. Dengue is currently the most important urban arboviral disease, affecting more than 50 million people annually in more than 100 countries in all WHO regions except Europe. Two fifths of the entire world population, approximately 2.5 billion individuals, are at risk for dengue. It is more prevalent in tropical and subtropical areas, where the environment is favorable for the mosquito's development. Several factors account for the rising incidence and widespread prevalence of dengue, such as climate changes (global warming, intensity and duration of rain season, hurricanes), ecosystem modifications, demographic increases, uncontrolled and unplanned urbanization, and migration of people.[57]

There are four serotypes of dengue flavivirus (DEN1 to DEN4). They are antigenically related, but immunity to one serotype does not confer enduring immunity to another. The introduction of a new serotype in a determinate area accounts for the occurrence of epidemics and the hemorrhagic fever dengue form, which is a more severe form of the disease that may be lethal.[57]

Dengue virus infection may manifest as undifferentiated fever, dengue fever, dengue hemorrhagic fever (DHF), or dengue shock syndrome (DSS). Common clinical manifestations of dengue fever are high fever, myalgia, arthralgia, retro-ocular pain, headache, anorexia, nausea, vomiting, and a cutaneous rash similar to measles or rubella. DHF and DSS are severe forms of the disease, characterized by fever, hemorrhagic phenomena, thrombocytopenia, evidence of plasma leakage (increased hematocrit, pleural effusion, ascites, and hypoalbuminemia), mental disorientation, shortness of breath, tachycardia, shock, and death.[57]

Kidney involvement in dengue includes AKI, proteinuria (sometimes nephrotic), GN, and HUS.[57-64] Peak proteinuria has been suggested to potentially predict DHF in patients with dengue.[65]

The reported frequency of dengue-associated AKI is extremely variable, ranging from 1% to approximately 30%, but AKI development and severity are consistently related to poor prognosis.[58-61] Dengue-induced AKI is usually associated with shock, hemolysis, and/or rhabdomyolysis[57] but may occur without any of these triggering factors.[64] DHF grade IV and obesity in children, and DSS in adults have been identified as risk factors for AKI development.[60,61]

There is no specific treatment for dengue fever. Therapy is mostly supportive, avoiding the use of aspirin and nonsteroidal anti-inflammatory drugs. [57]

Yellow Fever

Yellow fever is a noncontagious infectious disease that is endemic in tropical Africa, South America, and Panama. The yellow fever virus is part of the *Flavivirus* genus (Flaviviridae family).[57,66]

Yellow fever is transmitted to humans by the bites of blood-eating insects, especially the *Aedes* and *Haemagogus* genera. There are sylvatic and urban cycles. The sylvatic cycle affects individuals who sporadically get in contact with the vectors when performing economic or recreational activities in infested forests. The urban cycle is characterized by virus transmission by *A. aegypti* to individuals living in urban areas. The urban cycle was eliminated in the Americas in the 1940s to 1950s, but its resurgence was recently documented in Bolivia. The movement of infected individuals when viremic to cities with high vector populations can potentially generate explosive urban epidemics affecting thousands of unvaccinated people.[57,66] It is interesting to note that there is no evidence of yellow fever in Asia, despite an extensive presence of vectors. It is possible that the hyperendemicity of dengue in southwest Asia has afforded protection as a result of cross-reactive antibodies. This mechanism might also explain why urban yellow fever has not reemerged in Brazil after the reintroduction and spread of the *Aedes* vector and why a large number of cases of dengue have occurred in the last 20 years.[57,66]

The diagnosis of yellow fever is made by measuring serum specific IgM, by viral isolation in insect or mammal cells, and by molecular methods such as reverse transcription polymerase chain reaction (RT-PCR). The most specific pathologic finding of yellow fever is liver injury with formation of Councilman bodies. Both viral RNA and antigens are found in these cells, suggesting a direct viral cytopathy.[57,67]

Clinically, yellow fever infection may be asymptomatic, may cause moderate febrile disease, or may be severe, causing hemorrhagic fever, liver failure, AKI, and death. Most patients (85%) fully recover after 3 to 4 days and become permanently immunized against the disease. About 20% develop the severe form, with mortality rates up to 50% in these patients.[57,66]

After 3 to 6 days of incubation, the clinical picture of yellow fever starts abruptly with high fever, chills, anorexia, myalgia, headache, vomiting, and bradycardia. Hemorrhagic manifestations may occur. There is then a remission period with symptom improvement, and patients with mild cases do not have any further manifestation. In the severe forms the fever comes back, followed by vomiting, epigastric pain, and jaundice, the so-called "intoxication phase." There are large increases in transaminases and bilirubin. Leukopenia and ST-segment abnormalities are also found. Hemorrhagic events, associated with hepatic damage and consumptive coagulopathy, can occur; these include hematemesis, melena, petechiae, bruises, mucosal bleeding, and metrorrhagia in women. Microcirculatory thrombosis, disseminated intravascular coagulation, tissue anoxia, oliguria, and shock may follow.[57,66]

Yellow fever–associated kidney injury is usually observed after 5 days of disease in the severe forms; it may evolve to anuria and acute tubular necrosis, with increased mortality. In Africa, AKI is observed earlier and in the absence of jaundice or liver abnormalities, with higher mortality. The mechanisms of kidney injury are poorly

understood. In experimental studies performed in Rhesus monkeys in the 1980s, the renal disorder appeared to be pre-renal until the last 24 hours of life of the animal. The final phase was characterized by marked oliguria, azotemia, and acidosis, with severe tubular necrosis found at autopsy. In humans, an eosinophilic degeneration of the renal epithelial cells has been described. Viral antigen identification in human kidney tissue and after experimental infection in animals suggests a direct viral action on renal tissue.[57,66,68,69]

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CHAPTER 71

Diagnosis and Clinical Evaluation of Acute Kidney Injury

Eric Judd, Paul W. Sanders, and Anupam Agarwal

The term *acute renal failure* (ARF) describes the clinical syndrome in which an abrupt (hours to days) decrease in renal function leads to the accumulation of nitrogenous waste products and, commonly, a reduction in urine output. *Acute kidney injury* (AKI) is the new consensus term for ARF.[1-4] This change in terminology served to standardize a definition for the syndrome as well as incorporate new knowledge that small rises in serum creatinine (0.3 mg/dl) are associated with increased mortality and morbidity.[5]

The Acute Dialysis Quality Initiative first defined AKI with the RIFLE criteria (risk, injury, failure, loss, end stage) in 2004 (Table 71-1).[2] The Acute Kidney Injury Network (AKIN) later supported the RIFLE criteria with minor modifications (see Table 71-1).[3,4] Both definitions have been validated in large patient cohorts, and the Kidney Disease: Improving Global Outcomes (KDIGO) group merged the two definitions in a recent guideline update (Table 71-2). AKI is now defined as an increase in serum creatinine of 0.3 mg/dl or more within 48 hours of observation or 1.5 times baseline or greater, which is known or presumed to have occurred within 7 days, or a reduction in urine volume below 0.5 ml/kg/h for 6 hours.[1]

The incidence of AKI varies depending on the population studied and the definition used in the analysis. In a community-based cohort in northern California, from 1996 to 2003, the annual incidence of AKI in which dialysis was not required was 3841 per million population per year when AKI was defined as an increase in serum creatinine of 0.5 mg/dl or more from a baseline of below 2.0 mg/dL, or an increase of 1.0 mg/dl or more from a baseline of 2.0 to 5.0 mg/dl.[6] In the United States, AKI is present in 1.9% of hospital inpatients and is especially common in critically ill patients, in whom the prevalence is higher than 60% during intensive care unit (ICU) stays.[7,8] AKI severity increases in the ICU, with 5% to 6% of patients requiring renal replacement therapy, and in the United States the incidence of AKI patients who require dialysis is growing at a rate of 10% annually.[9,10]

The development of AKI has significant short- and long-term consequences. Despite major advances in dialysis and intensive care, the mortality rates for patients with AKI in the ICU remain high, 37% to 60%.[9,11] In a large population of almost 20,000 hospitalized adults, AKI severity was directly associated with increased in-hospital mortality, lengthened hospital stay, and higher overall cost. The associations were present for changes in serum creatinine as low as 0.3 mg/dl.[5] Patients with AKI who survive hospitalization also have an increase in long-term mortality, with an adjusted mortality risk of 1.4, which is amplified with increasing AKI stage.[12] Furthermore, AKI survivors are at increased risk for developing comorbidities including chronic kidney disease (CKD).[13]

DIAGNOSIS AND CLINICAL EVALUATION OF ACUTE KIDNEY INJURY

Early Detection of Acute Kidney Injury

With the knowledge that patient outcomes worsen with increasing severity of AKI beginning with small declines in renal function, research efforts have focused on early detection of AKI. Increases in serum creatinine levels currently define AKI, yet when used as a marker of renal function, serum creatinine concentrations have multiple limitations. In addition to a steady-state balance of creatinine production and excretion being required for appropriate estimation of glomerular filtration rate (GFR), serum creatinine concentrations may not rise for subtle declines in GFR and are slow to rise for rapid falls in GFR. Furthermore, the generation of creatinine from muscle is reduced in sepsis-induced AKI, and serum creatinine concentrations may not increase proportionally to GFR decline.[14] A window of time exists in which kidney injury goes undetected until serum creatinine concentrations rise (8 to 48 hours) (Fig. 71-1).[15] Novel serum and urine biomarkers are undergoing investigation as potential early indicators of AKI. These biomarkers, which include kidney injury molecule 1 (KIM-1), neutrophil gelatinase–associated lipocalin (NGAL), cystatin C, interleukin (IL)–18, and others, not only offer the potential for early detection of AKI but also may allow for improved prognostication and insight into the specific cause of AKI.

Figure 71-2 depicts the continuum of kidney injury severity and a number of biomarkers that have been proposed to be useful in early detection. Serum cystatin C, a cysteine protease inhibitor that is freely filtered at the glomerulus and normally reabsorbed by proximal tubule cells, may be more sensitive than serum creatinine concentrations at detecting small reductions in GFR.[16] Urinary cystatin C has been shown to detect AKI in multiple clinical settings including after cardiac surgery, sepsis-AKI, and delayed graft function after kidney transplantion.[15]

Kidney injury molecule 1 is a cell membrane glycoprotein that is upregulated in proximal tubular cells injured by ischemia or nephrotoxins in animals and humans. KIM-1 can act as a nonmyeloid phosphatidylserine receptor that transforms epithelial cells into semiprofessional phagocytes.[17] The ectodomain of this membrane-associated mucin-rich molecule is shed into the urine of human and rodent kidneys with renal injury, but it is not found in urine produced by healthy kidneys. Urinary levels are increased specifically with AKI resulting from ischemia or toxin exposure.[18,18a]

Neutrophil gelatinase–associated lipocalin (NGAL), a protein expressed in proximal and distal renal tubule cells as well as neutrophils, binds and traffics free iron. It also mediates the tubular response

Acute Kidney Injury Network (AKIN) and RIFLE Classifications of Acute Kidney Injury			
AKIN Staging **Serum Creatinine**	**Urine Output (Common to Both)**	**RIFLE Class**	**RIFLE Serum Creatinine or GFR**
Stage 1: Increase of ≥0.3 mg/dl (≥26.5 µmol/l) or increase to ≥150% to 200% (1.5-fold to twofold) from baseline	<0.5 ml/kg/h for >6 h	Risk	Increase in serum creatinine ×1.5 or GFR decrease >25%
Stage 2: Increased to >200% to 300% (more than twofold to threefold) from baseline	<0.5 ml/kg/h for >12 h	Injury	Serum creatinine ×2 or GFR decreased >50%
Stage 3: Increased to >300% (more than threefold) from baseline, or ≥4.0 mg/dl (≥354 µmol/l) with an acute increase of at least 0.5 mg/dl (44 µmol/l) or on RRT	<0.3 ml/kg/h for 24 h or anuria for 12 h	Failure	Serum creatinine ×3, or serum creatinine > 4 mg/dl (>354 µmol/l) with an acute rise >0.5 mg/dl (>44 µmol/l) or GFR decreased >75%
		Loss	Persistent acute renal failure = complete loss of kidney function for longer than 4 weeks
		End-stage kidney disease	ESRD > 3 months

Table 71-1 AKIN and RIFLE classifications of acute kidney injury. For conversion of creatinine expressed in SI units to mg/dl, divide by 88.4. For AKIN, the increase in creatinine must occur in less than 48 hours. For RIFLE, AKI should be both abrupt (within 1 to 7 days) and sustained (more than 24 hours). *ESRD,* End-stage renal disease; *GFR,* glomerular filtration rate; *RIFLE,* risk, injury, failure, loss, end stage; *RRT,* renal replacement therapy. *(Modified from reference 1.)*

Kidney Disease: Improving Global Outcomes (KDIGO) Composite Staging of AKI		
Stage	**Serum Creatinine**	**Urine Output**
1	1.5-1.9× baseline OR ≥0.3 mg/dl (≥26 µmol/l) increase	<0.5 ml/kg/h for 6-12 h
2	2.0-2.9× baseline	<0.5 ml/kg/h for ≥12 h
3	3.0× baseline OR Increase in serum creatinine to ≥4.0 mg/dl (≥352 µmol/l) OR Initiation of renal replacement therapy OR, in patients younger than 18 years, decrease in eGFR to <35 ml/min/1.73 m^2	<0.3 ml/kg/h for ≥24 h OR Anuria for ≥12 h

Table 71-2 KDIGO composite staging of AKI. *AKI,* Acute kidney injury; *eGFR,* estimated glomerular filtration rate. *(From reference 1.)*

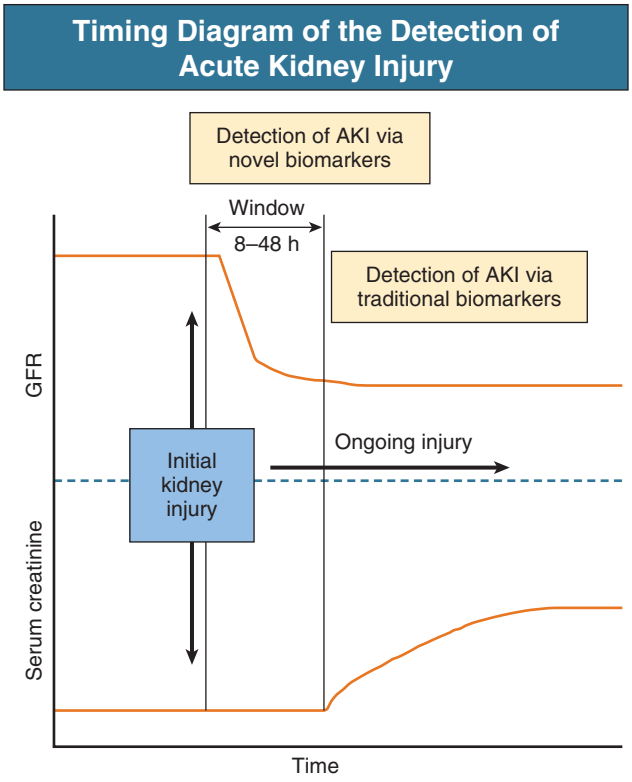

Figure 71-1 Timing diagram of the detection of acute kidney injury (AKI). *GFR,* Glomerular filtration rate. *(Adapted from reference 15.)*

to epidermal growth factor and is thereby involved in the progression of renal disease.[19] Urinary NGAL levels are increased in the setting of tubular stress or injury, but not in pre-renal disease.[20] NGAL is the most studied renal biomarker, with a large number of studies correlating urinary NGAL levels to the early detection of AKI.[15]

Interleukin (IL)-18 is an inflammatory cytokine found in macrophages and proximal tubule cells. Urinary IL-18 levels are upregulated in the setting of renal ischemic injury in multiple clinical settings: general ICU care, acute respiratory distress syndrome, contrast nephropathy, and cardiac surgery.[15]

Novel biomarkers of AKI have not reached clinical practice; however, they hold potential for detecting AKI early, identifying minor kidney injuries that do not raise serum creatinine concentrations, monitoring therapeutic benefits of novel treatment interventions, and specifying the cause of AKI. Whether the additional cost of screening for AKI or whether early detection of AKI will permit research that produces beneficial therapies for human AKI has not been established.[20]

Diagnostic Approach to Acute Kidney Injury

The basic diagnostic approach to patients with AKI is to determine the cause (see Chapter 69). This process should start by excluding or correcting both pre-renal and post-renal causes. In hospitalized patients, determining the correct causative diagnosis often involves selecting the most probable cause among many potential choices.[21] In this setting, assessing urine volume can narrow the differential diagnosis, dividing AKI into oliguric (less than 500 ml of urine output per day) and nonoliguric causes.

To correctly identify the cause of AKI, one needs an understanding of the natural history of AKI from different causes, a chronologic sequence of events preceding the AKI, and analysis of the available patient data. Although the differential diagnosis for AKI in

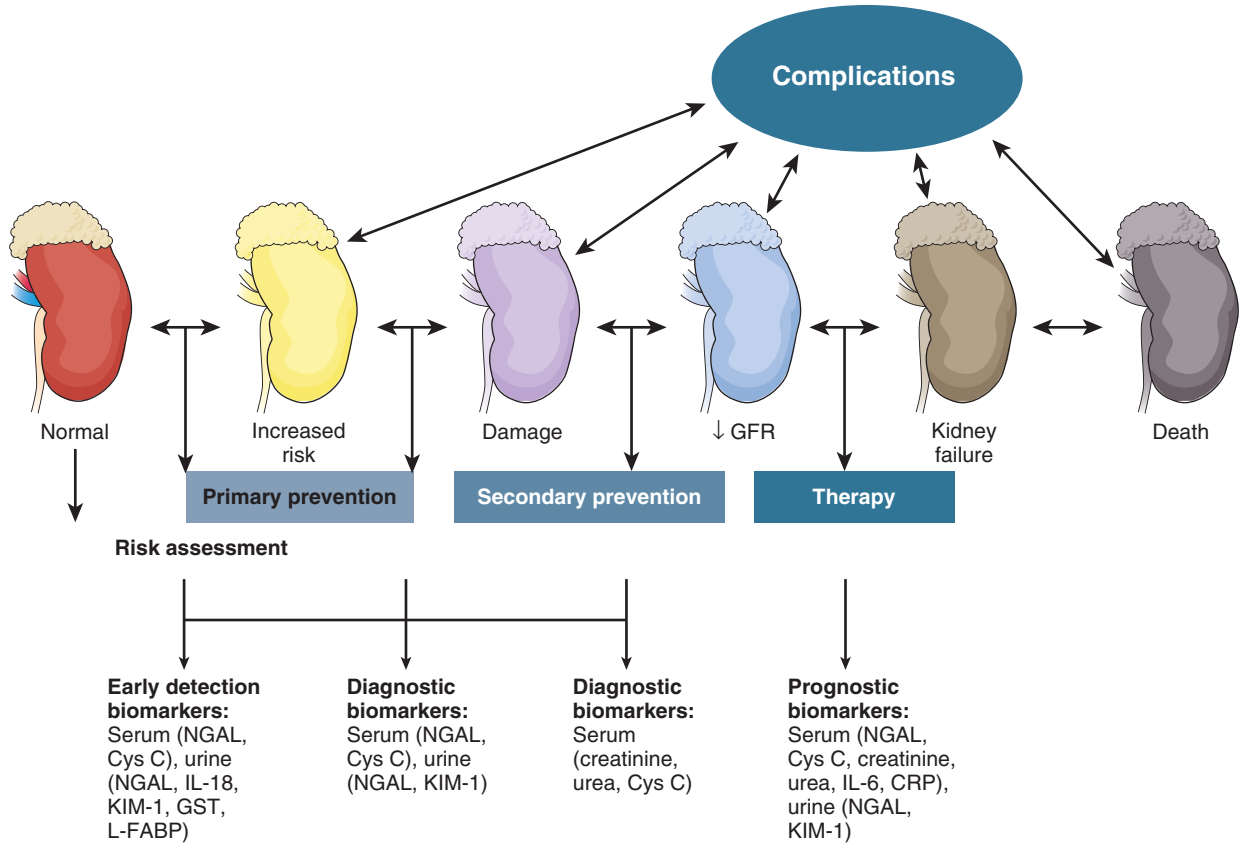

Figure 71-2 Continuum of kidney injury and biomarkers of acute kidney injury (AKI). Injury begins before excretory function is lost (i.e., decreased GFR) and can potentially be detected by the measurements of biomarkers. *CRP,* C-reactive protein; *Cys C,* cystatin C; *GFR,* glomerular filtration rate; *GST,* glutathione-*S*-transferase; *IL-6,* interleukin-6; *IL-18,* interleukin-18; *KIM-1,* kidney injury molecule 1; *L-FABP,* liver fatty acid–binding protein; *NGAL,* neutrophil gelatinase-associated lipocalin. *(Modified from reference 20.)*

hospitalized patients is large, a careful history and physical examination and basic laboratory tests often suffice for diagnosis (Table 71-3).[21]

Acute Kidney Injury Versus Chronic Kidney Disease

On occasion, it can be difficult to determine if a patient with renal failure has AKI or AKI superimposed on CKD. The patient's history and information about prior serum creatinine values are invaluable for differentiation of AKI and CKD. Ultrasonographic evidence of small, scarred kidneys is consistent with CKD. Notably, CKD caused by diabetic nephropathy, infiltrative disorders such as amyloidosis, human immunodeficiency virus–related nephropathy, or polycystic kidney disease can be present with normal or increased kidney size. The findings on presentation of normocytic anemia, hyperparathyroidism, peripheral neuropathy, and broad waxy casts in the urinary sediment would suggest CKD. Patients with CKD are at high risk for the development of episodes of AKI.[22] For patients with AKI superimposed on CKD, knowledge of prior serum creatinine concentrations is required to determine the degree of potentially reversible AKI.

Clinical Assessment

The evaluation of a hospitalized patient with AKI should begin with a complete medical history and review of the hospital records. Once the prior serum creatinine concentration or other evidence of underlying kidney disease has established the level of baseline kidney disease, the history should be directed toward the events preceding the AKI. These events may be part of a systemic disease process (e.g., sepsis, rhabdomyolysis), an inpatient event (e.g., surgical procedure, radiocontrast exposure, nephrotoxic medication exposure), or an outpatient event (e.g., medication or drug use, intravascular volume contraction from diarrhea or vomiting). Particular attention should be paid to the medication record including the use of nonsteroidal anti-inflammatory drugs (NSAIDs), renin-angiotensin-aldosterone antagonists, and antibiotic medications. Other features of the history include the use of Chinese herbs that contain aristolochic acid, a known nephrotoxin, or the use of a synthetic cannabinoid, a newly identified potential nephrotoxin.[23] In Africa and India the accidental or intentional ingestion of hair dyes containing paraphenylenediamine (PPD) may result in AKI. Clues in the history that point toward a post-renal cause (e.g., urinary hesitancy, frequent nocturia, pelvic or flank pain, overflow urinary incontinence, metastatic cancer) should be assessed early to prevent further kidney injury from a delay in treatment.

Physical examination often reveals signs that support a particular cause of AKI. Reduced body weight, marked orthostatic decrease in blood pressure, an increase in pulse, and lack of jugular venous distention all suggest a reduction in extracellular fluid volume. Notably, patients with pre-renal AKI can appear volume overloaded in cases of heart failure, cirrhosis, and nephrotic syndrome when effective arterial blood volume is reduced. In critically ill patients, assessment of intravascular volume status by physical examination can be challenging, and invasive hemodynamic monitoring of central

Differential Diagnosis by Pathophysiologic Classification of Acute Kidney Injury (AKI)	
Cause	**Comments**
Pre-renal	30%-60% of AKI
Volume depletion	Renal losses, GI losses, hemorrhage
Decreased cardiac output	Right- or left-sided heart failure, cardiac tamponade
Systemic vasodilation	Sepsis, anaphylaxis, anesthetics
Afferent arteriolar vasoconstriction	NSAIDs, calcineurin inhibitors, radiocontrast, hepatorenal syndrome, hypercalcemia
Efferent arteriolar vasodilation	ACE inhibitors, ARBs
Intrinsic	Approximately 40% of AKI
Acute tubular injury Ischemic Nephrotoxic (drug) Nephrotoxic (pigment)	 Aminoglycosides, lithium, amphotericin, pentamidine, cisplatin, ifosfamide, radiocontrast Rhabdomyolysis, intravascular hemolysis
Acute interstitial nephritis (AIN) Drug induced Infection related Autoimmune diseases Malignancy	 Penicillins, cephalosporins, NSAIDs, PPIs, allopurinol, rifampin, sulfonamides Pyelonephritis, viral nephritides Sjögren syndrome, sarcoidosis, SLE Lymphoma, leukemia
Intratubular obstruction Paraprotein Crystals	 Immunoglobulin light chains Acute phosphate nephropathy, tumor lysis syndrome, ethylene glycol, acyclovir, indinavir, methotrexate
Acute glomerulonephritis	Postinfectious, cryoglobulinemia, RPGN, SLE
Macrovascular	Increased renal vein pressure from increased intra-abdominal pressure, bilateral renal vein thrombosis, bilateral renal artery emboli
Microvascular	Atheroembolic disease, HUS, TTP, scleroderma renal crisis, malignant hypertension
Post-renal (Obstruction)	Approximately 10% of AKI
Intrinsic	Bilateral ureteral stones, bladder outlet obstruction (prostatic enlargement or blood clot), neurogenic bladder
Extrinsic	Retroperitoneal fibrosis, metastatic cancer

Table 71-3 Differential diagnosis by pathophysiologic classification of AKI. *ACE,* Angiotensin-converting enzyme; *ARBs,* angiotensin receptor blockers; *GI,* gastrointestinal; *HUS,* hemolytic uremic syndrome; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *PPIs,* proton-pump inhibitors; *RPGN,* rapidly progressive glomerulonephritis; *SLE,* systemic lupus erythematosus; *TTP,* thrombotic thrombocytopenic purpura.

venous pressure or pulmonary capillary wedge pressure (PCWP) may be necessary to differentiate volume overload from noncardiogenic pulmonary infiltrates. A low PCWP suggests noncardiogenic pulmonary edema.[21] Trends in daily intake and output volumes also assist in determining the extracellular fluid volume of the critically ill patient.

The initial physical examination should include a careful examination of the abdomen. A tender, distended bladder indicates a lower urinary tract obstruction, and when this is present, sterile postvoid bladder catheterization should be performed. A distended, tense abdominal wall may represent ascites, aggressive intravenous fluid resuscitation, or recent abdominal surgery. Intra-abdominal pressure can be measured in the ICU to identify AKI from abdominal compartment syndrome, defined as an intra-abdominal pressure exceeding 20 mm Hg.[24]

Fever, skin rash, and arthralgias may be signs of a systemic disease process, such as systemic lupus erythematosus, vasculitis, endocarditis, or drug allergy with acute interstitial nephritis (AIN). A leukocytoclastic rash on the lower extremities may, for example, be Henoch-Schönlein purpura in a younger patient or cryoglobulinemia in an older patient with a hepatitis C infection. A history of recent aortic catheterization (e.g., cardiac catheterization) and the findings of livedo reticularis or a discolored toe are diagnostic clues for cholesterol or atheromatous emboli. Painless hematuria suggests acute glomerulonephritis (GN) or genitourinary malignancy, whereas painful hematuria is more consistent with obstruction.[21]

Laboratory Tests

Differentiating the two most common causes of AKI in hospitalized patients, pre-renal AKI and acute tubular necrosis (ATN), may be difficult when both the effective arterial blood volume and the time course of the kidney injury are unknown.[25] Here the term *acute tubular injury* (ATI) may be added to ATN to more accurately describe the pathology involved in intrinsic AKI from ischemic or toxic insults.[26] Evaluation of urine volume, urinary sediment, and urinary indices (the last is useful only in patients with oliguria) is particularly helpful in making the correct diagnosis (Table 71-4). Initial laboratory tests include a urinalysis and basic metabolic panel with measurement of blood urea nitrogen (BUN) and serum sodium, potassium, bicarbonate, and creatinine levels. These tests are important not only for the diagnosis but also for assessment of complications of AKI.[21]

Results from initial laboratory testing may prompt further testing. For example, glycosuria occurring with a normal plasma glucose level offers evidence for proximal tubular dysfunction. The presence of amino acids and bicarbonate in the urine along with elevated urinary levels of phosphate and uric acid confirm Fanconi syndrome, a form of proximal tubular injury seen with AKI from cisplatin or tenofovir use and immunoglobulin free light-chain (FLC) cytotoxicity.

Ratio of Blood Urea Nitrogen to Creatinine

The BUN-creatinine ratio is 10:1 to 15:1 (when both are expressed in mg/dl; 40 to 60 when expressed in mmol/l) in normal individuals.

Clinical and Laboratory Variables in the Differential Diagnosis Between Pre-renal and Renal Acute Kidney Injury (AKI)

	Pre-renal	Renal
History	GI, urinary, skin volume loss, blood loss, or third spacing	Drugs or toxin exposure, hemodynamic change
Clinical presentation	Hypotension or volume depletion	No specific symptoms or signs
Laboratory studies		
BUN/S_{Cr}	>20	<20
Sediment	Normal to few casts	"Muddy brown" casts
U_{osm} (mmol/kg)	>500	<350
Proteinuria	None to trace	Mild to moderate
U_{Na} (mmol/l)	<20	>40
FE_{Na} (%)	<1	>1
FE_{Urea} (%)	<35	>35
Novel biomarkers	None	KIM-1, cystatin C, NGAL, CYR61, others

Table 71-4 Clinical and laboratory variables in the differential diagnosis between pre-renal and renal AKI. *BUN,* blood urea nitrogen; *CYR61,* cysteine-rich protein 61; FE_{Na}, fractional excretion of sodium; FE_{Urea}, fractional excretion of urea; *GI,* gastrointestinal; *KIM-1,* kidney injury molecule 1; *NGAL,* neutrophil gelatinase–associated lipocalin; S_{Cr}, serum creatinine; U_{Na}, urinary sodium; U_{osm}, urinary osmolality.

In pre-renal AKI the ratio may be greater than 20:1 because of a disproportionate increase in urea reabsorption resulting from elevated antidiuretic hormone levels. A high ratio is not specific for pre-renal injury because gastrointestinal bleeding, impaired protein anabolism (e.g., systemic corticosteroid or tetracycline administration), increased catabolism (e.g., sepsis), and increased protein intake can raise BUN levels. Pre-renal AKI should not be excluded by a normal ratio because diminished urea production from decreased protein intake or underlying liver disease can prevent the expected rise in the BUN by increased tubular reabsorption. Also, elevations in creatinine levels may exceed BUN levels in patients with creatinine kinase release from muscle breakdown, as in rhabdomyolysis.

Urine Volume

In AKI, urine volume has been shown to directly correlate with residual GFR.[27] Urine volume therefore can both indicate the severity of AKI and provide important diagnostic information. Oliguric AKI (urine output less than 500 ml/day) is typically associated with worse outcomes than AKI with preserved urine volume, especially with a positive fluid balance in the critical care setting.[28-30] Oliguria commonly occurs in AKI caused by ATN, although it can also be seen in pre-renal AKI with early detection or AIN. Wide variations in daily urine output suggest obstruction. Complete anuria (no urine output) suggests obstruction or an acute vascular catastrophe, such as renal vein or renal artery occlusion, although it can be seen in ATN and AIN. For a vascular event to cause complete anuria, it must affect both kidneys or a single functioning kidney.[21]

Urinalysis and Urine Microscopy

In the setting of AKI a dipstick urinalysis provides the first clue to the presence of red blood cells (RBCs) or protein in the urine. However, urinary dipstick results have significant limitations and must be interpreted in conjunction with more specific tests such as a spot urinary protein- or albumin-creatinine ratio and urine microscopy. A few notable limitations of the dipstick urinalysis include an inability to detect FLC protein components of immunoglobulins and the false-positive detection of protein in the setting of radiographic contrast or alkaline urine. The dipstick urinalysis can provide useful diagnostic information when used in conjunction with urine microscopy. For example, the presence of hemoglobin or myoglobin in the urine is supported by finding blood by dipstick and no RBCs by urine microscopy. Urine microscopy has been validated as a diagnostic and prognostic tool in hospitalized patients with AKI.[25] A fresh urine sample is centrifuged and the sediment examined by light microscopy for the presence of cells, casts, and crystals (Figs. 71-3 and 71-4). A normal urine sediment contains few cells or casts, termed a "bland" sediment. Urine microscopy in early pre-renal AKI is typically normal with occasional hyaline casts. "Muddy brown" granular casts and renal tubular epithelial cells in the urine support ATN-related AKI. In a study of 197 hospitalized patients with AKI defined by the AKIN criteria, the presence of more than 10 granular casts per low power field had a positive predictive value of 100% for a final diagnosis of ATN. In this same study, a urine sediment score based on granular casts and renal tubular epithelial cells was directly associated with worsening AKI, defined as a composite outcome of higher AKIN stage, dialysis requirement, and death. These findings suggest that urine microscopy is useful both in distinguishing ATN-related AKI from pre-renal AKI and in predicting the severity of AKI.[25]

Findings on urinalysis and urine microscopy may offer insights into renal history (broad, waxy casts are often seen in CKD) but, more important, may be diagnostic clues to a rare cause of AKI. A proliferative GN is characterized by a urinary dipstick with 3+ to 4+ blood and 2+ to 3+ protein with an active sediment of RBCs and RBC casts identified with urine microscopy. In this setting the history and physical examination findings should be supported by serologic testing and a kidney biopsy, if the kidneys are normal in size. The presence of white blood cells in clumps and casts, in the absence of bacteria, suggests AIN.[21] Renal tubular epithelial cells, granular casts, RBCs, and even RBC casts can be seen in the urinary sediment of patients with AIN. Urinary eosinophils are neither highly sensitive nor specific for diagnosis of drug-associated AIN. Cystitis, prostatitis, pyelonephritis, atheroembolic disease, ATN, and rapidly progressive glomerulonephritis (RPGN) may all cause eosinophiluria in the absence of AIN.[31,32] A urine sediment with abundant uric acid crystals accompanying high serum phosphorus levels in a patient undergoing chemotherapy may indicate tumor lysis syndrome.

Urinalysis and urine microscopy are discussed further in Chapter 4.

Fractional Excretion of Sodium and Urea

The urine-serum concentrations of sodium in relation to the urine-serum concentrations of creatinine (fractional excretion of sodium [FE_{Na}]) has been used to approximate renal tubular function:

$$FE_{Na} = \frac{[U/S]_{Na}}{[U/S]_{Cr}} \times 100\%$$

where U = urine, S = serum, Na = sodium, and Cr = creatinine.

The basic premise is that renal tubular cells will reabsorb sodium in the pre-renal setting, whereas tubules damaged by ATN will not.[33] FE_{Na} below 1% is consistent with pre-renal AKI, and FE_{Na} above 3% is typical of ATN. However, many exceptions to these cutoffs have been discovered since FE_{Na} was first introduced into clinical practice in 1976. FE_{Na} may be less than 1% despite the presence of ATN in the setting of sepsis, hemoglobinuria or myoglobinuria, radiocontrast exposure, nonoliguria, heart failure, and advanced cirrhosis. Underlying CKD, diuretic use, recent intravenous fluid administration, glucosuria, bicarbonaturia, and salt-wasting disorders may be

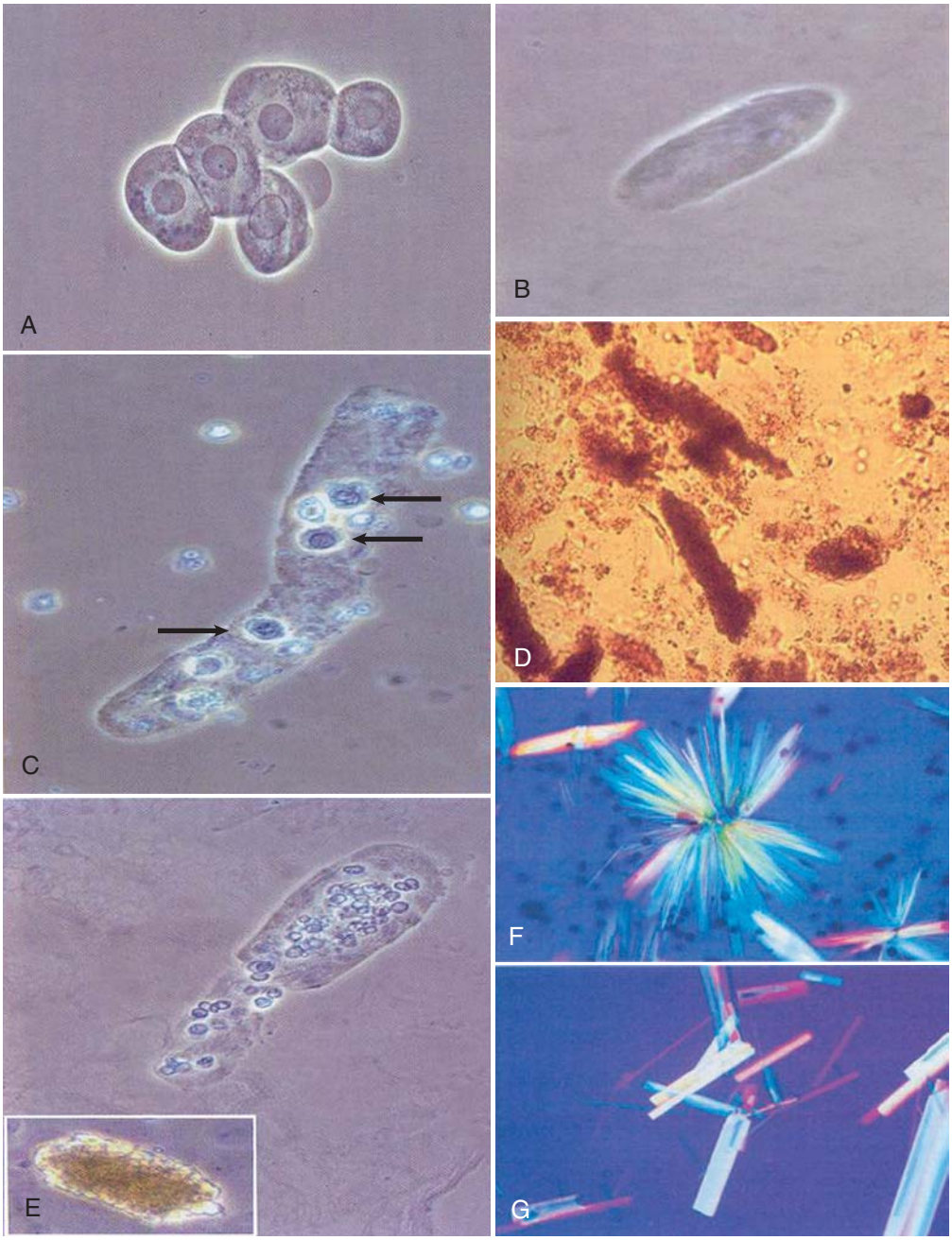

Figure 71-3 Examples of urinary sediments seen in acute kidney injury. **A,** Epithelial cell aggregate. **B,** Hyaline cast as can be seen in pre-renal acute kidney injury. **C,** Epithelial cast as can be seen in early acute tubular necrosis (*arrows* indicate epithelial cells). **D,** Muddy brown cast, typical of established acute tubular necrosis. **E,** Erythrocyte cast as seen in glomerulonephritis and vasculitis. *Inset:* Hemoglobin cast. **F** and **G,** Two forms of indinavir crystals.

associated with elevated FE_{Na} despite the presence of pre-renal AKI.[33] Therefore FE_{Na} has significant limitations in the setting of hospital-acquired AKI, where confounders abound, yet may be helpful in differentiating pre-renal AKI from ATN in specific patient populations with oliguria. Urea reabsorption, primarily occurring in proximal tubules, is less affected by loop and thiazide diuretics, and the fractional excretion of urea (FE_{Urea}) may be a useful alternative to FE_{Na} in patients receiving diuretics. FE_{Urea} calculation is identical to that of FE_{Na}, with replacement of urea for sodium, and values less than 35% favor pre-renal AKI over ATN.

Imaging Studies

Kidney imaging may not be necessary if a clear diagnosis of AKI exists (e.g., pre-renal AKI or ATN). However, when the diagnosis is uncertain, and especially if the clinical picture supports urinary obstruction or renal vascular occlusion, then further diagnostic testing is indicated.[21] Renal ultrasound is a reliable, noninvasive method of assessment of the kidney and urinary tract. It can identify urinary obstruction, polycystic kidney disease, and the size and number of kidneys. When Doppler flow is used, renal artery and veins can be assessed for patency. High-resolution, noncontrast computed tomographic imaging is the preferred test for the detection of urinary tract calculi. Radioisotope renography may be used to estimate the renal plasma flow in a transplanted kidney with AKI but is increasingly replaced by Doppler ultrasound. Other radionuclide methods are less useful in AKI (e.g., tagged white blood cell scan for AIN). Magnetic resonance imaging without contrast is now recommended to evaluate renal arterial or venous thrombosis.[21]

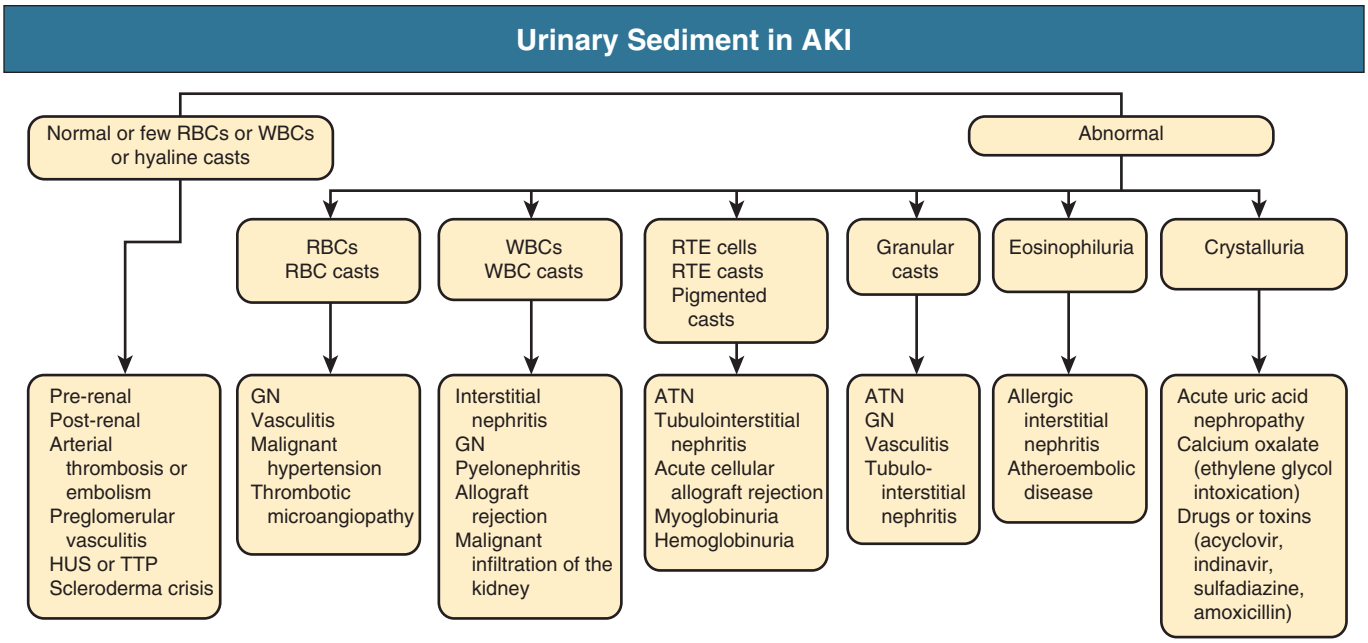

Figure 71-4 Urinary sediment in acute kidney injury (AKI). *ATN,* Acute tubular necrosis; *GN,* glomerulonephritis; *HUS,* hemolytic uremic syndrome; *RBC,* red blood cell; *RTE,* renal tubular epithelial; *TTP,* thrombotic thrombocytopenic purpura; *WBC,* white blood cell.

Renal Biopsy

Renal biopsy is reserved for patients in whom pre-renal and post-renal AKI have been excluded and the cause of intrinsic renal AKI remains unclear. Renal biopsy is particularly useful when clinical assessment and laboratory investigations suggest diagnoses other than ischemic or nephrotoxic injury that may respond to disease-specific therapy. Examples include RPGN, vasculitis, systemic lupus erythematosus, and AIN.

ACUTE KIDNEY INJURY IN SPECIFIC SETTINGS

Acute Tubular Necrosis

Acute tubular necrosis is a clinical syndrome of abrupt and sustained decline in GFR that is triggered by an acute ischemic or nephrotoxic event and develops within minutes to days after the insult.[21] Apart from kidney biopsy, no definitive test exists to diagnose ATN. The diagnosis is suggested by a history of recent hypotension, volume depletion, sepsis, or nephrotoxic exposure. Muddy-brown, coarse, granular casts are present on urine microscopy in the majority of patients with ATN, particularly those who are oliguric.[21] Other laboratory findings consistent with the diagnosis of ATN are shown in Table 71-4.

The pathophysiology of ATN involves multiple pathways (see Chapter 69). Obstruction of flow within the tubule by cellular debris, disruptions of tubular cell polarity and cytoskeleton, loss of the lining epithelium with resulting backleak of glomerular filtrate into the renal interstitium, and afferent arteriolar constriction have all been proposed as playing pathophysiologic roles in ATN. In general, ATN has been described as a (mal)adaptive response of the kidney—"trading away" GFR for the preservation of medullary oxygenation and tubular integrity.[26]

Acute tubular necrosis in the setting of ischemia-reperfusion is usually most severe within the outer medulla of the kidney (see Chapter 69).[34] The typical histologic features of human proximal tubular injury include vacuolation, loss of brush border, disruption of the epithelial cells lining the tubule, and presence of intratubular casts. Necrosis of tubular cells is patchy and is not usually dominant in the biopsy specimen, perhaps in part because most biopsy specimens are from the cortex and the outer medulla is not sampled adequately. Apoptosis of tubular cells is present in renal biopsy specimens from humans with ATN, and evidence of cellular regeneration is often seen, most commonly in those areas of greatest tubular cell loss. Furthermore, regenerative changes and signs of fresh epithelial injury are often observed in the same biopsy specimen, suggesting that recurrent episodes of tubular ischemia continue to occur during the maintenance phase of ATN. The morphologic appearance of the common forms of nephrotoxin-induced ATN is similar to that of ischemic ATN. Correlations of morphologic findings to functional endpoints has been difficult, especially because the biopsy represents a limited view of the pathologic process at one point in time and usually samples only the cortex of the kidney.

Acute Interstitial Nephritis

Acute interstitial nephritis is characterized by the presence of inflammatory infiltrates and edema within the interstitium, with an accompanying, acute deterioration in renal function (see Chapter 69).[35] It is not an uncommon cause of AKI, accounting for 15% to 27% of renal biopsies performed because of AKI, yet AIN may be overlooked as a cause of AKI in settings where ATN is common (e.g., sepsis). Drug use is the most common cause of AIN (see Table 71-3), with antimicrobials and NSAIDs being the most frequently responsible agents.[35]

The variability in clinical presentation of patients with AIN makes the diagnosis, which generally requires kidney biopsy, challenging. In patients with drug-induced AIN the mean delay between drug exposure and the appearance of renal manifestations is 10 days, although the latent period can be as short as 1 day with some antibiotics or as long as several months with NSAIDs.[35] In a total of 121 pooled patients with AIN, the reported frequency of symptoms included arthralgias, 45%; fever, 36%; and skin rash, 22%. In the same analysis, urinary findings included non-nephrotic proteinuria (93%), leukocyturia (82%), and microscopic hematuria (67%).[35] The classic

clinical presentation of maculopapular rash, peripheral eosinophilia, and arthralgias may not be present in drug-induced AIN and is uncommon in infection-related or idiopathic AIN (see Table 71-3).

Acute Kidney Injury from Intratubular Obstruction

Several endogenous and exogenous molecules can precipitate in the tubular lumen to produce AKI. These include uric acid, calcium phosphate, calcium oxalate, immunoglobulin free–light chains, myoglobin, and medications (e.g., acyclovir, indinavir, methotrexate and methotrexate analogues, sodium phosphate–containing cathartics, and sulfadiazine).[21] Medication-induced crystal nephropathy occurs more commonly when high doses of medication are combined with low tubular flow rates from volume contraction or underlying CKD.

Ethylene glycol ingestion may result in AKI from calcium oxalate crystal deposition. Ethylene glycol is an odorless, sweet-tasting liquid found in solvents and antifreeze. Patients with ethylene glycol poisoning typically present with disorientation and agitation and are found to have a plasma osmolar gap that progresses into a high anion gap metabolic acidosis as the ethylene glycol is metabolized into glycolic acid. The glycolic acid is converted to oxalic acid, which binds free calcium to form calcium oxalate crystals. Crystal deposition resulting in AKI typically manifests 48 to 72 hours after ingestion; however, calcium oxalate crystals can be readily identified in the urine soon after exposure.

Intratubular obstruction from calcium phosphate and uric acid crystals is the presumed pathogenesis of AKI in tumor lysis syndrome. Tumor lysis syndrome is characterized by a constellation of metabolic derangements caused by massive and abrupt release of intracellular components in the blood after rapid lysis of malignant cells. It is typically seen after initiation of cytotoxic therapy for hematologic malignancies with large tumor burden or cell counts as in acute lymphoblastic lymphoma (ALL), Burkitt lymphoma, or acute myeloid leukemia (AML).[36] Clinical features of tumor lysis syndrome result from the effects of the metabolic derangements. Hyperkalemia may induce cardiac arrhythmias, weakness, and paresthesias. Hyperphosphatemia initially produces muscle cramps and lethargy but can also promote nausea, vomiting, diarrhea, and seizure. Hypocalcemia, primarily caused by phosphorus binding, causes similar symptoms with muscle cramps, tetany, cardiac arrhythmias, and seizures.[36] The presence of hyperkalemia and hypocalcemia associated with AKI in a patient receiving cytotoxic chemotherapy may be the only initial clues to the syndrome because blood uric acid and phosphate levels are not routinely monitored. In this setting, urine microscopy can assist in the diagnosis of AKI by revealing the presence of many uric acid crystals.

Rhabdomyolysis

Rhabdomyolysis is characterized by the leakage of muscle-cell contents, including myoglobin, electrolytes, creatinine kinase, aldolase, lactate dehydrogenase, and aspartate aminotransferase (AST) into the circulation.[37] AKI, occurring primarily in severe rhabdomyolysis, results from renal vasoconstriction, proximal tubular cell injury from oxidant stress, and intranephronal obstruction. Myoglobin, a heme pigment protein that contains iron in the ferrous (Fe^{2+}) state, has less nephrotoxicity in alkaline urine. Intravascular volume contraction and acidic urine promote distal tubule obstruction from myoglobin precipitation.

Muscle injury leading to rhabdomyolysis frequently follows trauma (e.g., crush syndrome or limb compression from prolonged immobilization); however, causes unrelated to trauma exist and include increased exertion (e.g., seizure, alcohol withdraw, strenuous exercise), genetic defects (e.g., disorders of glycolysis or gluconeogenesis, disorders of lipid metabolism, and mitochondrial disorders), infections (e.g., influenza A and B), body temperature changes (e.g., heat stroke, neuroleptic malignant syndrome, and hypothermia), and drug or toxin exposure (e.g., lipid-lowering drugs, alcohol, cocaine, and heroin).[37]

Patients with acute rhabdomyolysis often present with muscle pain and reddish-brown urine. The presence of pigmented granular casts and the lack of RBCs on urine microscopy coupled with a blood-positive urinary dipstick are important diagnostic clues for rhabdomyolysis-related AKI. However, the diagnosis must be confirmed by elevated serum creatinine kinase levels and the presence of urinary myoglobin.[21] A weak correlation exists between creatinine kinase values and the incidence of AKI, and the risk of AKI is lower when creatinine kinase levels at admission are less than 20,000 U/l. Rhabdomyolysis may contribute to AKI with creatinine kinase levels as low as 5000 U/l when coexisting conditions such as sepsis, intravascular volume contraction, and acidosis are present.[37]

Acute Kidney Injury in Multiple Myeloma

Monoclonal immunoglobulin FLCs are responsible for the majority of severe AKI in patients with multiple myeloma. In the setting of plasma cell dyscrasia, monoclonal FLCs are overproduced, often with circulating levels hundreds times higher than normal.[38] These low-molecular-weight proteins are freely filtered through the glomerulus and reabsorbed in the proximal tubule. Unlike most endogenously produced proteins, monoclonal FLCs have a strong propensity to cause tubular damage (see Chapter 27).[38] Some monoclonal FLCs are cytotoxic and promote proximal tubular cell injury, with one mechanism resulting in a defect in sodium-coupled cotransport processes producing type II renal tubular acidosis, aminoaciduria, phosphaturia, and glycosuria (i.e., Fanconi syndrome).[39] A separate mechanism of FLC-mediated AKI is intratubular obstruction from precipitation of monoclonal FLCs in the distal nephron, cast nephropathy.[21] Cast formation occurs under specific conditions mediated by the ionic composition of tubule fluid, tubule fluid flow rates, the concentration of Tamm-Horsfall glycoprotein and FLCs, the strength of the binding interaction between Tamm-Horsfall glycoprotein and FLC, and the presence of furosemide.[38] AKI attributed to cast nephropathy occurs in approximately one third of patients with multiple myeloma and AKI. Other causes of AKI include extrarenal obstruction (e.g., nephrolithiasis, amyloid deposition in the ureters), hypercalcemia, hyperviscosity syndrome, and non–myeloma-related causes (e.g., AIN or contrast-induced nephropathy [CIN]).[21]

Cast nephropathy should be considered, particularly in an older patient with unexplained AKI. Predisposing conditions may include hypercalcemia, intravascular volume contraction, furosemide use, exposure to radiocontrast, and/or NSAID use. AKI may be the presenting event in patients with an undiagnosed plasma cell dyscrasia. Because FLC may not be detected on dipstick analysis, urinalysis in cast nephropathy will often show no or trace protein, and the urinary sediment is typically bland. Assay of serum FLC levels is critical in assisting in the differential diagnosis of unexplained AKI: levels above 500 mg/L strongly support a diagnosis of cast nephropathy. However, cast nephropathy may still occur when the monoclonal FLC level is below 500 mg/l if the FLC is particularly nephrotoxic, and kidney biopsy may be needed to diagnose cast nephropathy. In a study querying a renal biopsy database, a low urinary albumin excretion (<10%) assessed with 24-h urine electrophoresis was found

useful in distinguishing cast nephropathy from ATN and less acute causes of kidney injury in multiple myeloma (e.g., amyloid light-chain [AL] amyloidosis and monoclonal immunoglobulin deposition disease).[40]

Contrast-Induced Nephropathy

Contrast-induced nephropathy, defined as AKI occurring shortly after exposure to intravenous radiocontrast, is a common cause of AKI. However the incidence of CIN is low (<1%) in patients with normal renal function and no other risk factors for AKI.[21] Risk factors for CIN include CKD, diabetic nephropathy, advanced heart failure, states of reduced renal perfusion, high total dose of contrast, and concomitant exposure to other nephrotoxins. Data from animal models suggest that both renal vasoconstriction from direct effects of the contrast media and toxic injury of tubular cells are the main factors in the pathophysiology of CIN.[41] The kidney injury likely occurs within minutes of contrast exposure; however, the detection of AKI is typically delayed by 24 to 48 hours after contrast exposure. The timing of AKI in relation to contrast exposure and the exclusion of other causes of AKI generally suffice for diagnosis. Urinalysis and urine sediment findings are typically consistent with ATN. Renal biopsy is generally not helpful in the setting of CIN because the expected findings of ATN are nonspecific, no CIN-specific treatment exists, and the renal injury is typically short lived.

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CHAPTER 72

Epidemiology and Prognostic Impact of Acute Kidney Injury

Neesh Pannu and Marcello Tonelli

Over the last decade, there has been a paradigm shift in our understanding of acute kidney injury (AKI). Although the condition was initially described and defined as a complete loss of kidney function, it is now widely recognized that lesser degrees of kidney injury have important implications for health. AKI represents a heterogeneous clinical syndrome with multiple causes rather than a specific disease. However, whether occurring in isolation or in critically ill patients with multiple organ failure, AKI (as defined by small, often reversible changes in kidney function) is consistently associated with an increased risk of adverse outcomes.[1] This chapter reviews the incidence, risk factors, and outcomes associated with AKI as well as recent evidence linking AKI to the development of chronic kidney disease (CKD).

INCIDENCE OF ACUTE KIDNEY INJURY

The incidence of AKI in unselected hospitalized patients has been estimated to be 0.4% to 18% depending on the definitions used, and AKI accounts for 1% to 4% of all hospital admissions. Several large U.S. studies suggest that the incidence of AKI in hospitalized patients has increased dramatically over the last several decades; one study suggested that the number of hospitalizations of patients with a diagnosis of acute renal failure (ARF; defined by *International Classification of Diseases,* Ninth Edition [ICD-9] codes) increased from 35,000 in 1979 to 650,000 in 2002—an increase of 13% per year.[2] Available studies are based on ICD-9 diagnostic codes, which are highly specific for AKI (defined as a 100% increase in serum creatinine) but are relatively insensitive, especially for milder forms of AKI. Thus the reported incidence of AKI in these studies is likely a gross underestimate of the true incidence. Also pointing to an increased burden of AKI in the general population are the observed 10% annual increase in acute dialysis episodes in the United States between 2000 and 2009 and the twofold increase in the number of deaths attributable to AKI over a similar period (Fig. 72-1).[3] The reasons underlying the increased incidence of AKI have not been determined but are likely related to increasing patient age and a higher burden of comorbidity, including a higher prevalence of CKD. Although these studies showed a decrease in attributable mortality over time, AKI survivors had prolonged hospital length of stay and a greater requirement for posthospitalization care,[4] therefore incurring significantly increased health care costs.[5]

The incidence of AKI as determined by use of consensus definitions based on serum creatinine (S_{Cr}) and urine output has been best characterized in critically ill populations in which laboratory and urine output data are frequently measured. Despite the use of common definitions for AKI in these populations, multicenter studies have reported the incidence of AKI to be 10% to 67%, likely reflecting case mix differences among health care systems and countries.

CAUSES OF ACUTE KIDNEY INJURY

The causes of AKI in hospitalized patients have not been well characterized. However, several smaller studies have reported acute tubular necrosis (nephrotoxic and ischemic) and prerenal causes to account for the majority of patients (see also Chapter 69).[6] Other potentially modifiable causes of AKI include more widespread use of radiocontrast and other nephrotoxic medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, diuretics, and chemotherapeutic agents. Exposure to potentially nephrotoxic medications is particularly common in patients with CKD, which further suggests that AKI could have increasingly important effects on the incidence of CKD.

RISK FACTORS FOR ACUTE KIDNEY INJURY

Risk factors for AKI have been determined in a variety of clinical settings, including cardiac surgery, contrast-induced AKI, and critically ill populations; however, risk prediction models that accurately predict the occurrence of AKI have been elusive. Diabetes and volume depletion as a result of drugs, gastrointestinal losses, and intercurrent illnesses are well described risk factors for AKI. Nonmodifiable risk factors common to all populations are presented in Box 72-1. Recent observational studies have more accurately quantified the risk associated with some of these factors.

Age

The incidence of AKI is highest in people aged 65 and older, and an independent association exists between AKI and older age (Fig. 72-2).[2,3] In a community-based prospective study, the very elderly (aged 80 to 89) were 55 times more likely to develop AKI than adults younger than the age of 50.[7] The association between age and AKI is found in studies that use administrative data (ICD-9 codes) to define AKI, and also in large databases in which inpatient and outpatient S_{Cr} values are used to define AKI. There are several possible reasons for this association: (1) structural and functional changes associated with age that lead to diminished nephron reserve and reduced renal capacity for autoregulation; (2) accumulation of comorbidities (e.g., vascular disease, diabetes, hypertension, CKD), which increases susceptibility to AKI; and (3) increased exposure among the elderly to medications (ACE inhibitors, NSAIDs,

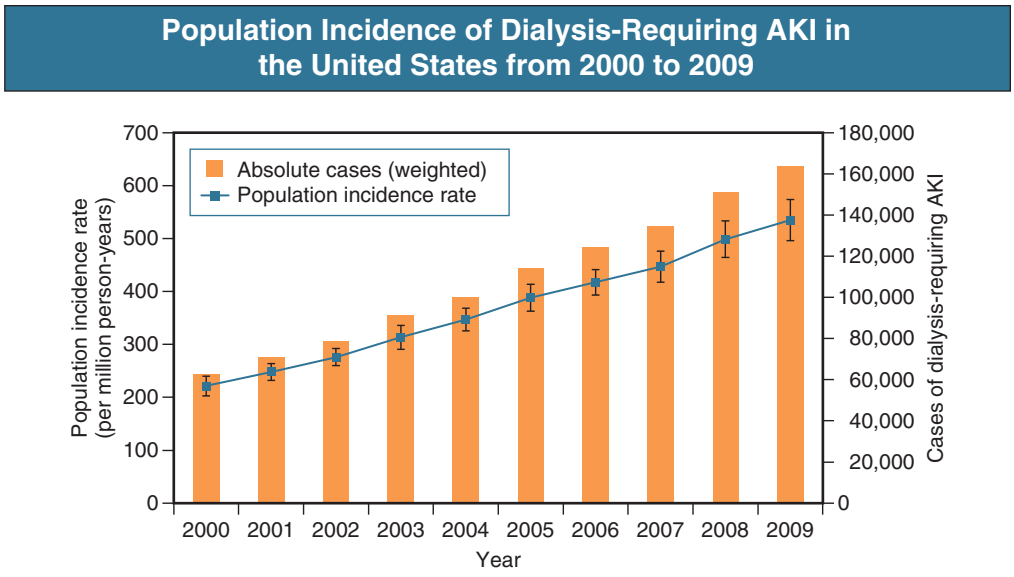

Figure 72-1 Population incidence of patients with AKI who require dialysis in the United States from 2000 to 2009 (absolute count and incidence rate per million person-years). Whiskers represent 95% confidence interval (CI) for incidence rates. The number of cases of AKI in which patients required dialysis increased from 63,000 in 2000 to almost 164,000 in 2009; the population incidence increased at 10% per year from 222 to 533 cases per million person-years. *(From reference 3.)*

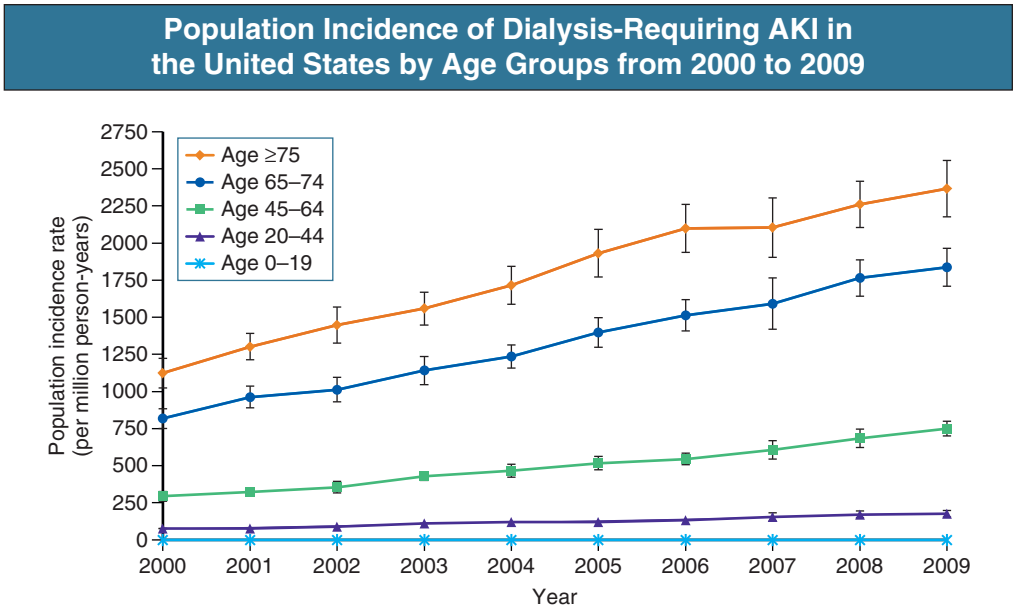

Figure 72-2 Population incidence of acute kidney injury (AKI) patients requiring dialysis in the United States by age group from 2000 to 2009. Whiskers represent 95% confidence interval (CI) for incidence rates. All age groups showed a similar pattern of increase in incidence. *(From reference 3.)*

Patient-Specific Risk Factors for Acute Kidney Injury (AKI)

Age	Congestive heart failure
Gender (male)	Sepsis
Chronic kidney disease	Volume depletion
Proteinuria	Chronic liver disease
Diabetes	Hyperuricemia

Box 72-1 Patient-specific risk factors for AKI.

diuretics) and procedures (surgery, diagnostic testing with radiocontrast) that are associated with the development of AKI.[8]

Chronic Kidney Disease

Chronic kidney disease appears to be among the most potent risk factors for AKI after exposure to radiocontrast, major surgery, and other medical conditions. A U.S. study demonstrated a direct relationship between underlying CKD stage and AKI in which renal replacement therapy (RRT) was required,[9] whereby even patients with mild underlying CKD (estimated glomerular filtration rate [eGFR] 45 to 60 ml/min/1.73 m^2) had a twofold increased risk of dialysis requirement. Patients with more severe CKD (eGFR below 30 ml/min/1.73 m^2) had a 30- to 40-fold higher risk of developing AKI. It is interesting to note that patients with CKD have been reported to have a lower absolute in-hospital mortality as compared with patients without CKD who develop AKI (see later).

Proteinuria

A case-control study of more than 600,000 patients that evaluated the association between CKD and AKI patients identified proteinuria as an independent predictor for AKI.[9] These findings have since been confirmed in a number of clinical settings. A cohort study of 1235 adults undergoing coronary artery bypass graft in Taiwan demonstrated that mild and heavy degrees of proteinuria detected by

dipstick were associated with an increasingly higher odds ratio of postoperative AKI, independent of CKD stage.[10] A U.S. study of more than 11,000 patients determined that elevated urine albumin-creatinine ratio (UACR) was an independent risk factor for hospitalizations with AKI; after stratification by albuminuria the adjusted relative hazards of AKI were 1.9, 2.2, and 4.8, for albumin creatinine ratios of <30 mg/g, 3-299 mg/g, and >300 mg/g, respectively, relative to patients without proteinuria.[11] A large population-based retrospective cohort of more than 900 000 adults in Canada found the same magnitude of association and demonstrated increased rates of hospital admissions with AKI for patients with mild and moderate dipstick proteinuria across all values of eGFR (Fig. 72-3).[12]

ASSOCIATIONS BETWEEN ACUTE KIDNEY INJURY AND ADVERSE OUTCOMES

Acute kidney injury is associated with high costs and adverse clinical outcomes, including excess mortality, increased length of hospital stay, the development and/or progression of CKD, and the requirement for chronic dialysis in survivors. In its most severe form (requirement for acute dialysis), AKI is associated with mortality ranging from 15% in patients with isolated AKI to as high as to 80% in critically ill patients.

MORTALITY

Mortality is increased among patients who experience AKI during hospitalization.[1] However, the comparison of patients with AKI to those without AKI does not distinguish between the increased risk for death caused by AKI and the increased risk imparted by the severity of illness that causes AKI. Nonetheless, the development of AKI is an important marker of prognosis.

A meta-analysis of studies of hospitalized patients confirms a graded relationship between increasing severity of AKI and short-term mortality. Most important, even mild forms of AKI were shown to be clinically relevant; an increase in serum creatinine of 26 µmol/l

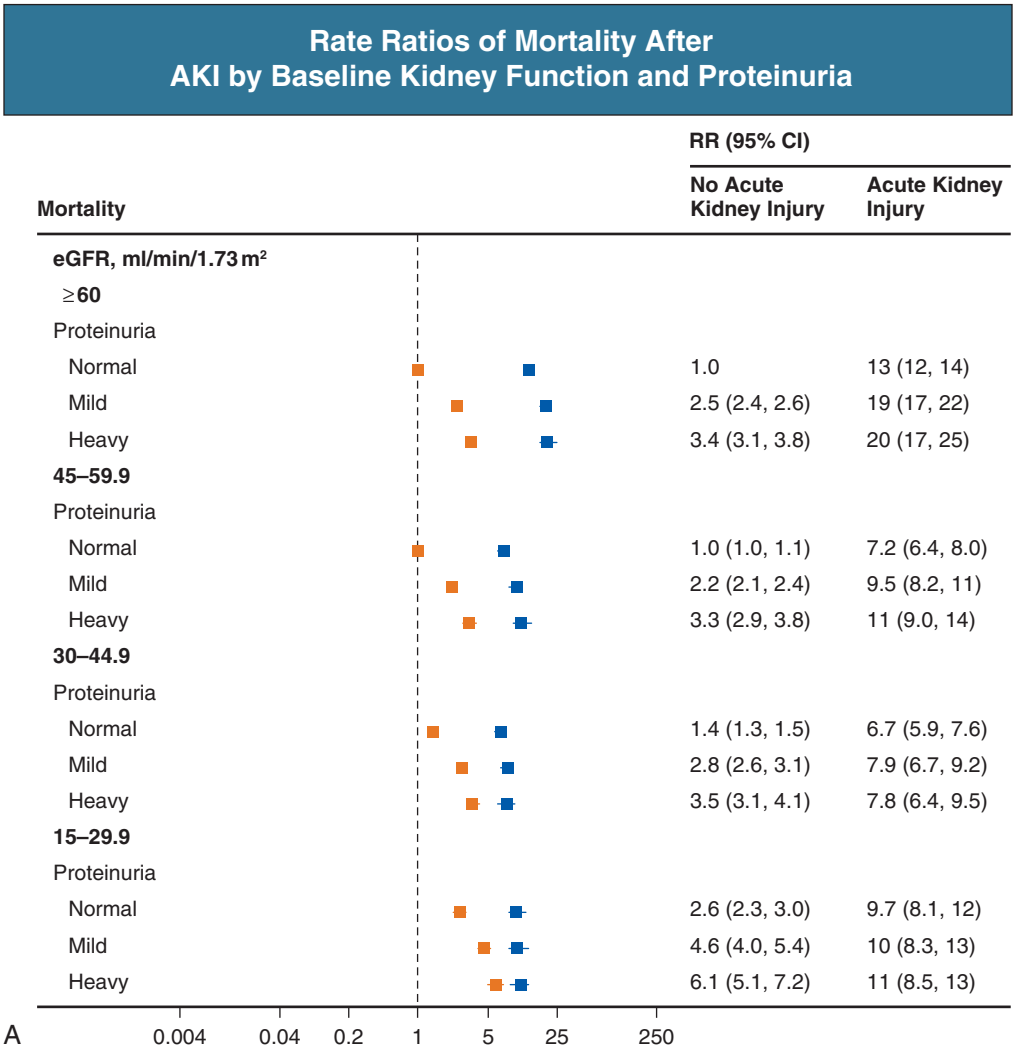

Figure 72-3 Rate ratios of mortality (A) and the composite outcome of end-stage renal disease or doubling of serum creatinine (B) after acute kidney injury (AKI) by baseline kidney function and proteinuria. *Blue squares* and *horizontal bars* represent point estimates and 95% confidence intervals (CIs), respectively, for rate ratios of participants who had AKI for various values of eGFR and proteinuria. The *orange squares* and *horizontal bars* similarly represent the point estimates and 95% CIs for participants who did not have acute kidney injury. The referent group for all rate ratios was participants who did not have AKI and had normal proteinuria and eGFR of 60 ml/min/1.73 m^2 or greater. *eGFR,* Estimated glomerular filtration rate; *ESRD,* end-stage renal disease; S_{Cr}, serum creatinine; *RR,* rate ratio. *(From reference 12.)*

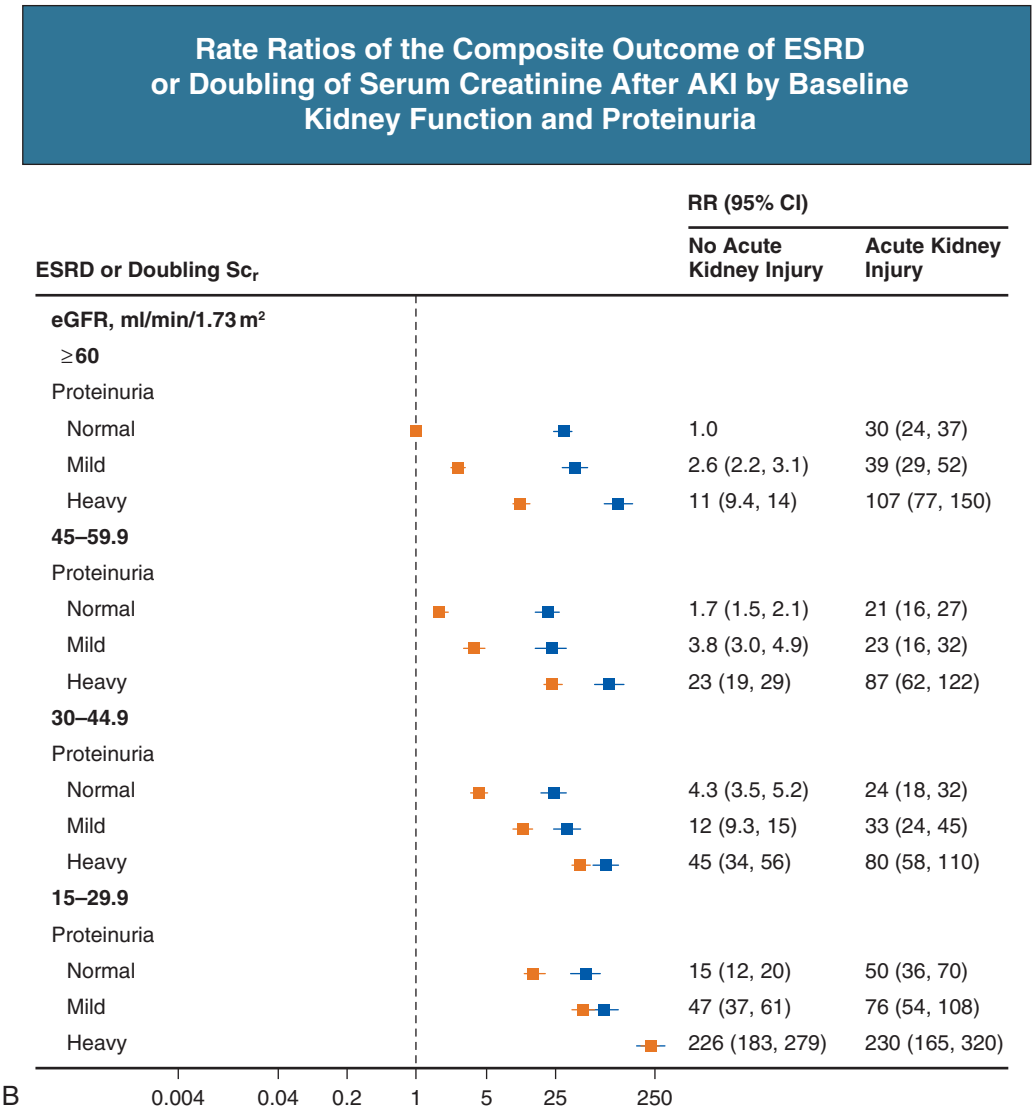

Figure 72-3, cont'd

(0.3 mg/dl) was associated with a short-term relative risk for death of 2.3 (95% confidence interval [CI] 1.8-3.0). In the studies that adjusted risks for comorbidities, the odds or hazards ratios for death ranged from 1.7 to 1.9, all of which were statistically significant. Similar findings were reported in a recent meta-analysis evaluating the RIFLE criteria for AKI. Whereas these studies have focused on critically ill patients or on specific patient populations (congestive heart failure [CHF] patients, patients who have undergone cardiac surgery) in which AKI may simply be a reflection of the burden of morbidity, several population-based studies of hospitalized patients confirm these mortality associations.

Recent findings suggest that the association between AKI and mortality is likely influenced by several factors including the presence of underlying CKD, the duration and severity of AKI, and the degree of recovery of kidney function. In a population-based cohort of CKD patients after hospitalization with an AKI episode, a graded relationship was observed between the risk of in-hospital death and prehospitalization eGFR; mortality was lowest in patients who had stage 5 CKD at baseline.[13] A population-based cohort study of hospitalized AKI patients in Canada found that the relation between AKI and in-hospital mortality was strongest in hospitalized patients with severe AKI and a baseline eGFR exceeding 60 mL/min/1.73 m^2 (adjusted hazard ratio [HR] 10.6, 95% CI 8.8-12.8).[14] By comparison, in patients with a baseline eGFR below 30 ml/min/1.73 m^2, the adjusted HR of in-hospital mortality in patients with the most severe AKI was 4.7 (95% CI 3.6-6.2).

Although the incidence of AKI continues to increase over time, there has been a corresponding improvement in survival. A recent analysis of AKI incidence and associated outcomes in a nationally representative dataset in the United States revealed a 19% decrease in mortality between 2000 and 2009 in patients who required acute dialysis. Although the observed increased incidence of AKI and the improved survival could both be explained by increased use of diagnostic codes for milder forms of AKI (code creep) and a trend toward earlier and more aggressive use of dialysis, similar improvements in survival have been reported in other cohorts in which alternative definitions of AKI were used.

Chronic Kidney Disease

Until recently it was accepted that whereas severe AKI was associated with a high mortality rate, survivors generally recovered renal function and were independent from dialysis. This assumption was supported by the findings of small cohort studies of critically ill patients.

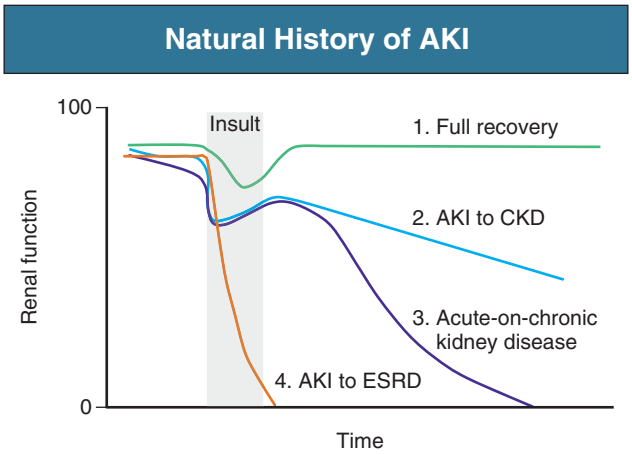

Figure 72-4 Natural history of acute kidney injury (AKI). Patients who develop AKI may experience (1) complete recovery of renal function, (2) development of progressive chronic kidney disease (CKD), (3) exacerbation of the rate of progression of preexisting CKD, or (4) irreversible loss of kidney function and evolution to end-stage renal disease (ESRD). *(From reference 21.)*

However, others have reported lower rates of renal recovery, particularly in patients with underlying CKD, and it is likely that the trajectory of kidney function in AKI survivors is variable depending on underlying kidney disease and AKI severity (Fig. 72-4).[15]

Recent studies have linked AKI survivorship to the development of CKD or end-stage renal disease (ESRD). A large U.S. cohort found that AKI was associated with an eightfold increased risk of ESRD as compared with patients without AKI or CKD.[16] A similar Canadian study compared the incidence of ESRD in patients who required dialysis for AKI but were independent of dialysis within 30 days of discharge, and a group of matched controls without AKI. There was a threefold increase in the risk of ESRD, with a population incidence of 26.3 per 1000 person-years in AKI survivors. Another U.S. study evaluated the risk of progressive CKD after AKI in patients with a baseline eGFR exceeding 45 ml/min/1.73 m^2.[17] Survivors of hospitalization who required dialysis for an episode of AKI but were dialysis independent at least 30 days after discharge had a 28-fold increased risk of subsequently developing CKD stage 4 or worse.

Since then, a meta-analysis of 13 cohort studies reported that the pooled incidences of CKD and ESRD after AKI were 25.8 and 8.6 per 100 person-years, respectively.[18] Pooled adjusted hazard ratios for CKD and ESRD were 8.8 (95% CI 3.1-25.5) and 3.1 (95% CI 1.9-5.0) compared with patients without AKI. In older adults the risk for ESRD after a single episode of AKI is elevated 2-fold to 13-fold depending on the severity of AKI. The annual absolute risk for developing ESRD after an episode of AKI ranges from 0.6% to 1.2% in those who experience mild AKI and up to 9% in those with preexisting CKD.[12]

The association between AKI and CKD could be confounded by age, frailty, and unmeasured comorbidity; however, AKI has also been linked to the development of CKD in children, who are generally free of these confounders. A study of 126 critically ill pediatric AKI survivors who fully recovered kidney function revealed that 10% of patients developed CKD (albumin-creatinine ratio at or above 30 mg/g or eGFR below 60 ml/min/1.73 m^2) over 3 years of follow-up.[19] It is important to note that 38% of the cohort had mildly decreased eGFR (60 to 90 ml/min) and 3.2% had hypertension—both risk factors for future CKD. Given its short-term follow-up, this study likely underestimates the long-term risk of CKD and its associated morbidity.

Health Care Costs

Most studies describing the costs associated with AKI are from the United States. A U.S. study of AKI in hospitalized patients demonstrated a direct relationship between severity of AKI and associated hospital length of stay and hospital costs.[1] AKI defined as a 0.3-mg/dl (26-µmol/l) increase in serum creatinine was associated with an incremental total hospitalization cost of $4886; a doubling of serum creatinine was associated with an incremental cost of $9000. Studies of specific populations of hospitalized patients support these findings; the average excess costs associated with AKI after cardiac surgery ranges from $9000 to $14,000 depending on AKI severity. In multivariable analysis, AKI was the single most costly postoperative complication for these patients and resulted in the largest proportion of resource use compared with all other complications. Another study of 5875 surgical patients found that severe AKI necessitating dialysis was the second most costly postoperative complication, with an estimated mean increase in hospital expenditures of $28,359 compared with an uncomplicated postoperative course, and resulted in almost twice the excess cost compared with a cardiac arrest. However, none of these studies accounted for the impact of CKD on AKI and attendant costs, which is likely to be substantial.

ACUTE KIDNEY INJURY AS A PUBLIC HEALTH ISSUE

Conservative population-based estimates of AKI incidence in hospitalized adults are in the range of 3000 per 100,000 person-years.[20] The majority of these patients will survive hospital discharge. The incidence of stage 4 CKD (eGFR below 30 ml/min/1.73 m^2) or greater in AKI survivors is approximately 120 per 100,000 person-years.[21] The number of adult Americans developing new CKD after AKI may be as high as 100,000 per year. Given adverse outcomes with progressive CKD, as well as the morbidity, mortality, and cost associated with ESRD, strategies that mitigate the progression of CKD after AKI should be a public health priority.

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CHAPTER 73

Prevention and Nondialytic Management of Acute Kidney Injury

Etienne Macedo, Josée Bouchard, and Ravindra L. Mehta

Acute kidney injury (AKI) acquired in the hospital is often a result of a combination of insults. The most commonly associated causes are failure of renal autoregulation, direct nephrotoxicity, ischemia-reperfusion, and inflammatory states. AKI severity predicts adverse outcomes, such as requirement for renal replacement therapy (RRT), length of hospital stay, and mortality. In addition, the widespread use of the RIFLE and Acute Kidney Injury Network (AKIN) classification systems (see Chapter 71) has shown that even small changes in creatinine levels are associated with short- and long-term increased mortality.[1-6] Furthermore, the distant effects of AKI contribute to dysfunction of other organs, such as the heart, lung, brain, and liver. Consequently, primary prevention and early diagnosis of AKI are of central clinical importance. Once a decline in glomerular filtration rate (GFR) has been detected, secondary prevention to attenuate the effects of injury and treatment of the consequences of injury are necessary.

RISK ASSESSMENT

Considering the conceptual model of AKI illustrated in Figure 73-1, the first step in preventing AKI is an adequate risk assessment. The initial care of patients at risk should be focused on identification and, if possible, reversal of the risk factors. Determination of baseline kidney function is fundamental for assessing the risk of AKI in hospitalized patients. However, baseline creatinine is not available for most patients, and the first creatinine measured in the hospital is likely to be affected by the disease process that occurred before hospital admission. This problem reflects the need for more sensitive and specific biomarkers of cellular damage to enable early risk assessment and limit the extent of renal injury. Tables 73-1 and 73-2 summarize risk factors for AKI in different clinical settings. For a further discussion of risk factors and scoring systems, see Chapters 69 and 71.

PRIMARY PREVENTIVE MEASURES

Optimizing Volume Status and Hemodynamic Status

Regardless of the nature of an insult, hemodynamic stabilization, with optimization of the cardiac output and blood pressure (BP), is a key factor in preventing AKI. The general aims are to optimize volume status based on physiologic measurements, to maintain adequate hemodynamic status and cardiac output to ensure renal perfusion, and to avoid further insults. In the injured kidney, autoregulation of blood flow, the mechanism responsible for maintaining a constant flow during fluctuations in BP, is lost. This loss increases the susceptibility to develop AKI after episodes of hypotension. Therefore, fluid and vasoactive drug management is an important intervention for patients in the initiation or extension phase of AKI. Volume expansion can decrease the risk of AKI in the perioperative period after major vascular surgeries, renal transplantation, and procedures to correct obstructive jaundice. In these clinical scenarios, fluid volume administration is most beneficial at the initiation phase. However, once the injury is initiated and the extension phase starts, the impact of volume expansion with intravenous fluids on clinical outcomes has not been well described and needs to be balanced with the unwanted consequence of fluid accumulation and overload.

Assessment of the volume status is challenging, particularly in patients in the intensive care unit (ICU).[7] In most patients the effect of fluid expansion on hemodynamic status and renal function is retrospective and frequently evaluated by trial and error. In patients in the pre-renal phase of AKI, fluid expansion can increase organ perfusion and improve renal function. In other circumstances, as in patients with severe congestive heart failure (CHF) or diastolic dysfunction, renal perfusion is inadequate despite normal volume status or volume overload. In these patients, fluid expansion can lead to worsening of cardiac function and pulmonary edema.

There are no specific guidelines for optimizing hemodynamic and fluid status for renal function preservation, but extrapolation of data from clinical settings associated with AKI can be instructive. International guidelines for sepsis management have been recently revised by the Surviving Sepsis Campaign. The recommendations include initial fluid resuscitation with crystalloids for a minimum of 30 ml/kg and adding albumin in patients who continue to require substantial amounts of crystalloid to maintain adequate mean arterial pressure (MAP).[8] Fluid challenge should be continued as long as there is hemodynamic improvement, based on dynamic or static variables. Vasopressors should be initiated to maintain MAP above 65 mm Hg, and norepinephrine is the first-choice vasopressor. With regard to the kidney, there is currently no evidence that norepinephrine has a different effect on kidney function and need for RRT than vasopressin in septic patients. Inotropic agents such as dobutamine should be administered if myocardial dysfunction or ongoing signs of hypoperfusion are present.[8] Late and prolonged aggressive fluid resuscitation in critically ill patients has also been associated with worse kidney outcomes and increased mortality. Therefore fluid expansion should be stopped when patients are no longer fluid responsive—not only patients with sepsis, but all patients. Data from the Fluid and Catheter Treatment Trial (FACTT) trial indicate that after initial resuscitation, a conservative approach to fluid administration is associated with faster weaning from mechanical ventilation and decreased length of ICU stay without any deterioration of kidney function or worse kidney outcomes in patients with acute lung injury.[9] The Vasopressin and Septic Shock Trial (VASST) study compared the effects of vasopressin (0.01 to 0.03 U/min) to norepinephrine (5 to 15 μg/min) infusion on mortality rates in patients with

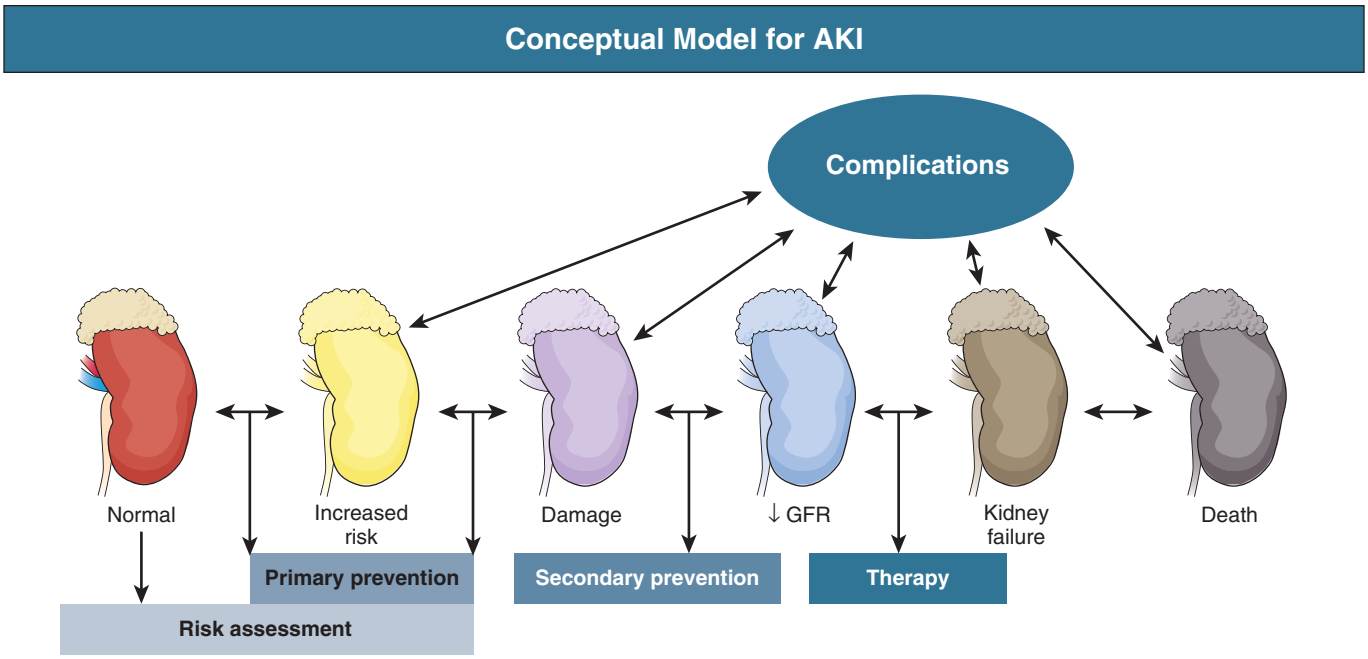

Figure 73-1 Conceptual model for acute kidney injury (AKI). *GFR,* Glomerular filtration rate. *(Modified from reference 7.)*

Major Risk Factors for Acute Kidney Injury (AKI)

Patient Factors	Medications and Agents	Procedures
Older age (>75 years) Diabetes Hepatic failure Chronic kidney disease Atherosclerosis Renal artery stenosis Hypertension Hypotension Hypercalcemia Sepsis Perioperative cardiac dysfunction Rhabdomyolysis Tumor lysis syndrome	Nonsteroidal anti-inflammatory drugs Cyclooxygenase-2 inhibitors Cyclosporine or tacrolimus Angiotensin-converting enzyme inhibitors Angiotensin receptor blockers Iodinated contrast agents Hydroxyethyl starch (HES) Aminoglycosides Amphotericin	Cardiopulmonary bypass procedures Surgery involving aortic clamp Increased intra-abdominal pressure Large arterial catheter placement with risk for atheroembolization Liver transplantation Kidney transplantation

Table 73-1 Major risk factors for AKI.

septic shock and did not show any differences between groups.[10] A secondary analysis from this study found that survival is optimal with a positive fluid balance of approximately 3 liters within 12 hours.[11] In conclusion, a liberal fluid approach as part of early goal-directed therapy appears to be beneficial during the first hours of shock, and a conservative approach should be followed after resolution of shock. Whether these same principles apply for patients with AKI in the absence of shock is unknown. The potential risks of fluid accumulation and overload in the setting of AKI need to be considered.[12]

There is controversy about the optimal fluid to use for resuscitation. The recent KDIGO AKI guidelines suggest that isotonic crystalloids should be used instead of synthetic (hydroxyethyl starch [HES]) and nonsynthetic colloids (albumin) for intracellular volume expansion in patients at risk or presenting with AKI, in the absence of hemorrhagic shock.[13] For albumin, the Saline Versus Albumin Fluid Evaluation (SAFE) trial of 6997 patients found that fluid resuscitation with saline or albumin resulted in similar relative risks of death in critically ill patients.[14] There were also no significant differences in the proportion of patients with new single-organ and multiple-organ failure or days on RRT. Two subgroup analyses from the same study showed that use of albumin may be deleterious in patients with traumatic brain injury[15] and potentially beneficial in sepsis.[16] In the past, HES preparations were commonly used as nonprotein intravascular volume expanders. In addition to their efficiency in fluid management, they also have anti-inflammatory properties and reduced cost compared with albumin. However, they potentially alter coagulation and platelet function, as well as increasing the risk for AKI. The mechanism of HES-induced kidney injury may be associated with proximal renal epithelial cell uptake of HES causing an acquired lysosomal storage disease. This dose-dependent phenomenon is more pronounced in patients with impaired renal function, potentially resulting in a diffuse tissue storage and acculation of foamy-appearing macrophages.[17] An experimental study with an isolated perfusion model of 10% HES 200/0.5 and 6% HES 130/0.42 compared with Ringer lactate proposed that renal interstitial proliferation, macrophage infiltration, and tubular damage are other potential pathologic mechanisms of HES-induced kidney injury.[18] HES solutions are identified by three numbers, indicating the concentration of the solution, the mean molecular weight, and—the most significant one—the molar substitution (e.g., 10% HES 200/0.5 or 6% HES 130/0.4). In the past, 6% HES 130/0.4 solutions were considered safer than 10% HES 200/0.5 solutions. A recent large multicenter randomized study, including 804 patients with severe sepsis, has shown that even 6% HES 130/0.4 is detrimental to kidney function and survival compared with Ringer acetate.[19] Another larger trial in 7000 ICU patients has shown that 6% HES 130/0.4 increased need for RRT but not mortality compared with 0.9% sodium chloride (saline).[20] Therefore, HES should be avoided in patients at risk for and with AKI. The use of albumin may be considered when patients require

Specific Risk Factors for the Development of Acute Kidney Injury (AKI) in Common Clinical Situations		
Postoperative (General)		
Miscellaneous	**Hemodynamic**	**Gastrointestinal and Endocrine**
Age <70 yr	Congestive heart failure	Cirrhosis/biliary surgery
Proteinuria	Aortic cross-clamping	Obstructive jaundice
Hyperglycemia	Cardiac instability	Diabetes mellitus
Hypertension	Major vascular surgery	
Massive blood transfusion	Infection/sepsis	
	Multiorgan failure	
Cardiac Surgery		
Female gender	ACE inhibitor therapy	Emergency surgery
COPD	Heart failure	Valve surgery only
Proteinuria	LV ejection fraction <35%	Previous cardiac surgery
Preoperative S_{Cr} >2.1 mg/dl	Preoperative IABP	Other cardiac surgery
Anemia	Hyperglycemia	Combination of CABG + valve surgery
Insulin-requiring diabetes		Blood transfusion
Critically Ill	**Sepsis**	
High A-a gradient*	Age	
Low serum albumin	S_{Cr} >1.3 mg/dl	
Proteinuria	Serum bilirubin >1.5 mg/dl	
Hyperglycemia	Elevated CVP >8 cm	
High intraabdominal pressure	Hemodynamic instability	
Active cancer		
Contrast Nephropathy		
Age >75 yr	Volume of contrast >100 ml	
Heart failure	Intra-arterial injection	
Diabetes mellitus	Systolic BP <80 mm Hg for >1 hr and need for inotropic support or IABP 24 hr after procedure	
S_{Cr} > 1.5 mg/dl or eGFR <60 ml/min/1.73 m^2	Use of IABP	
History of pulmonary edema		
Anemia/blood loss (Hct: <39% for men; <36% for women)		
Nephrotoxic antibiotics		
Aminoglycosides	**Amphotericin**	
Old age	Volume depletion	
Pre-existing renal dysfunction	Concurrent other nephropathy	
Duration of therapy >7 days		
Volume depletion		
Divided dose regimens		
Liver disease		

Table 73-2 Specific risk factors for the development of AKI in common clinical situations. *CABG,* Coronary arterial bypass graft; *COPD;* chronic obstructive pulmonary disease; *CVP,* central venous pressure; *Hct,* hematocrit; *IABP:* intra-aortic balloon pump. *A-a gradient, alveolar-arterial oxygen gradient calculated with the sea level standard formula (713 × Fio_2) – (Pco_2/0.8) – Pao_2, where Fio_2 is fractional inspired oxygen concentration, Pao_2 is arterial partial oxygen pressure, and Pco_2 is partial carbon dioxide pressure. *(Modified from reference 77.)*

substantial amounts of crystalloid to maintain adequate MAP, and its effect must be balanced against its potential risks (possibly deleterious in patients with trauma and low potential for transmitting infectious diseases).

Some animal studies have suggested that hyperchloremia resulting from 0.9% saline infusion may affect renal hemodynamics. In healthy male adults, a double-blind crossover study compared renal artery flow velocity and renal cortical tissue perfusion after a 2-liter intravenous infusion of 0.9% saline (chloride: 154 mmol/l) and a balanced buffered solution with a chloride concentration of 98 mmol/l. They showed a significant reduction in mean renal artery flow and renal cortical tissue perfusion with saline but not with the use of chloride-restrictive fluids.[21] A recent retrospective study showed that chloride-restrictive fluids (lactated solution with

balanced buffer–chloride concentration of 98 mmol/l or chloride-poor 20% albumin–chloride concentration of 19 mmol/l) compared with chloride-rich intravenous fluids (0.9% saline, 4% succinylated gelatin solution, or 4% albumin solution) were associated with a significant decrease in AKI incidence and RRT requirement.[22] These results will need to be confirmed with other studies.

Prevention of Contrast-Induced Acute Kidney Injury

The Prevention of Contrast-Induced Acute Kidney Injury (CI-AKI) Consensus Working Panel recommends that measures to reduce the AKI risk should be implemented in patients with a baseline estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m^2. According to the KDIGO guidelines, this threshold could probably be lowered to 45 ml/min/1.73 m^2. For prevention of CI-AKI, patients at risk should receive intravenous hydration (Fig. 73-2). Hydration with isotonic saline started the morning of the procedure or immediately before in cases of emergency interventions is superior to half-isotonic (0.45%) saline.[23] A randomized controlled trial (RCT) compared isotonic saline with isotonic sodium bicarbonate (three 50-ml ampules of 1 mmol/ml sodium bicarbonate added to 850 ml of 5% dextrose) at 3 ml/kg/h for 1 hour before the procedure followed by 1 ml/kg/h for the 6 hours after the procedure. CI-AKI was significantly lower in the bicarbonate compared with the saline group (2% vs. 14%).[24] The rationale for isotonic bicarbonate is based on animal studies showing that bicarbonate is capable of scavenging reactive oxygen species, and the increased pH in the proximal tubule and the renal medulla associated with bicarbonate administration could reduce generation of superoxide. In addition, isotonic saline contains high amounts of chloride, with a potential renal vasoconstrictor effect. Considering that most hydration studies with isotonic bicarbonate use shorter infusion protocols (7 hours) than those with isotonic saline (usually 12 to 24 hours), hydration with bicarbonate is also an attractive alternative for emergency procedures. The superiority of bicarbonate was observed in some but not all further RCTs. The KDIGO AKI guidelines recommend either isotonic sodium chloride or sodium bicarbonate solutions in patients at risk for CI-AKI unless there are contraindications to volume expansion.[13] The Prevention of Serious Adverse Events Following Angiography (PRESERVE) study is an ongoing RCT (NCT01467466) with a 2×2 factorial design aiming to compare the effectiveness of sodium bicarbonate with isotonic sodium chloride and oral *N*-acetylcysteine (NAC) with placebo in 8680 high-risk patients scheduled to undergo coronary or noncoronary angiography. The study should be completed in 2016. The use of NAC is discussed later in this chapter.

Iodinated contrast medium can be categorized according to osmolality into high-osmolar contrast medium (approximately 2000 mOsm/kg), low-osmolar contrast medium (600 to 800 mOsm/kg), and iso-osmolar contrast medium (290 mOsm/kg), and clinical studies suggest that the risk of nephrotoxicity increases with increasing osmolarity of the contrast medium. The higher cost of the iso-osmolality agents bars their universal use. The KDIGO AKI guidelines recommend the use of either iso-osmolar or low-osmolar iodinated contrast medium for patients at risk of CI-AKI.

The volume of contrast material administered is also a crucial risk factor and an independent predictor of CI-AKI and should be lowered as much as possible. Based on the volume of contrast given (V) and the creatinine clearance (CrCl), a V/CrCl ratio above 3.7 has been shown to be a significant and independent predictor of CI-AKI

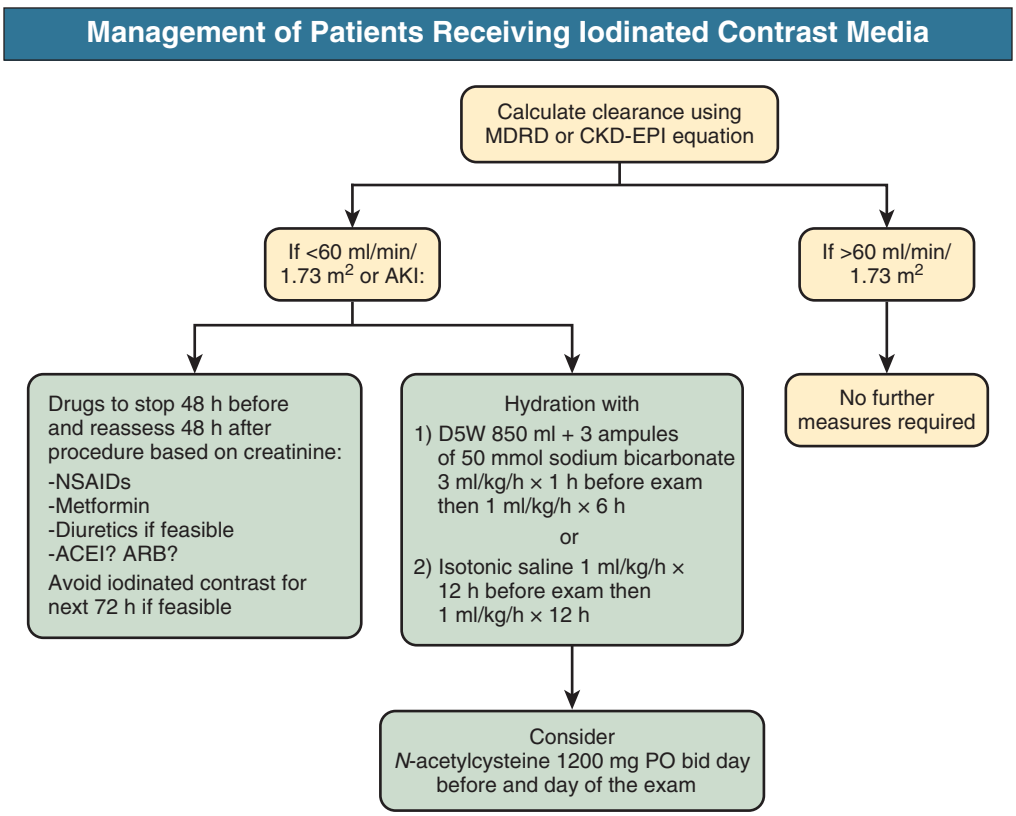

Figure 73-2 Management of patients receiving iodinated contrast media. *ACEI,* Angiotensin-converting enzyme inhibitor; *AKI,* acute kidney injury; *ARB,* angiotensin receptor blocker; *CKD-EPI,* Chronic Kidney Disease Epidemiology Collaboration; *D5W,* 5% dextrose in water; *MDRD,* Modification of Diet in Renal Disease; *NSAIDs,* nonsteroidal anti-inflammatory drugs.

in the general population. Administration of contrast material more than once in a short period is another risk factor, and contrast studies should be postponed at least 48 to 72 hours after the last infusion of contrast medium if possible. The drugs used for CI-AKI prevention are included in the section on pharmacologic approaches.

Prevention of Drug- and Nephrotoxin-Induced Acute Kidney Injury

Drug-induced nephrotoxicity can often be predicted because it is more common in certain patients and in specific clinical situations. Prevention involves the knowledge of mechanisms of renal injury, patient-related risk factors, and drug-related risk factors. The most important patient-related factors associated with higher risk of nephrotoxicity are age older than 60 years, preexisting chronic kidney disease (CKD), volume depletion, diabetes, heart failure, and sepsis. A fundamental step in prevention includes drug monitoring of potential nephrotoxins in at-risk patients. Preventative measures include correctly estimating the GFR before initiation of therapy, adjusting the dosage, and monitoring renal function during therapy. Alternative non-nephrotoxic drugs should be used whenever possible, and nephrotoxic drug combinations should always be avoided if feasible.

Amphotericin

Amphotericin-associated nephrotoxicity can occur in as many as one third of treated patients, and the risk of AKI increases with higher cumulative doses. Lipid formulations cause less nephrotoxicity compared with the standard formulation, and therefore amphotericin deoxycholate is preferred over conventional amphotericin; however, it is significantly more expensive. Recently, alternative antifungal agents such as itraconazole, voriconazole, and caspofungin have been more commonly used in patients at high risk for AKI and should be used rather than conventional amphotericin.

Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Blockers, and Nonsteroidal Anti-Inflammatory Drugs

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) cause vasodilation of the efferent glomerular arteriole, further reducing intraglomerular pressure already compromised by the BP-lowering effect of these agents. In patients with renal dysfunction, they can contribute to a reduction in GFR. In patients with an increase in serum creatinine higher than 30% after the initiation of ACE inhibitor and ARB treatment, bilateral renal artery stenosis, stenosis of the renal artery in a solitary kidney, diffuse intrarenal small-vessel disease, or generalized volume depletion should be suspected, and these drugs should be discontinued.

Nonsteroidal anti-inflammatory drugs (NSAIDs) should be used with caution in patients with atherosclerotic cardiovascular diseases (CVDs). NSAIDs should be avoided in CKD and intravascular volume depletion because they inhibit cyclooxygenase, which blocks prostaglandin-induced vasodilation of the afferent arteriole, potentially reducing GFR and renal blood flow. In critically ill patients, renal hypoperfusion caused by decreased effective circulating volume is relatively common, and inhibition of prostaglandin-induced vasodilation may further compromise renal blood flow and exacerbate ischemic injury.

Aminoglycosides

Acute kidney injury caused by aminoglycoside nephrotoxicity usually occurs 5 to 10 days after initiation of the treatment; this type of AKI is typically nonoliguric and associated with decreased urine concentrating ability and urinary magnesium wasting. Because of nephrotoxicity, ototoxicity, and vestibular toxicity, the AKI KDIGO guidelines have recommended avoiding the use of aminoglycosides in patients with AKI and those at risk unless no other alternative is available. With multiple daily administration schedules, elevated aminoglycoside peak levels appear to correlate with nephrotoxicity. Because aminoglycoside uptake by proximal tubular cells is a saturable process, once-daily administration can decrease tubular cell toxicity by reducing drug taken up by proximal tubular cells. In the general population, extended intervals between doses maintains the target dose while decreasing the risk of nephrotoxicity compared with multiple daily doses; therefore, in patients with normal kidney function who are not at risk for AKI, aminoglycosides should be administered daily if needed.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is caused by uric acid and calcium-phosphate precipitation in the tubules. Correct identification of those at high risk is the first step toward preventing AKI in this setting. In patients with high-grade hematologic malignant neoplasms, risk factors for TLS are lactate dehydrogenase levels above 1500 IU, large tumor burden, extensive bone marrow involvement, CKD, and high tumor sensitivity to chemotherapeutic agents. In patients with low or intermediate risk of TLS, a xanthine oxidase inhibitor such as allopurinol can be used as a hypouricemic agent and should be started 2 days before chemotherapy. Aggressive hydration with isotonic saline is initiated 2 days before the chemotherapy to maintain a high urinary output, allowing the elimination of uric acid and phosphate. If urinary output decreases despite adequate fluid intake, a loop diuretic should be added, but RRT will be required if oliguria persists.[25] The use of urine alkalinization to promote elimination of urates is not recommended because it can induce calcium phosphate deposition and therefore aggravate TLS. In addition to the hydration, recombinant urate oxidase can reduce uric acid levels and the risk of uric acid deposition nephropathy.[26] Recombinant urate oxidase should be initiated in high-risk patients or for established TLS when hyperuricemia is severe.

SECONDARY PREVENTION

After the renal insult has occurred, secondary preventive measures should be directed to avoid further injury, to facilitate repair and recovery, and to prevent AKI complications. The timeliness of interventions is crucial to their effectiveness for secondary prevention. Various approaches have been applied but are best appreciated in the context of specific clinical scenarios.

Traumatic and Nontraumatic Rhabdomyolysis

In the prevention of myoglobin-induced nephropathy after crush syndrome, intravenous hydration should be initiated with isotonic saline before the crushed limb is relieved to prevent precipitation of the pigment in the tubular lumen. A solution with 2.7% sodium bicarbonate (50 mmol/l) should be given every second or third liter to maintain urinary pH above 6.5 and to prevent intratubular deposition of myoglobin and uric acid. The urine output should be maintained around 300 ml/h, which may require an infusion of up to 12 liters of fluid per day. The volume administered is generally much greater than the urinary output; the accumulation of fluid in the damaged muscles may exceed 4 liters. This protocol should be continued until clinical or biochemical evidence of myoglobinuria disappears, usually by day 3. It has also been suggested that mannitol

is beneficial because of its diuretic, antioxidant, and vasodilatory properties. Mannitol could prevent renal tubular cast deposition, expand extracellular volume, and reduce intracompartmental pressure, muscle edema, and pain.[15] However, mannitol may exacerbate CHF and nephrotoxicity, requires close monitoring, and is contraindicated in oliguria, hypervolemia, hypertension, and heart failure. Mannitol administration is considered, if urinary flow is sustained above 20 ml/h, given at a rate of 5 g/h added to each liter of infusate and not exceeding 1 to 2 g/kg/day.[27] Muscle damage induces stretch-activated ion channels, allowing for influx of calcium into cells after reperfusion. The resultant hypocalcemia is usually asymptomatic but can lead to cardiac dysrhythmias. Hence, care must be taken to avoid an $NaHCO_3$ (sodium bicarbonate)–induced decrease in ionized calcium (caused by metabolic alkalosis), which can trigger tetany, seizures, and cardiotoxicity and worsen existing muscle damage. During the AKI recovery phase, hypercalcemia is frequent, mainly in patients who received calcium infusion, as a result of the mobilization of previously precipitated calcium in muscles. Thus, hypocalcemia should be treated only if symptomatic. The importance of early fluid administration and the most important aspects of the treatment of crush victims have been recently summarized.[28]

In nontraumatic rhabdomyolysis, prevention of AKI involves vigorous fluid expansion to maintain renal perfusion pressure and to dilute myoglobin and other toxins. A urine output of 200 to 300 ml/h is desirable until myoglobinuria disappears. Urine alkalinization may help prevent tubular pigment cast formation; however, there is no clinical evidence that mannitol and bicarbonate are more effective than saline solution alone. Furthermore, there are potential risks to bicarbonate therapy, including precipitation of calcium phosphate and hypocalcemia.

In treating patients with rhabdomyolysis, it is important to consider when to stop aggressive fluid resuscitation. Although fluid expansion is the main therapeutic intervention to reduce the myoglobin precipitation in the tubular lumen, the risk of fluid accumulation and compartmental expansion should always be part of the clinical judgment. Frequent assessment of renal functional parameters (e.g., every 6 to 12 hours) associated with uric acid and creatine kinase levels help the clinician decide how intense the volume expansion should be.

Hyperglycemia

There have been conflicting results from studies of the effects of strict control of blood glucose concentration in reducing the incidence and mortality of AKI. In the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, a large multicenter randomized trial in critically ill patients, intensive glucose control (target blood glucose of 81 to 108 mg/dl [4.5 to 6.0 mmol/l]) increased the absolute risk of death at 90 days compared with conventional glucose control (target blood glucose of <180 mg/dl [<10 mmol/l]).[29] Intensive glucose control also increased the risk for severe hypoglycemia. There was no change in the incidence of AKI or need for RRT. Other studies have not found an increase in mortality with intensive glucose control. In summary, intensive glucose control in critically ill medical and surgical patients increased the incidence of severe hypoglycemia and either increased mortality or had no effect on mortality when compared with the more permissive blood glucose ranges of 140 to 180 mg/dl (7.8 to 10 mmol/l) and 180 to 200 mg/dl (10 to 11 mmol/l). Therefore, in critically ill patients, in concordance with the KDIGO AKI guidelines, we recommend maintaining appropriate control of blood glucose concentration in the range of 110 to 149 mg/dl (6.1 to 8.3 mmol/l) rather than intensive glucose control.

Pharmacologic Approaches

Because of the multiple different causes of AKI, various pathways have been targeted in studies to prevent or alter the course of AKI. These pathways include inhibition of inflammatory mediators, enhancement of renal perfusion by blocking vasoconstrictor mechanisms and intensifying vasodilator mechanisms, attenuation of leukocyte infiltration, inhibition of the coagulation cascade, and administration of growth factors to accelerate renal recovery.[30] Most of these preventive strategies were successful in animal models but did not translate into beneficial effects in patients. Only a few have consistently shown benefits (Table 73-3).

N-Acetylcysteine

N-acetylcysteine is a tripeptide analogous to glutathione and is able to cross cellular membranes. NAC may reduce vasoconstriction and oxygen free radical generation after the administration of contrast material. Because an increased production of free radicals by the kidneys is partly responsible for their cellular damage in postischemic and nephrotoxic AKI, several clinical studies have attempted to use NAC to prevent AKI, mainly in CI-AKI and during cardiac surgery.

In the first study, NAC at a dose of 600 mg orally twice daily the day before and the day of the procedure prevented AKI after radiocontrast dye administration. However, numerous further studies have shown conflicting results. Oral NAC is inexpensive and has an excellent side effect profile compared with intravenous NAC. A recent large study in patients undergoing coronary arteriography and peripheral vascular angiography did not show a benefit associated with oral NAC.[31] In addition, in an accompanying meta-analysis of the use of oral NAC, stratification of trials according to adequacy of methodologic characteristics (allocation concealment, double blinding, and intention-to-treat analysis) revealed a reduction in the pooled relative risk of CI-AKI with NAC treatment observed among low-quality studies, yet no effect of NAC in studies meeting all three methodologic criteria. If NAC is to be used, the preferred dose is 1200 mg administered orally twice daily on the day before and the day of the procedure in patients at risk for CI-AKI. Oral NAC should never replace intravenous fluids, which have a more substantial benefit.

Loop Diuretics and Natriuretics

Diuretics are often used to manage fluid in patients who develop AKI.[32,33] Although nonoliguric AKI has been associated with better outcomes than oliguric AKI, diuretics have been shown to be ineffective in the prevention of AKI or for improving outcomes once AKI occurs.[34] In addition, diuretics should be avoided when AKI is attributed to pre-renal causes. Meta-analyses have confirmed that the use of diuretics to prevent AKI did not reduce in-hospital mortality, the risk for requiring dialysis, the number of dialysis sessions required, or the proportion of oliguric patients.[34,35] An RCT, including 94 patients treated with prophylactic nesiritide undergoing high-risk cardiac surgery, did not show any effect on RRT requirement or lengths of stay, although AKI rates were lower with nesiritide.[36]

Vasoactive Agents

"Renal-dose" dopamine (0.5 to 3 μg/kg per minute) given as a renal vasodilator increases urine output but does not affect AKI outcome or mortality.[37] Dopexamine, a synthetic dopamine analogue, is a dopamine type-1 and less potent dopamine type-2 receptor agonist. Small studies performed in patients undergoing liver transplant surgery have not found a beneficial effect of dopexamine in preventing AKI.

Summary of Drugs Used in Prevention of Acute Kidney Injury (AKI)			
Drug	**Level of Evidence**	**Results**	**Comments**
Dopamine	RCTs	No effect on kidney function	
Fenoldopam	Small RCTs One meta-analysis	No effect on kidney function Beneficial effect on kidney function	Further studies required
Loop diuretics	RCTs and meta-analysis	No effect on kidney function	
N-acetylcysteine	RCTs and meta-analysis	Variable effect in CI-AKI, mostly related to the quality of RCTs	1200 mg PO bid before and on the day of administration of iodinated contrast with saline or bicarbonate
Statins	Retrospective perioperative period One RCT in CI-AKI	Beneficial effect on kidney function No effect on kidney function	Further studies required
Insulin	Meta-analyses	Controversial effect	KDIGO recommends to target blood glucose 110-149 mg/dl (6.1-8.3 mmol/l)
Calcium channel blockers	RCT in peritransplant period	No effect on kidney function	Further studies required
Adenosine antagonists	RCTs	Controversial effect on kidney function	Further studies required
Nesiritide	RCT	Decreased incidence of AKI No effect on renal replacement therapy requirement	Further studies required
Erythropoietin	Animal models	Beneficial effect on kidney function	Human studies required*
Small interfering RNA targeting p53	Animal models	Beneficial effect on kidney function	Human studies required
Multipotent stem cells	Animal models	Beneficial effect on kidney function	Human studies required
Mesenchymal stem cells	Phase I clinical trials	Decreased incidence of AKI	Further studies required

Table 73-3 Summary of drugs used in prevention of AKI. *CI-AKI,* Contrast-induced acute kidney injury; *KDIGO,* Kidney Disease: Improving Global Outcomes (KDIGO); *PO,* by mouth; *RCTs,* randomized controlled trials; *RNA,* ribonucleic acid. *Current study results are conflicting and not definitive (see text for more information).

The effect of norepinephrine on prevention of AKI has not been assessed in RCTs. Fenoldopam is a pure dopamine type-1 receptor agonist with hemodynamic renal effects similar to those of low-dose dopamine, without systemic α- or β-adrenergic stimulation. In a meta-analysis, fenoldopam was shown to reduce the risk of AKI in postoperative or critically ill patients (odds ratio 0.43).[38] Intrarenal administration of fenoldopam allows the use of a substantial dose of fenoldopam mesylate while avoiding systemic adverse effects, such as hypotension. In a registry of 268 patients treated with intrarenal fenoldopam infused for at least 1 hour, the incidence of CI-AKI was less than 1%, compared with 27% based on historic rates in that population. Data from experimental models suggest that fenoldopam may have additional anti-inflammatory effects.[39] Currently, we do not recommend use of fenoldopam to prevent AKI because no high-quality trial has been performed with this agent.

Statins

Although the pathogenesis of CI-AKI is not completely known, multiple mechanisms may be involved. Statins induce downregulation of angiotensin receptors, decrease endothelin synthesis, decrease inflammation, improve endothelial function by inhibiting nuclear factor (NF) κB, decrease expression of endothelial adhesion molecules, increase nitric oxide (NO) bioavailability, attenuate production of reactive oxygen species, and protect against complement-mediated injury. Those mechanisms may be involved in the protective effect against CI-AKI. A number of observational publications support the potential for renal protection with statin administration.[40] However, the only RCT that included 304 patients with eGFR below 60 mL/min showed no benefit of atorvastatin compared with placebo.[41] Patients who are already receiving statin therapy or need it for other indications should be maintained on statins, but there is no basis to recommend the initiation of statin therapy specifically to prevent CI-AKI.

Statins may also reduce the risk of AKI after elective surgery.[42] A large retrospective study identified 213,347 patients who underwent surgery in Canada, among whom 32% were treated with a statin before surgery. AKI occurred in 1.9% of these patients. After multivariable adjustment, the use of statins was associated with a significantly decreased risk of AKI, of acute requirement for RRT, and 30-day mortality. There was no difference between groups in dialysis requirement 90 to 120 days after surgery. Because this was a retrospective study, there was likely residual confounding that could not be adjusted for. These results need to be validated before clinical recommendations can be made regarding the use of statins to prevent perioperative AKI.

Calcium Channel Blockers

Calcium channel blockers (CCBs) have been shown to reverse the afferent arteriolar vasoconstriction induced by a variety of stimuli and also have an independent natriuretic effect.[43] These drugs have been exhaustively evaluated in the prevention of AKI, especially in the context of transplant-associated nephropathy. Administered prophylactically, CCBs protected against post-transplantation delayed graft failure in some studies. However, a large multicenter RCT evaluating the effect of isradipine on renal function, incidence and severity of delayed graft function, and acute rejection after kidney transplantation did not find any benefit.[44] A systematic review evaluated the benefits and harms of using CCBs in the peritransplant period and did not find strong evidence for the routine use of CCBs to reduce the incidence of acute tubular necrosis (ATN) after transplantation.[42] Studies have shown improved long-term outcomes without any significant improvement in perioperative function. It is

possible that the use of CCBs during renal transplant surgery may be of benefit in extended donor criteria transplants (e.g., donors older than 60 years, predonation serum creatinine level higher than 1.5 mg/dl (132 µmol/l), cerebrovascular disease as the cause of death) or those with prolonged ischemia times.

Adenosine Antagonists

Theophylline, a nonselective adenosine receptor antagonist, prevents the adenosine-mediated vasoconstriction of the afferent arteriole. Adenosine is released in response to increased luminal chloride concentrations in the distal renal tubules, as part of the tubuloglomerular feedback. Small clinical studies evaluating the role of theophylline in the prevention of contrast nephropathy have shown discordant results. A meta-analysis including seven RCTs concluded that the prophylactic administration of theophylline or aminophylline appeared to protect against CI-AKI.[45] However, this meta-analysis included studies that did not control for hydration status. A recent RCT adding theophylline to NAC showed reduced incidence of CI-AKI. Currently, it remains unclear whether theophylline as a solo agent might be useful in preventing CI-AKI, and the KDIGO AKI guidelines do not suggest using theophylline to prevent CI-AKI.

Selective adenosine blocking agents, such as rolofylline, have been used in trials for prevention and treatment of cardiorenal syndrome. In a double-blind placebo-controlled trial of 63 patients with decompensated heart failure, whereas patients receiving furosemide presented a deterioration in GFR, the coadministration of adenosine A_1 antagonist with furosemide increased diuresis and prevented decrease in GFR.[46]

Emerging Agents

Multipotent mesenchymal stem cells (MSCs) were shown to prevent ischemia-reperfusion–induced AKI in rats. A Phase I clinical trial evaluated the feasibility and safety of suprarenal aorta infusion of allogeneic MSCs in patients undergoing on-pump cardiac surgery.[47] No adverse events were associated with the MSC infusion, and lengths of hospital stay and readmission rates were decreased by 40% compared with matched historical case controls. Postoperative kidney function remained at baseline levels, and no patients in the treatment group required hemodialysis (HD), whereas 20% of controls developed AKI. In addition, kidney function in the treatment group was stable for up to 16 months in patients with underlying CKD, whereas matched control patients showed progressive deterioration in kidney function.[47] The long-term safety of this approach is currently unknown.

From the results of animal and preliminary human studies, therapeutic use of erythropoietin (EPO) seems promising. EPO can prevent AKI and improve recovery through limitation of apoptosis, promotion of neovascularization, anti-inflammatory action, and tissue regeneration. In mice, EPO administered 30 minutes before the infusion of endotoxin significantly improved kidney function 16 hours after injury. EPO also seems to have a protective effect against ischemia-reperfusion injury in the rat kidney. A clinical trial of preoperative EPO in patients who underwent elective coronary artery bypass graft surgery showed a reduction in the incidence of AKI from 29% to 8% ($P = .035$) and improved postoperative renal function. In another trial, different doses of recombinant EPO administered to patients after cardiac surgery did not result in a difference in urine NGAL between 48 hours and randomization compared with placebo, and the incidence of AKI was similar.[48] In the intensive care setting, a recent study also failed to show therapeutic renoprotective benefits of EPO. Although the timing of treatment was not ideal—more than 6 hours after kidney injury had been detected by biomarkers—in this study, high-dose EPO did not alter outcome in AKI patients.[49] Another RCT comparing the effect of EPO or placebo in preventing AKI in patients receiving intravenous contrast material has finished, but the results are not yet available.

Small interfering ribonucleic acids were evaluated against placebo for prevention of AKI in a Phase I clinical trial. In an animal model of AKI, animals treated with small interfering ribonucleic acid targeting p53 presented a significant decrease in blood urea nitrogen (BUN) and creatinine levels 24 hours after ischemic injury, compared with those treated with a placebo. Because p53 has, among other activities, a tumor suppression function, one of the major drawbacks to the use of an inhibitor of p53 is its potential carcinogenic effect, and the study was stopped because of difficulties in enrolling patients.

TREATMENT OF ACUTE KIDNEY INJURY

Once measures to prevent AKI have failed, a key question is whether AKI can be managed with nondialytic therapy alone or if RRT is necessary (see Chapter 74). Management of AKI in the setting of cardiac failure and liver failure is discussed in Chapters 75 and 76, respectively.

General Management

Appropriate therapeutic management requires timely diagnosis of the clinical condition. Considerable effort and investment have been directed in the search for a more sensitive and specific biomarker to diagnose AKI. Because serum creatinine is a relatively late indicator of renal injury, significant AKI can occur without major increases in serum creatinine levels. Appropriate therapeutic interventions to reduce kidney function loss and for prevention and treatment of the associated complications of AKI need to be instituted even with minimal changes in serum creatinine. Initial management of established AKI includes careful assessment of the cause of renal dysfunction and the patient's volume status. The main goal includes maintenance of adequate hemodynamic status to ensure renal perfusion and avoidance of further kidney injury. Any potentially nephrotoxic agents should be avoided, including intravascular radiocontrast dye. Gadolinium-based contrast agents should be avoided because of the risk of development of nephrogenic systemic fibrosis (NSF). If gadolinium-based contrast agents need to be used in AKI, patients should be informed about the risk of NSF, and macrocyclic chelate (i.e., gadobutrol, gadoteridol, or gadoterate meglumine) should be preferred over linear chelates. The lowest dosage possible should be administered, and repeated exposures should be avoided. Antimicrobial agents such as aminoglycosides, amphotericin, acyclovir, and pentamidine should be avoided whenever possible, or their dose should be adjusted to prevent further insult. Any other medications associated with AKI (hemodynamic, nephrotoxic, immune mediated) should also be avoided if possible.

Fluid and Electrolyte Management

Whereas early and vigorous resuscitation with crystalloid solutions and aggressive infection control can reduce the incidence of AKI (see earlier discussion), the role of fluid resuscitation in established AKI is less clear. Volume status is one of the most difficult parameters to assess, and fluid resuscitation should target a predefined preload, stroke volume, or cardiac output rather than a set MAP. Nevertheless, many clinical studies have emphasized the poor value of right atrial pressure and pulmonary artery occlusion pressure in predicting volume expansion efficacy. Other bedside indicators of preload,

Summary of Drugs Used in Treatment of Acute Kidney Injury (AKI)			
Drug	**Level of Evidence**	**Results**	**Comments**
Dopamine	RCTs	No effect on mortality or kidney function	
Fenoldopam	Small RCTs One meta-analysis	No effect on mortality or kidney function Beneficial effect on mortality and need for dialysis	Further studies required
Norepinephrine	Prospective observational studies	Possible beneficial effect on kidney function	Further studies required
Loop diuretics	RCTs and meta-analyses	No effect on kidney function	Further studies required; two RCTs ongoing
Atrial natriuretic peptide	RCTs	Possible beneficial effect on survival and kidney function	Further studies required
B-type natriuretic peptide	RCT in acute heart failure	No effect on kidney function	
Multipotent stem cells	Animal models	Beneficial effect on kidney function	Further studies required
Erythropoietin	Animal models	Beneficial effect on kidney function	Further studies required*
Alkaline phosphatase	Small RCT	Beneficial effect on kidney function	Further studies required

Table 73-4 Summary of drugs used in treatment of AKI. *RCTs,* Randomized controlled trials. *Current study results are conflicting and not definitive (see text for more information).

such as the right ventricular end-diastolic volume (evaluated by thermodilution) and the left ventricular end-diastolic area (measured by echocardiography), have also been shown to be ineffective in differentiating volume responder from nonresponder patients.[50]

In critically ill patients receiving mechanical ventilation, respiratory changes in left ventricular stroke volume can predict fluid responsiveness. In hypovolemic patients, positive-pressure ventilation may induce a fall in the venous return and consequently in cardiac output. Based on the positive relationship between ventricular end-diastolic volume and stroke volume, the expected hemodynamic response to volume expansion is an increase in right ventricular end-diastolic volume, left ventricular end-diastolic volume, stroke volume, and cardiac output. Because a decrease in ventricular contractility decreases the slope of the relationship between end-diastolic volume and stroke volume, the increase in stroke volume as a result of end-diastolic volume increase depends on ventricular function.

Volume expansion in critically ill patients can frequently result in a relative increase in body weight of 10% to 15% or more, sometimes doubling the total body water in a short time. Studies have demonstrated an association between fluid accumulation and mortality in children and adults with AKI. A prospective multicenter observational study (Program to Improve Care in Acute Renal Disease [PICARD]) found that patients with fluid overload at AKI diagnosis, defined as an increase in body weight relative to baseline of more than 10%, had a threefold increase in mortality after multivariable adjustment. The risk of death was proportional to the magnitude and duration of fluid accumulation. The effect of fluid overload on renal recovery was inconsistent.[12] A second analysis from the FACTT trial in patients with AKI also confirmed that in patients with early AKI a positive fluid balance after AKI diagnosis is strongly associated with mortality.[51] The study showed a protective effect on mortality from furosemide, which disappeared after fluid balance was controlled for.[51] Other studies have shown a deleterious effect of fluid overload on kidney function. In summary, results from observational studies suggest that a conservative fluid approach may be beneficial in terms of mortality and kidney recovery in patients with severe AKI; however, RCTs are required to confirm these findings before any clear recommendation can be made.

In addition, increases in the total body water alter the volume of distribution of creatinine, resulting in underestimation of serum values. The resulting underestimation of the severity of renal dysfunction may delay recognition and adequate treatment of AKI. In AKI patients presenting with fluid overload, the evaluation of renal function should consider the effect of fluid balance to prevent underestimation of AKI severity, to modify drug dosage correctly, and to avoid use of nephrotoxic agents.

Drugs to Promote Recovery from Acute Kidney Injury

See Table 73-4 for a summary of drugs used in treatment of AKI.

Loop Diuretic Therapy

Although loop diuretics are often prescribed in established AKI,[52] a meta-analysis confirmed that their use is not associated with reduced mortality or better kidney recovery.[53] Two other meta-analyses have shown that loop diuretics do not affect mortality, need for dialysis, or number of dialysis sessions required.[35,54] With regard to morbidity, diuretics are associated with an increased risk of ototoxicity.[55] Concomitant prescription of aminoglycosides and diuretics should be avoided because of an increased risk of ototoxicity. Well-designed trials of diuretics are required to assess the benefits of these drugs and potential side effects in AKI, and RCTs are currently being performed in this field. In the meantime, we suggest avoiding diuretics to treat AKI, except for managing fluid overload.

Natriuretics

Atrial natriuretic peptide (ANP) has been studied as a treatment for AKI in four RCTs.[56-59] ANP was shown to reduce need for dialysis but not mortality.[56] In the largest study published so far, ANP improved overall dialysis-free survival in the subgroup of oliguric patients only.[57] Unfortunately, a subsequent trial including 222 oliguric patients did not confirm that ANP reduces mortality or dialysis-free survival.[40] Both trials delivered ANP for 24 hours and at high doses, which could have influenced the results. The most recent study included 61 patients who underwent cardiac surgery and were treated with ANP for a mean of 5.3 ± 0.8 days. In this small study the use of ANP decreased the probability of dialysis and improved dialysis-free survival.[58] Currently the KDIGO AKI guidelines do not suggest ANP to treat AKI. Larger studies are required to confirm the benefits of ANP in AKI. Nesiritide, a B-type natriuretic peptide, can be used for the treatment of heart failure. Nesiritide induces vasodilation and an indirect increase in cardiac output but has no inotropic effects and neutral effect on heart rate. In

addition, it inhibits adverse neurohormonal activation and can result in natriuresis and diuresis in some individuals. However, in a recent large RCT in patients with acute heart failure,[60] this drug did not decrease mortality or rehospitalization rates and had a nonsignificant effect on dyspnea. Nesiritide did not adversely affect renal function, but increased hypotension. Nesiritide has also been assessed in high-risk cardiovascular surgery, where it reduced AKI rates in the immediate postoperative period but did not improve long-term survival. The KDIGO AKI guidelines do not support the use of nesiritide to treat AKI.[13]

Vasoactive Agents

Dopamine use for the treatment of established AKI is no longer recommended (see earlier discussion).

Vasopressors are often considered to be detrimental for organ perfusion. In septic shock, a small prospective study including 14 patients showed that norepinephrine improved serum creatinine and creatinine clearance when MAP was raised above 70 mm Hg.[61] However, in a small RCT including 28 patients, increasing MAP from 65 to 85 mm Hg with norepinephrine did not improve renal function.[62]

In a meta-analysis, fenoldopam decreased the need for dialysis (7% vs. 10%) and in-hospital mortality (15% vs. 19%) in postoperative or critically ill patients.[38] Several limitations were present in this meta-analysis, such as no standardized criteria for initiation of dialysis, heterogeneity of populations and AKI definitions, and dosage and duration of treatments, and absence of an independent measure of GFR. In addition, fenoldopam has hypotensive properties and may be more dangerous in the "real world" outside of RCTs.[40,63] No single prospective study has shown that fenoldopam can reduce the need for dialysis. These results need to be confirmed with an adequately powered trial, and we do not suggest using fenoldopam to treat AKI in concordance with the KIDGO AKI guidelines.

Specific therapy for patients with the hepatorenal syndrome includes the use of terlipressin in combination with octreotide (see Chapter 76). In the United States, terlipressin is not available, and most centers use a combination of midodrine, octreotide, and albumin infusions. Norepinephrine has also been used in these settings with good response, equivalent to that of terlipressin.

Current ongoing clinical trials registered on www.clinicaltrials.gov have been recently summarized, and we expect that some will bring new preventive and therapeutic options for AKI.[30,64]

Other Agents

Other agents have been studied for treatment of established AKI. One promising therapy is the use of MSCs.[65] MSC are multipotent cells with anti-inflammatory and immunomodulatory properties proven to be beneficial in animal models of myocardial ischemia, sepsis, and AKI. In AKI models, infusion of MSCs improved recovery of renal function in cisplatin-induced, ischemia-reperfusion injury, and glycerol-induced AKI. A dose-escalating Phase I clinical trial was conducted to test the safety, feasibility, and preliminary efficacy of MSCs in patients at high risk of AKI.[47] An experimental study using a model of progressive mesangioproliferative nephritis evaluated the long-term effects of intrarenal, syngeneic MSC transplantation.[66] Although patients in the MSC-treated group had lower proteinuria and better kidney function on day 60, 20% of the glomeruli of MSC-treated rats contained single or clusters of large adipocytes with pronounced surrounding fibrosis.[66] Therefore the MSC benefit of maintaining kidney function in the short term needs to be balanced with a possible long-term effect of partial maldifferentiation of intraglomerular MSC into adipocytes and subsequent glomerular sclerosis.[66]

Erythropoietin might also be beneficial in the treatment of AKI, as shown in two animal models. A randomized trial including 71 patients scheduled for elective CABG EPO showed a beneficial effect on recovery after AKI.[66a] However, in a retrospective study including 187 patients with AKI, the use of EPO was not associated with renal recovery.[67]

In severe sepsis and septic shock, a study including 36 patients has shown that the infusion of alkaline phosphatase improves kidney function, possibly through reduced NO metabolite production and attenuated tubular enzymuria.[68]

Another potential agent is the endogenous antioxidative enzyme heme oxygenase-1 (HO-1), a stress inducible enzyme.[69] HO-1 has important antiapoptotic and anti-inflammatory functions, and the induction of HO-1 has been shown to be protective in several forms of injury, including AKI.[70]

Treatment of Acute Kidney Injury Complications

Fluid Overload

When fluid overload occurs in a patient with AKI, all intakes should be minimized and medical treatment should be attempted before dialysis initiation. In patients with positive fluid balance with large fluid intakes and inadequate urine output and in those presenting with symptomatic volume overload, loop diuretic therapy can be initiated in conjunction with measures to optimize systemic and renal perfusion. Intravenous bolus doses of diuretics may be necessary to optimize the response, especially in patients with CHF and nephrotic syndrome. If there is a response to an intravenous bolus, continuous infusion can be tried because they are less ototoxic.

In addition to diuretics, new drugs that selectively influence the excretion of water or sodium have been developed and can be used in specific clinical settings. Aquaretics act in the collecting duct of the kidney in the vasopressin-2 receptors, contributing to free water excretion. Vasopressin receptor antagonists require further studies to establish their role in the treatment of AKI with volume overload and hyponatremia. Natriuretic peptides inhibit sodium reabsorption in the nephron, resulting in net sodium excretion. There is currently no evidence to support the use of natriuretic peptides as an adjunctive treatment in AKI.

Morphine and nitrates can be used to alleviate the respiratory symptoms in urgent situations. Morphine reduces the patient's anxiety and decreases the work of breathing; it can be administered intravenously at an initial dose of 2 to 4 mg during a 3-minute period and can be repeated if necessary at 5- to 15-minute intervals. Nitrates are the most commonly used vasodilators in pulmonary edema. Nitroglycerin reduces left ventricular filling pressure through venodilation; an initial dose of 5 μg of intravenous nitroglycerin per minute can be used, commonly in addition to diuretic therapy. When fluid overload cannot be quickly treated with medical management, positive-pressure ventilation may need to be initiated with or without endotracheal intubation and dialysis, depending on the clinical situation (see Chapter 75).

Potassium Disorders

Hyperkalemia, covered in detail in Chapter 9, is a frequent complication of AKI. Its primary risk is its effect on cardiac conduction, and it may cause bradycardia or asystole. If electrocardiographic changes are present, the intravenous administration of calcium is urgently needed. Concomitantly, sources of oral or intravenous potassium should be identified and removed, including drugs with effect on potassium handling, such as β-adrenergic antagonists, potassium-sparing diuretics, ACE inhibitors, ARBs, and other drugs that inhibit renal potassium excretion.

The next step is to enhance the shift of potassium to the intracellular space by parenteral glucose and insulin infusions. The onset of action is within 20 to 30 minutes, and their effect lasts 2 to 6 hours. Continuous infusions of insulin and glucose-containing intravenous fluids can be used to prolong their effects. Sodium bicarbonate also promotes shift of K^+ into the intracellular space; the effect occurs in less than 15 minutes and has 1 to 2 hours of duration. This therapy can be started if there is no concern regarding fluid overload (50 mmol intravenously during 5 minutes), although the potassium-lowering effect of sodium bicarbonate is most prominent in patients with metabolic acidosis. β-Adrenergic agonists given as aerosols are effective but more likely to produce side effects and therefore are not often prescribed to treat hyperkalemia.

Potassium excretion should be increased by the administration of saline, loop diuretics, and cation exchange resins such as sodium polystyrene sulfonate or calcium resins. The resins can be administered orally or rectally as a retention enema. In patients with hyperkalemic emergencies, rectal administration is preferred, as the colon is the major site of action of this drug. There is concern that the risk of intestinal necrosis may be increased when sodium polystyrene sulfonate is administered with sorbitol. Sodium polystyrene sulfonate should be avoided postoperatively until normal bowel function resumes or in patients with stool impaction. If hyperkalemia is unresponsive to conservative measures, emergency HD is the treatment of choice. Continuous renal replacement therapy (CRRT) can also be used for hyperkalemia with higher volumes of replacement solution or dialysate with low or no potassium content if intermittent HD is unavailable. Because it may take some time to initiate RRT, medical management should always be used pending initiation of dialysis. Monitoring of potassium levels should continue after conservative or dialytic management to prevent and to treat rebound hyperkalemia from the underlying process.

Sodium Disorders

Hyponatremia is more common in AKI associated with heart failure, liver failure, or diuretics. In these settings, water restriction to below the level of output is mandatory. Sodium restriction is usually necessary to treat fluid overload and edema. In patients with true volume depletion with associated pre-renal AKI, isotonic saline will need to be administered to correct both disorders (see Chapters 7 and 8).

Intensive care patients with hypernatremia are more prone to AKI. In most patients, treatment of the underlying cause will be necessary and water deficit will need to be estimated. Water should be administered orally or intravenously as dextrose in water to correct serum sodium concentration at a maximum rate of 8 to 10 mmol/l/day. Dialysis and CRRT in particular may be required to optimally correct sodium disorders in AKI.

Calcium, Phosphorus, and Magnesium Disorders

Hyperphosphatemia and hypocalcemia are common in AKI. Hyperphosphatemia is usually caused by reduced excretion by the kidneys, although it can also be caused by a continuous release from rhabdomyolysis or TLS (see Chapters 10 and 69). As phosphorus levels increase, calcium levels decrease, resulting in hypocalcemia. The levels of reduction are usually mild to moderate, with total calcium levels dropping to 7 to 8 mg/dl (1.75 to 2.0 mmol/l). Other causes of hypocalcemia in AKI are skeletal resistance to parathyroid hormone (PTH) and low calcitriol production from the dysfunctional kidney. Hypocalcemia can also occur during rhabdomyolysis and pancreatitis, two conditions often associated with AKI. Hypocalcemia is also aggravated when bicarbonate is administered to correct acidosis. A high-calcium, high-phosphorus product could theoretically trigger tissue calcium deposition, which can cause cardiac arrhythmia. No randomized study has evaluated the benefits of treating these disorders. However, because hyperphosphatemia caused by oral phosphorus-containing medications and TLS can cause AKI,[71] severe hyperphosphatemia should be avoided to prevent further damage. Calcium-based phosphate binders and other phosphate binders can be used in this setting.[72] If there are symptoms of hypocalcemia or hemodynamic instability, a calcium gluconate infusion should be administered.

Hypercalcemia is rare in AKI and is usually seen in the recovery phase of rhabdomyolysis when calcium is released from calcium-containing complexes in muscle (see Chapters 10 and 69). In addition, when production of calcitriol is reestablished by the recovering kidney, an enhanced responsiveness to PTH can be seen. Hypercalcemia in this setting is rarely problematic and can be easily treated with medical management. Mild hypermagnesemia is frequent in AKI and usually does not have clinical consequences.

Acid-Base Disorders

In AKI, metabolic acidosis is the most common acid-base abnormality (see Chapter 12) and is caused by reduced regeneration of bicarbonate and failure to excrete ammonium ions. Accumulation of phosphate and unexcreted unmeasured anions, such as sulfate, urate, hippurate, hydroxypropionate, furanpropionate, and oxalate, is contributory. Hypoalbuminemia can attenuate this acidification process, and it is exacerbated by lactic acidosis. Despite retention of unmeasured anions, the anion gap remains within normal limits in 50% of patients. Whereas metabolic acidosis is frequent, triple acid-base disturbances can also occur.

The approach to acid-base disturbances in AKI needs to be adjusted according to the underlying causes.

There is controversy surrounding the optimal treatment of acute metabolic acidosis. When metabolic acidosis is simply a complication of AKI, sodium bicarbonate can be administered if the serum bicarbonate concentrations fall below 15 to 18 mmol/l. Volume overload can occur after the administration of bicarbonate. Bicarbonate administration in lactic acidosis caused by an underlying shock is controversial, given the possibility of an increase in carbon dioxide generation, worsening of the intracellular acidosis, and volume overload. Rapid improvement in the metabolic status may also enhance hypocalcemia, which may lower cardiac output. Therefore, in patients with lactic acidosis, most physicians would restrict the administration of sodium bicarbonate to patients with severe metabolic acidosis (arterial pH below 7.10 to 7.15) to maintain the pH above 7.15 to 7.20 until the primary process could be reversed. Alternative forms of base treatment have not been studied extensively in patients with AKI. Tris(hydroxymethyl)aminomethane (THAM) is excreted in the urine, and its clinical efficacy compared with that of sodium bicarbonate remains unproven.[47] We do not recommend its use in patients with AKI, especially in patients with hyperkalemia, because, in contrast to bicarbonate, THAM does not decrease serum potassium and can even cause hyperkalemia. Restriction of protein intake has also been suggested as a method of acidosis control because protein breakdown has been associated with worsening acidosis, such as in CKD.[73] However, protein restriction is not recommended in AKI (see later discussion of nutritional considerations).

Nutrition

Patients with AKI have an increased risk of protein-energy malnutrition because of poor nutrient intake and high catabolic rate. Nutritional support should be directed toward ensuring adequate

nutrition, preventing protein-energy wasting with its concomitant metabolic complications, promoting wound healing and tissue repair, supporting immune system function, and reducing mortality.

Nutritional assessment is difficult, especially in AKI patients with high metabolic demands. Subjective global assessment evaluates nutritional status, requires no additional laboratory testing, and is highly predictive of outcome.[74]

Patients with AKI should receive a basic intake of 0.8 to 1.0 g of protein per kilogram per day if not catabolic and a total energy intake of 20 to 30 kcal/kg/day, as recommended in the KDIGO AKI guidelines. In addition, in patients on RRT, 1.0 to 1.5 g of protein per kilogram per day should be administered up to a maximum of 1.7 g/kg/day in patients on CRRT and in hypercatabolic patients. Protein catabolism can be ascertained by the urea nitrogen appearance rate over a set interval with appropriate adjustments for dialysis sessions and CRRT.[75]

Monitoring of nitrogen balance to assess the effectiveness of supplemental nutritional therapy is determined by measuring protein intake during 12 or 24 hours and urinary excretion of urea nitrogen during the same time interval. A positive or negative protein balance is used to determine the adequacy of protein intake of the patient. It is calculated as follows:

$$\text{Nitrogen balance} = (\text{Protein intake}/6.25) - (\text{UUN} + 4)$$

Protein intake and urinary urea nitrogen (UUN) are each expressed in grams. The enteral route should be the first choice for nutritional support if the gastrointestinal tract is functioning; parenteral nutrition should be reserved for when the gastrointestinal tract cannot be used or when the enteral route appears inadequate to reach nutrient intake goals.[76] AKI itself and other factors commonly present in critically ill patients, such as medication use, hyperglycemia, and electrolyte disorders, can impair gastrointestinal motility.

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CHAPTER 74

Dialytic Management of Acute Kidney Injury and Intensive Care Unit Nephrology

Mark R. Marshall and Luis A. Juncos

Intensive care unit (ICU) nephrology can be defined as a subspecialty that focuses on abnormalities of fluid, electrolyte, and pH homeostasis in ICU patients, and the prevention and management of functional renal impairment relative to physiologic demand. This chapter describes agreed-on best practices with respect to acute renal replacement therapy (ARRT) and provides strategies for avoiding common treatment-related complications. The chapter uses appropriate clinical practice guidelines as starting points for discussion and summarizes their recommendations (Box 74-1).[1-8]

When the Acute Kidney Injury Network (AKIN) criteria are applied, approximately 40% of ICU patients develop evidence of acute kidney injury (AKI), an independent risk factor for death. The nondialytic therapy of AKI is discussed in Chapter 73. Approximately 5% of ICU patients require ARRT, and mortality in this population is improving over time despite a higher degree of illness severity.[9] Death attributable to AKI appears to result from nonresolving infection, hemorrhage, or nonresolving shock, despite optimal care. Such conditions may therefore be considered a systemic "acute uremic syndrome" that is specific to AKI and a possible target for modulation with ARRT—analogous to the traditional uremic syndrome in the setting of maintenance dialysis.

ORGANIZATIONAL ASPECTS OF ACUTE RENAL REPLACEMENT THERAPY PROGRAMS

Intensive care units can be described as open (patient care remains under the attending physician of record), closed (patient care is transferred to an intensivist), or comanaged (an open ICU, as defined earlier, in which patients receive mandatory consultation from an intensivist). Most ICUs in the United States are open, whereas most in Australia and New Zealand are closed. Those in Europe are approximately equally split. When AKI and ARRT are considered, advantages of intensivist-based management include immediate availability of service and decreased fragmentation of care. This model of care is supported by ecologic studies that suggest improved overall patient outcomes in health care systems with closed ICUs. Alternatively, advantages of nephrology-based management include greater understanding of the dialysis process and underlying AKI. This model of care is supported by studies that show improved outcomes in ICU patients with AKI associated with earlier referral to nephrology. All of these studies have disparate definitions and analyses that make interpretation difficult. Clinical governance over ARRT is therefore likely to remain contentious, although the expertise of staff providing care probably influences patient outcomes more than the specialty to which they belong. Specific training in ICU nephrology and exposure to ARRT is inadequate in many critical care and nephrology training schemes and should be a component of both core curricula.

In many parts of the world, ICU nursing staff members deliver all modalities of ARRT; in other countries, support from nephrology staff is required. As machinery platforms become universal for continuous renal replacement therapy (CRRT) and intermittent hemodialysis (HD), it is likely that ICU expertise in all modalities will grow, provided in-service education and support are adequate to develop and maintain the skill base.

OVERVIEW OF ACUTE RENAL REPLACEMENT THERAPIES

The main modalities of ARRT are acute intermittent HD and its variants, CRRT, and acute peritoneal dialysis (PD). Acute intermittent HD and CRRT are most popular, although practice patterns vary regionally because of cost, availability of technology, and reimbursement policies. Recently, intermittent HD has undergone resurgence through variants that provide slower fluid removal over longer periods of time, resulting in improved hemodynamic stability and increased solute clearance. These variants are most commonly referred to as *sustained low-efficiency dialysis* (SLED). Collectively, however, they are best referred to with the umbrella term *prolonged intermittent renal replacement therapy* (PIRRT), a term more aligned to nomenclature endorsed by the Acute Dialysis Quality Initiative (www.adqi.net) (Fig. 74-1). *Acute PD* is mostly used in the developed world for pediatric patients, and it is not considered further in this chapter.

Therapeutic goals for ARRT are not well defined. The usual minimum recommendation is to correct acidosis or hyperkalemia, refractory hypervolemia, and uremic features such as pericarditis or coma. Serum electrolyte and bicarbonate concentrations should be maintained in the normal range. Although specific laboratory thresholds for starting and stopping therapy are unknown, dialysis dose should be measured and adjusted to meet minimum targets, which are discussed later. It is important to note that the process of ARRT itself should not jeopardize the patient by exacerbating hemodynamic instability, increasing end-organ damage, or delaying renal recovery.

Determining goals with respect to a patient's extracellular volume status is not straightforward. Assessment itself is difficult; physical signs such as jugular venous distention are generally not informative, especially for mechanically ventilated patients. Moreover, baseline values of central venous pressure, pulmonary capillary wedge pressure, and echocardiographic left ventricular diastolic dimensions may be inaccurate surrogates for intravascular volume status, especially for patients with sepsis. An alternative approach is to use the effect of therapeutic maneuvers such as fluid challenge on blood pressure, stroke volume, or vena cava collapsibility. Even after fluid status has been adequately assessed, determining the therapeutic

Key Clinical Practice Guidelines

Kidney Disease: Improving Global Outcomes (KDIGO): Clinical practice guideline for acute kidney injury[1]

Kidney Disease Outcomes Quality Initiative (KDOQI) Vascular Access Work Group: Clinical practice guidelines for vascular access[2]

Healthcare Infection Control Practices Advisory Committee (HICPAC) of the Centers for Disease Control and Prevention (CDC): Guidelines for the prevention of intravascular catheter-related infections[3]

National evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England[5]

Institute for Healthcare Improvement: *How-to Guide: Prevent Central Line–Associated Bloodstream Infections*[4]

International Organization for Standardization documents ISO 11663 *(Quality of Dialysis Fluid for Haemodialysis and Related Therapies),* ISO 13958 *(Concentrates for Haemodialysis and Related Therapies),* ISO 13959 *(Water for Haemodialysis and Related Therapies),* and ISO 26722 *(Water Treatment Equipment for Haemodialysis Applications and Related Therapies)* (www.iso.org)

Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition)[6]

European Best Practice Guidelines Expert Group on Hemodialysis, European Renal Association. Section V: Chronic intermittent haemodialysis and prevention of clotting in the extracorporeal system[8]

Locking solutions for haemodialysis catheters; heparin and citrate—a position paper by the American Society of Diagnostic and Interventional Nephrology[7]

Box 74-1 Key clinical practice guidelines quoted in this chapter.

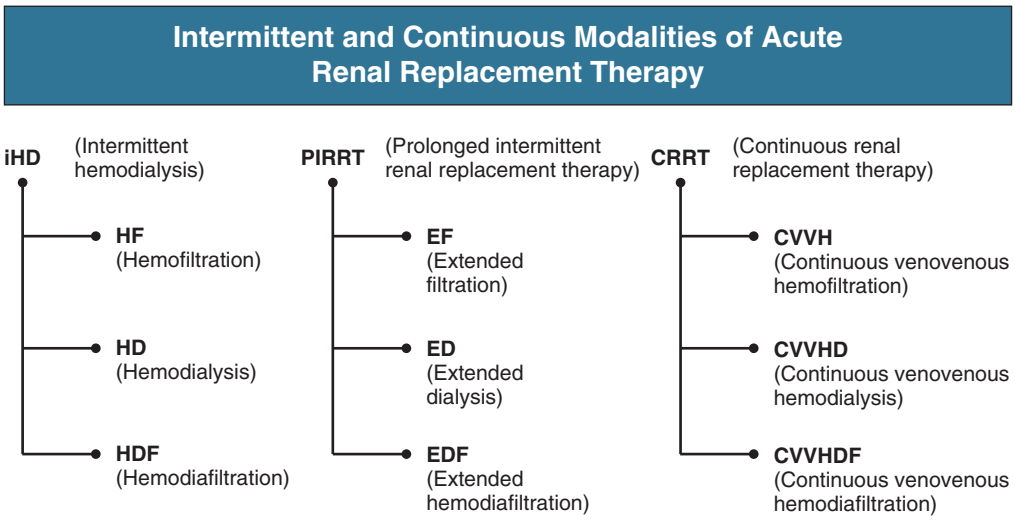


Figure 74-1 Intermittent and continuous modalities of acute renal replacement therapy. *(Adapted from reference 40.)*

goal is also difficult; patients with extracellular fluid excess in the absence of intravascular hypervolemia may benefit from fluid removal if they develop abdominal compartment syndrome, impairment of lung compliance and oxygenation, or poor wound healing. In particular, patients with acute lung injury require a shorter period of ventilation with less fluid loading (guided by central filling pressures).

Variations of ARRT have been used to enhance removal of cytokines. Cytokines are medium (300 to 12,000 d) and large (>12,000 d) molecules that are essential in modulating the immune response. However, their production is increased with acute illness, and their clearance decreased during AKI, resulting in excessive levels that have cardiodepressant, vasodilatory, and immunosuppressive properties.[10] Consequently, this has sparked interest in enhancing cytokine clearance during acute illness or AKI. Differing degrees of cytokine removal can be achieved through the use of high-flux or super-high-flux membranes (molecular weight cutoff of approximately 60 to 150 kd), bioadsorption and coupled plasma filtration–adsorption filters, and high levels of convective clearance. The last is achieved by ultrafiltering large amounts of plasma through a standard hemofilter and replacing the ultrafiltrate with a physiologic replacement fluid, thus diluting the remaining solutes in the body. It should be noted, however, that ARRT will remove both proinflammatory and anti-inflammatory cytokines, with potential to inadvertently exacerbate the inflammatory milieu. Notwithstanding, a promising technique is high-volume hemofiltration, supported by observations of improved outcomes in ICU patients with sepsis with higher doses of hemofiltration (≥45 ml/kg/h), and improved hemodynamic stability with even higher doses (60 to 100 ml/kg/h) applied either as a "pulse" or continuous maneuver. At present, only preliminary outcome data support the approach, although clinical trials are under way.[11]

Timing of ARRT initiation is controversial. Proponents of early initiation argue that it is in the patients' interest to prevent rather than treat the acute uremic syndrome and recommend initiation once kidney injury or failure is present. Indeed, this view is supported by observational studies suggesting that earlier initiation might achieve better outcomes (none suggest more harm). However, there is no high-quality evidence, and the single clinical trial designed to answer the question was inadequately powered.[12] Currently, timing of initiation is variable; a large multinational cohort study showed ARRT was initiated when the median (interquartile range [IQR]) serum creatinine and urine output were 309 (202 to 442) µmol/l and 576 (192 to 1272) ml/day, respectively.[13]

INTERMITTENT ACUTE RENAL REPLACEMENT THERAPY

Techniques for Acute Intermittent Hemodialysis

Acute intermittent HD is categorized according to hemodialyzer membrane and mechanism of solute removal. High-flux membranes allow greater convective removal of middle and larger solutes, but limited clinical data do not show obvious advantages in the ICU setting. Biocompatibility is a membrane characteristic that includes a low capacity for activating complement and leukocytes. After complement activation, there is stasis of leukocytes in the lungs, renal parenchyma, and other organs and the release of products of leukocyte activation. Although studies have been inconsistent, the use of biocompatible membranes should in principle favorably affect mortality and recovery of renal function in ICU patients with AKI, and are recommended.

Hemodiafiltration (HDF) is usually performed in the ICU as a continuous modality. However, acute intermittent HDF can be performed with use of sterile replacement fluid generated from ultrapure dialysate ("online"), which is infused directly into the extracorporeal blood circuit. As with high-flux dialysis, limited clinical data do not show obvious advantages.

Dialysate for intermittent ARRT can either be delivered by a batch system or generated online by a single-pass system. The latter uses concentrate and tap water that is purified by reverse osmosis in a central water purification plant or portable unit. Most ICUs do not have a central plant, although this is increasingly common in units in which on-line HDF is performed. There is concern about the possibility of backfiltration of bacterial contaminants, specifically endotoxin, which could exacerbate cytokine-mediated injury. At this time, the reference standards for water purity in the ICU setting are the same as those for the end-stage renal disease (ESRD) setting (www.iso.org; see Box 74-1). Online replacement fluid for HDF is sterilized with ultrafilters in the dialysate pathway and does not differ from commercial preparations in terms of microbial counts, endotoxin concentration, and cytokine-inducing activity. Sterile dialysate is suggested by some for all acute intermittent HD, although there are insufficient data to support a strong recommendation.

Strategies to Reduce Intradialytic Hemodynamic Instability During Intermittent Hemodialysis

Intradialytic hypotension is detrimental for end-organ function and recovery. Fresh ischemic lesions in kidney biopsy specimens can be found in patients on ARRT of longer than 3 weeks' duration. The relatively high ultrafiltration rate (UFR) with acute intermittent HD often leads to intradialytic hypotension, which reduces residual renal function. Increasing the frequency and treatment time of intermittent HD minimizes ultrafiltration goals and is the most effective measure to minimize intradialytic hypotension. Certain technical features on dialysis machinery are also helpful. Hemodynamic stability is facilitated by precise and predictable fluid removal, especially when the fluid removal is greater than that required for the restoration of euvolemia, such as for HDF. Hence, machines with computerized flow or volumetric ultrafiltration control are preferred.

Bicarbonate-buffered dialysate should be used routinely in critically ill AKI patients. It is associated with less hypotension than acetate dialysate, which has a peripheral vasodilating and myocardial depressant effect.

Hemodynamic stability is also facilitated by sodium profiling during intermittent HD. The rapid reduction in serum osmolality with intermittent HD promotes water movement into cells, thus reducing effective circulating volume. Dialysate sodium concentration can vary from approximately 130 to 150 mmol/l. The default for intermittent HD and PIRRT is approximately 145 mmol/l and avoids changes in sodium mass balance that can lead to marked fluid shifts and therefore intradialytic hypotension. Sodium profiling further ameliorates this process by inducing water flux into the vascular compartment, although an alternative and simpler approach of use of a high-sodium dialysate (e.g., 145 to 150 mmol/l) may also work and needs to be tested. A randomized study showed that intermittent HD with sodium profiling (starting at 160 mmol/l, reducing to 140 mmol/l) combined with ultrafiltration profiling (50% of ultrafiltration volume removed in first third of treatment) improved hemodynamic stability.[14] Profiling seems to be effective, although it should be used carefully in patients with dysnatremias, in whom serum sodium concentrations should be corrected slowly to minimize the risk of neurologic complications.

Online blood temperature and blood volume monitoring involves biofeedback systems that automatically adjust intermittent HD operating parameters. Blood volume monitoring adjusts UFR and dialysate sodium content in response to a fall in circulating blood volume, and blood temperature monitoring maintains blood temperature at a target value by controlling thermal transfer to and from dialysate to avoid vasodilation and decreased vascular resistance. Although helpful in the ESRD setting, neither technique has been shown to prevent intradialytic hypotension in the ICU setting.[15,16] The likely reasons pertain to different causes and compensatory mechanisms for hypotension that probably differ in the two settings.[17]

High dialysate calcium (1.75 mmol/l) has been used to improve hemodynamic stability during intermittent HD in ESRD patients with cardiomyopathy. This technique is limited by the development of hypercalcemia, however, and has not been studied in the ICU setting.

A number of early observational studies demonstrated less intradialytic hypotension during intermittent HDF in the ESRD setting, although prospective controlled trials, such as the Convective Transport Study (CONTRAST), have not supported this finding.[18] It is unlikely that intermittent HDF reduces intradialytic hypotension in critically ill AKI patients.

Extensive cumulative clinical experience shows that lower-efficiency modalities of ARRT provide better hemodynamic stability because of slower fluid and solute removal. This is supported by meta-analyses showing better preservation of blood pressure and lower vasopressor requirements in those treated with CRRT rather than intermittent HD.[1,19] Several prospective clinical trials and many observational studies have also shown comparable hemodynamic stability between CRRT and PIRRT.[20-23] Lower-efficiency prescriptions of PIRRT and CRRT are therefore suitable for ameliorating intradialytic hypotension, and the first choice of ARRT modality for hemodynamically unstable patients.

Prolonged Intermittent Renal Replacement Therapy

Prolonged intermittent renal replacement therapy uses standard intermittent HD equipment and consumables, but with lower solute clearances and UFR maintained for prolonged periods of time.[24] Typically, treatment duration is 6 to 18 hours. Dialysate flow rate *(Qd)* is usually 200 to 300 ml/min, and urea clearances are therefore lower and higher than in intermittent HD and CRRT, respectively, allowing for scheduled downtime without compromising dialysis

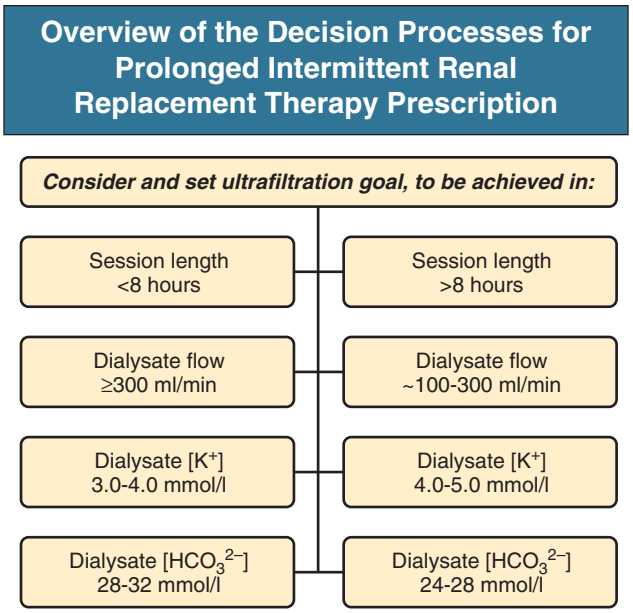


Figure 74-2 Overview of the decision processes for prolonged intermittent renal replacement therapy prescription.

dose. With longer treatments, phosphate replacement may be required at 0.1 to 0.2 mmol/kg or by adding 30 to 45 ml of a bowel preparation containing sodium dihydrogen phosphate dihydrate and disodium phosphate (e.g., Fleet Phospho-Soda) to dialysate. In addition, dietary protein should be supplemented by 0.2 g of protein per kilogram per day. A prescription algorithm is shown in Figure 74-2.

Prolonged intermittent renal replacement therapy provides a high dose of dialysis with minimal urea disequilibrium, excellent control of electrolytes, and good tolerance to ultrafiltration.[20] PIRRT is usually delivered as a diffusive therapy, although there is increasing experience with combined diffusive and convective clearance.

Dosage of Acute Intermittent Renal Replacement Therapy

The relationship between small-solute clearance and the outcomes of critically ill AKI patients is now established. A key study from 20 years ago showed that delivered single-pool *Kt/V (spKt/V)* above 1.0 per intermittent HD treatment was associated with improved survival in patients with intermediate illness severity, although the study did not relate outcomes to frequency of treatments.[25] Most recently, a well-conceived and executed prospective, randomized controlled trial showed that delivered *spKt/V* of 1.2 to 1.4 per intermittent HD or PIRRT treatment five to six times per week did not improve survival compared with this dose thrice weekly.[26] There are consistent data restricted to PIRRT from the Hannover Dialysis Outcome Study, a smaller but well-executed randomized clinical trial (see later).[27]

Optimal intermittent HD dose therefore appears to be related to small-solute clearance, although there appears to be a dose above which survival becomes dose independent. The minimum recommended intermittent HD and PIRRT dose in ICU patients with AKI is a delivered *spKt/V* of at least 1.3 per treatment at least thrice weekly.[1] Because routine dialysis regimens used in the United States in this setting have been reported to deliver a dose of *spKt/V* that is less than 1, routine measurement of dose should be undertaken to guide appropriate adjustment of operating parameters as summarized in Box 74-2. If this dosage target cannot be achieved, dose should be maintained as high as possible and treatment frequency

Measures to Increase Intermittent Hemodialysis Dose

- **Maximize hemodialyzer surface area** (up to 2 to 2.2 m^2)
- **Maximize hemodialyzer porosity** (high flux)
- **Maximize blood flow rate** by:
  - Maximizing internal lumen diameter of catheter (up to 2.0 to 2.2 mm)
  - Titrating blood flow to maximum arterial and venous pressure (up to − and + 300 to 350 mm Hg, respectively)
  - Correcting position of catheter tip in SVC and IVC as appropriate
  - Use right-sided IJ and SC in preference to left-sided IJ and SC
- **Minimize access recirculation** by correcting position of catheter tip in superior or inferior vena cava as appropriate using internal jugular and subclavian, rather than femoral, catheters
- **Maximize dialysate flow** (up to 800 to 1000 ml/min)
- **Add postdilution HDF**
- **Optimize anticoagulation** to reduce hemodialyzer fiber bundle clotting
- **Optimize circulation** to reduce compartmental urea sequestration
- **Increased treatment frequency** (up to daily)
- **Increased treatment duration** (up to 6 to 8 hours, then consider PIRRT [SLED] or CRRT)

Box 74-2 Measures to increase intermittent hemodialysis dose. *CRRT,* Continuous renal replacement therapy; *HDF,* hemodiafiltration; *IJ,* internal jugular; *IVC,* inferior vena cava; *PIRRT,* prolonged intermittent renal replacement therapy; *SC,* subclavian; *SLED,* sustained low-efficiency dialysis; *SVC,* superior vena cava. *(Modified from reference 55.)*

increased. The required number of treatments per week and administration interval can be established from the nomogram in Figure 74-3, expressing combinations of intermittent HD dose and treatment frequency as a continuous small-solute clearance (expressed as the corrected equivalent renal urea clearance [EKRc]), aiming for a value of 13 ml/min or higher.[28,29] This expression of dose is useful to frame interpretation of outcomes in the Hannover Dialysis Outcome Study: patients treated with daily PIRRT to keep plasma urea at 11.3 ± 4 mmol/l (EKRc equal to 20 ml/min, assuming urea generation of 20 mg/min) had outcomes indistinguishable from those of patients treated to keep plasma urea at 19 ± 6 mmol/l (EKRc equal to 13 ml/min).[27] In both arms, the doses expressed as EKRc were above the value that defines adequate intermittent HD delivering an *spKt/V* of 1.3 or higher at least thrice weekly (EKRc ≥ 13 ml/min in Fig. 74-3).

CONTINUOUS RENAL REPLACEMENT THERAPY

Continuous renal replacement therapy involves the application of lower UFR and solute clearances for substantial periods every day. The lower UFR provides comparatively better hemodynamic stability than intermittent HD, especially during ultrafiltration of large obligatory fluid loads, and the lower solute clearances result in single-pool solute kinetics despite disparities between regional blood flows resulting from pressor use. The longer treatment duration results in better and more consistent control of uremic solutes, especially for severely catabolic patients.

Interruptions to CRRT because of circuit clotting or out-of-unit procedures lead to a reduction in dose from downtime as well as expense related to blood circuitry changes. Mean operating time for

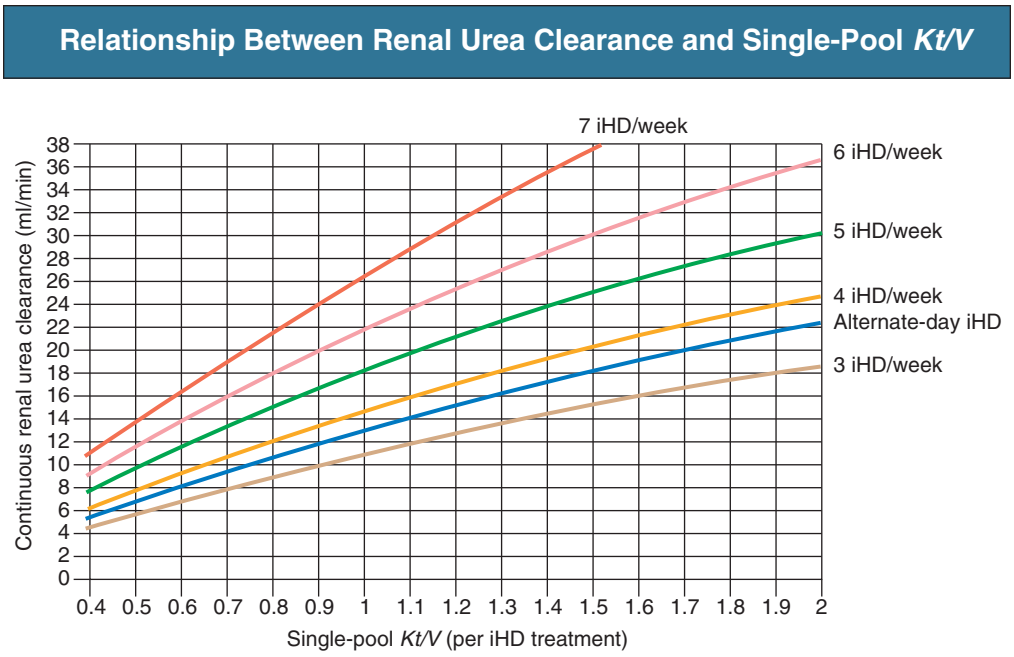


Figure 74-3 Relationship between corrected continuous renal urea clearance and single-pool *Kt/V* (weekly urea clearance/volume of distribution of urea) per treatment for a frequency of three to seven treatments per week. *iHD,* Intermittent hemodialysis. *(From reference 56.)*

CRRT has been reported to be between 17 and 22 h/day.[30] It is therefore important to apply rigorous protocols, including proper catheter tip positioning and anticoagulation, to ensure adequate delivery of CRRT.

Techniques for Continuous Renal Replacement Therapy

The Acute Dialysis Quality Initiative (www.adqi.net) classification of CRRT is accepted as standard and uses nomenclature based on the type of vascular access and the method of solute removal.

Venovenous (VV) denotes a circuit with a central venous catheter, achieving more reliable and rapid blood flow rate *(Qb)* of approximately 250 ml/min by a mechanical pump. Pumped VV circuits are more complex and costly and have the disadvantage of potential inadvertent disconnection of lines, resulting in hemorrhage or air embolism with continued pump operation; this risk is minimized by monitors and alarms. *Arteriovenous* (AV) denotes an extracorporeal blood circuit in which an arterial catheter allows blood to circulate by systemic blood pressure. A venous catheter is placed for return. AV circuits are simple but involve arterial puncture, which can lead to distal embolization, hemorrhage, and vessel damage. A *Qb* of 90 to 150 ml/min is typical in patients with mean arterial pressure above 80 mm Hg, although flow can be erratic, predisposing to clotting.

Mechanisms of Solute Removal

Hemodialysis

Continuous HD provides diffusive small-solute transport. *Qb* and *Qd* during CRRT are usually relatively low (approximately 150 ml/min and approximately 2 l/h, respectively). Under these conditions, the ratio of dialysate-urea nitrogen to blood urea nitrogen (DUN/BUN) is 1.0, indicating complete saturation. Urea clearance therefore equals *Qd* and is unaffected by *Qb* until it decreases to below 50 ml/min.

With increasing *Qd*, there are proportionally decreasing gains in small-solute clearance as the DUN/BUN progressively decreases.

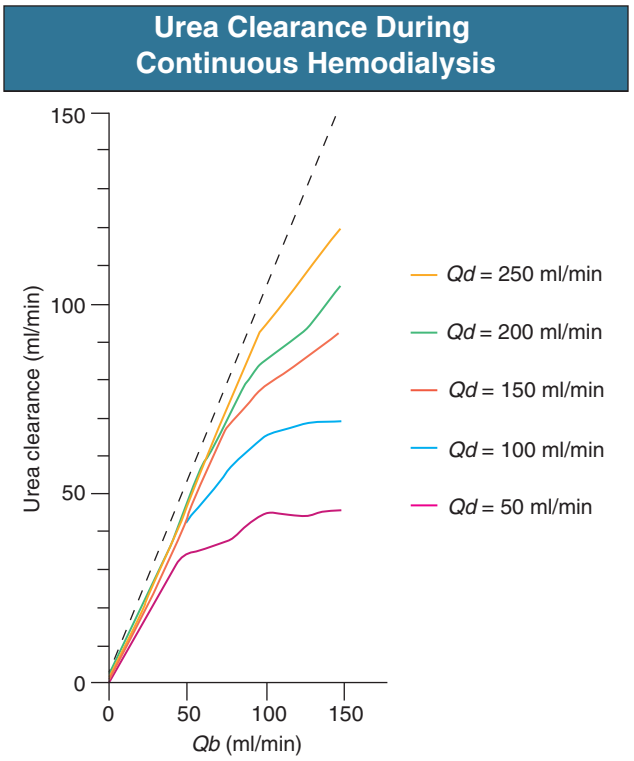


Figure 74-4 Determinants of urea clearance during continuous hemodialysis. Relationship among urea clearance, *Qb* (blood flow), and *Qd* (dialysate flow) during continuous hemodialysis. The flattening of the urea clearance curves describes the conditions in which increases in *Qb* do not enhance clearance. *(From reference 31.)*

Figure 74-4 illustrates this principle.[31] The flattening of the curves describes the conditions where increasing *Qb* does not enhance clearance. At a *Qb* of 200 ml/min, urea clearance will correspond to *Qd* at a rate of 2 l/h (or less) and will not increase with increased *Qb*. If *Qd* is increased to 4 l/h, this will correspond to a urea clearance

of approximately 3 l/h that will progressively increase with increasing *Qb*.

Hemofiltration

Continuous HF provides convective small- and medium-sized–solute transport. An important determinant of clearance is the site of fluid replacement, which can be infused either into the arterial blood line leading to the hemofilter (predilution) or into the venous blood line leaving the hemofilter (postdilution). The standard method is postdilution. However, higher UFR can lead to hemoconcentration in the hemofilter, increased resistance in the blood flow pathway, reductions in *Qb*, and ultimately increased risk for clotting of the hemofilter. In practice, UFR should not exceed 30% of the plasma water flow rate (i.e., filtration fraction should be below 0.30). The problem can be resolved by increasing *Qb* to at least 200 to 250 ml/min or by diluting the blood and clotting factors with replacement fluid before it reaches the hemofilter (predilution), thereby improving filter patency and decreasing anticoagulant requirements.

The disadvantage of predilution is that filtrate is generated from blood diluted with replacement fluid and therefore contains a lower concentration of uremic solutes. Small-solute clearance is reduced by approximately 15% at low UFR, although this figure increases to approximately 40% with a higher UFR.[32,33] Clearance of any given solute during continuous HF is calculated as follows:

$$K\,(\text{postdilution}) = \text{UFR} \times S$$

$$K\,(\text{predilution}) = \text{UFR} \times S \times [\text{Qbw}/(\text{Qbw} + \text{Qr})]$$

where *K* is clearance (ml/min), *S* is the sieving coefficient of the solute, *Qbw* is blood water flow rate equal to the product of *Qb* and (1 – hematocrit), and *Qr* is the replacement fluid rate.

Hemodiafiltration

Continuous HDF refers to a combination of the preceding techniques. With large enough membranes, the small-solute clearances obtained approach the sum of the individual techniques.[32]

Specific Techniques

Continuous renal replacement therapy techniques are shown in Figure 74-5. The choice of technique is dependent on equipment availability, clinician expertise, prospects for vascular access, and whether the primary need is for fluid and/or solute removal. This last factor is often the most important because each technique provides different rates of fluid and solute removal. Most clinicians avoid AV circuits because of higher vascular complication rates.

For isolated fluid removal, slow continuous ultrafiltration (SCUF) can be used. Given its minimal solute clearance (equal to the UFR at generally 4 to 5 ml/min), SCUF has primarily proven useful for treatment of the cardiorenal syndrome.

Most ICU patients require removal of solute in addition to that of fluid. For this, most clinicians prefer pumped VV rather than AV circuits because of higher and more reliable *Qb*, allowing for greater solute clearance. It should be noted that the benefit of larger-solute clearance is uncertain in this population, whereas the benefits of small-solute clearance are more evident (see later). It should also be

Continuous Renal Replacement Therapies

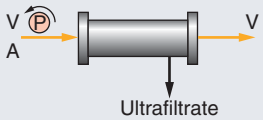
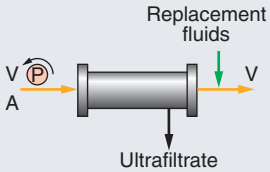
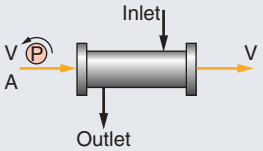
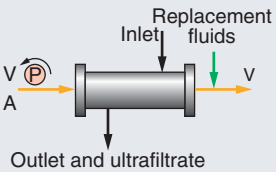
	Slow continuous ultrafiltration	Continuous hemofiltration	Continuous hemodialysis	Continuous hemodiafiltration
				
Arteriovenous (AV) or venovenous (VV)	AV or VV	AV or VV	AV or VV	AV or VV
Blood flow (ml/min)	50–100	50–200	50–200	50–200
Dialysate flow (ml/min)	–	–	10–20	10–20
Clearance (l/24 h)	–	12–36	14–36	20–40
Ultrafiltration rate (ml/min)	2–5	8–25	2–4	8–12
Blood filter	Highly permeable filter	Highly permeable filter	Low-permeability dialyzer with countercurrent flow through the dialyzer compartment	High-permeability dialyzer with countercurrent flow through the dialyzer compartment
Ultrafiltrate	Corresponds exactly to the patient's weight loss	Replaced in part or completely to achieve purification and volume control	Corresponds to patient's weight loss; solute clearance by diffusion	In excess of patient's weight loss; solute clearance by both diffusion and convection
Replacement fluid	None	Yes	None	Yes, to achieve fluid balance
Efficiency	Used only for fluid control in overhydrated states	Clearance for all solutes equals ultrafiltration	Limited to small molecules	Extends from small to large molecules

Figure 74-5 Continuous renal replacement therapy modalities. The pump *(P)* is used only in venovenous modes. *(Modified from reference 57.)*

noted that the practice of treating lactic acidosis with CRRT should be discarded. The only effective treatment for lactic acidosis is addressing the cause of lactate formation (improving tissue oxygenation, removing dead gut, and so on); extracorporeal lactate clearance is 10-fold to 100-fold lower than plasma clearance through hepatic metabolism.

Dosage of Continuous Renal Replacement Therapy

Continuous renal replacement therapy dose is expressed as effluent volume flow rate per unit of premorbid or pre-ICU weight (ml/kg/h). Despite mixed results in earlier single-center studies, the relationship between CRRT dose and mortality has been established in several well-powered and definitive clinical trials, the most important of which are the Acute Renal Failure Trial Network Study and the Randomised Evaluation of Normal Versus Augmented Level of Replacement Therapy (RENAL) trial. As with intermittent HD, there appears to be a dose of CRRT above which survival becomes dose independent. This "break point" in the CRRT dose-response curve varies by study, although taken together the data show no benefit of increasing CRRT doses above an effluent volume flow rate of 20 to 25 ml/kg/h. In clinical practice, interruptions to CRRT will compromise dose, and it is generally necessary to prescribe in the range of 25 to 30 ml/kg/h while minimizing downtime. As for intermittent HD, quality assurance mandates routine measurement of dose to guide appropriate adjustment of operating parameters. Of note, optimal CRRT dose appears to be related more to small- than larger-solute clearance, although several clinical trials of increased convection through high-volume hemofiltration are awaited.

Technical Aspects of Continuous Renal Replacement Therapy

Equipment

Machines are commercially available that are dedicated to VV CRRT, with an integrated blood pump, arterial and venous pressure monitors, an air detection system, a method for removing air bubbles, and computerized volumetric or gravimetric systems to balance dialysate inflow and replacement fluid with dialysate outflow/filtrate.

Hemofilters

Specific devices for CRRT are usually referred to as *hemofilters*. However, conventional inexpensive hemodialyzers can serve as hemofilters. For adequate UFR to be achieved, the surface area must be large (approximately 2 m^2) for low-flux or, alternatively, more modest (approximately 0.5 m^2) for high-flux hemodialyzers. Some CRRT machines use a specific hemofilter because of a unique cartridge system. Sieving coefficients of small solutes are maintained throughout the life of hemofilters only in the absence of fiber bundle clotting, and a progressive decrease in DUN/BUN or filtrate urea nitrogen–BUN ratio may be noted throughout treatments. Monitoring of this parameter is recommended by some to guide prophylactic changes of hemofilters, thereby avoiding the advent of total extracorporeal circuit clotting and wastage of blood, as well as any associated compromise of CRRT dose from declining saturation of effluent.

There is promise in the use of superflux hemofilters as discussed previously, and studies are under way to determine effects on clinical outcomes. Albumin losses may prevent the prolonged use of such filters.

Replacement Fluids and Dialysate

Continuous renal replacement therapy requires sterile replacement fluid or dialysate for blood purification, with composition that is determined by the clinical requirements for acid-base control and electrolyte management. Fluids are available commercially or can be prepared aseptically in hospital pharmacies.

Buffer choice is between bicarbonate and lactate, the latter being metabolized in the liver to bicarbonate in a 1 : 1 ratio. Although many patients tolerate lactate solutions, bicarbonate solutions are superior in terms of acid-base control, hemodynamic stability, urea generation, cerebral dysfunction, and possibly survival in patients with a history of cardiac failure. Overall, bicarbonate has become the buffer of choice and is preferred in patients with lactic acidosis and/or liver failure. If lactate-buffered fluids are used, the development of lactate intolerance (>5 mmol/l increase in serum lactate during CRRT) may require a switch to bicarbonate-based fluid. Bicarbonate concentrations in fluid are typically 25 to 35 mmol/l: concentrations in the lower part of this range are indicated during high-dose or prolonged CRRT and during regional citrate anticoagulation therapy to prevent metabolic alkalosis.

Glucose concentrations in fluids range from 0.1% in commercially prepared fluids to 1.5% to 4.25% in PD fluids adapted for use with CRRT. Up to 3600 kcal/day may be derived from these latter solutions, although hyperglycemia may supervene to the detriment of patient outcomes. It is recommended that glucose intake be less than 5 g/kg/day and that glucose concentration in fluid be approximately 100 to 180 mg/dl (approximately 5.5 to 10 mmol/l) to maintain zero glucose balance.

Intravenous phosphate supplementation is often required during CRRT and is usually administered separately because of the potential for precipitation with calcium and magnesium in dialysate or replacement fluid. This concern may have been overstated in the past, and phosphate has been safely supplemented by injecting phosphate into these solutions. Moreover, replacement solutions containing up to 1.2 mmol/l of phosphate are commercially available or will soon become available.

VASCULAR ACCESS

A prerequisite for all ARRT modalities is reliable vascular access characterized by low resistance to flow and minimal access recirculation. AV fistulas and prosthetic bridge grafts should be used in patients who have them. However, access is usually via uncuffed untunnelled (temporary) double-lumen polyurethane or silicone catheters in the internal jugular, femoral veins, or less frequently subclavian catheters because they are associated with a higher incidence of procedural complications, venous stenosis, and thrombosis.

For CRRT and PIRRT, *Qb* below 250 ml/min is usually sufficient. For acute intermittent HD, higher *Qb* is sometimes required to allow sufficient solute clearance within a clinically or logistically appropriate dialysis schedule. Flows can be safely increased until venous and arterial pressures are plus and minus 350 mm Hg, respectively, after which hemolysis can occur. Left-sided internal jugular and subclavian catheters provide flows that are more erratic and up to 100 ml/min lower than elsewhere. Femoral and right-sided internal jugular or subclavian catheters provide the best *Qb*.[34]

Access recirculation for all sites is approximately 10% at *Qb* 250 to 350 ml/min and may increase to as much as 35% at *Qb* above 500 ml/min. It is least in internal jugular catheters and highest in femoral catheters less than 20 cm in length. Up to half of acute intermittent HD treatments will require catheters to be used in

reversed configuration, such that the original venous line is used as for blood inflow (relative to dialyzer) and the original arterial line for outflow. Access recirculation in this situation doubles to approximately 20% at 250 to 350 ml/min.[34] It also affects dialysis dose, and several studies have shown lower dialysis dose with femoral catheters despite identical operating parameters. Recent advances in catheter design minimize access recirculation through the use of symmetric (nonstepped) bias-cut spiraled ports on their tips. In both animal and preliminary human studies, this design results in minimal or acceptable access recirculation in both normal and reversed configuration. Overall, the data support a recommendation for right-sided internal jugular catheters with bias-cut spiraled ports as the first choice for intermittent HD and PIRRT, with femoral and left-sided internal jugular catheters as the second and third choices, respectively.

In the ICU setting, catheter associated bloodstream infection is common and is associated with a mortality risk estimated at 10% to 50%. There is ongoing controversy around the risk of infection with different insertion sites, but on balance the internal jugular site is preferred—although it is likely that the way the catheter is handled is more important at preventing infection than the site in which it is inserted.

Low rates of infection require both adherence to specific clinical guidelines and grounding of activities within a formal quality improvement framework.[35] There is strong evidence that standardizing catheter insertion techniques and adhering to the previously mentioned quality initiatives result in a close to zero catheter-related infection rate.[36] The relevant guidelines in choosing interventional bundles are those contained in the position statements of the Institute for Healthcare Improvement (IHI) and the Center for Disease Control and Prevention (CDC) Healthcare Infection Control Practices Advisory Committee (HICPAC).[3,4] The core elements in these guidelines appropriate for dialysis catheters are listed in Box 74-3.

Best Practices to Minimize Catheter-Associated Bloodstream Infection

Insertion

- Hand hygiene and aseptic technique (including early replacement of catheters inserted in uncontrolled settings if adherence to these measures cannot be ensured)
- Maximum barrier precautions (hat, mask, sterile gloves, sterile gown, and full patient drape)
- Appropriate skin preparation (2% chlorhexidine in 70% alcohol)
- Avoidance of the femoral site for catheter placement, especially in obese patients
- Avoidance of catheter placement near open wounds

Maintenance

- Daily review of the need for the line, with prompt removal of unnecessary lines
- Appropriate dressing with sterile gauze or a sterile, transparent, semipermeable dressing
- Appropriate schedule for dressing changes according to condition and type of dressing
- Daily review of the catheter exit site by inspection or palpation with minimal disturbance to the dressing unless clinically indicated
- Appropriate skin preparation before ports are accessed
- Daily cleansing of patients with a 2% chlorhexidine wash
- Use of a sutureless securing device for catheter stabilization

Box 74-3 Best practices to minimize catheter-associated bloodstream infection.

Antibiotic- or antiseptic-impregnated lines are recommended by the CDC for patients whose catheters are expected to remain in place for a prolonged period (longer than 5 days), when there is optimal adherence to measures to reduce infection, and also in patients at high risk for infection (patients with extensive burn injury, neutropenia, and arguably AKI). A potential downside of these impregnated lines is anaphylaxis.[37] Topical antibiotic ointments are not recommended because of their potential to promote fungal infections and antimicrobial resistance. Catheter-restricted locking solutions are effective at reducing catheter-associated infections in chronic intermittent HD.[3,5] However, their efficacy in critically ill AKI patients is unresolved and warrants further study.

ANTICOAGULATION IN ACUTE RENAL REPLACEMENT THERAPY

Most ICU patients can successfully avoid any anticoagulation during intermittent HD because of the short treatment duration. Only a minority can do so during PIRRT or CRRT, however, and anticoagulation is required to prevent clotting in the extracorporeal circuit without producing significant bleeding. Most commonly, unfractionated heparin is infused into the most proximal part of the extracorporeal circuit, keeping the activated partial thromboplastin time (APTT) in the venous blood line 1.5 to 2 times the control value and the systemic APTT below 50 seconds. This typically requires an initial bolus dose of approximately 2000 U and a maintenance infusion of approximately 500 U/h. Advantages of unfractionated heparin include low cost, relative safety, and ease of monitoring. Risks include bleeding, hyperkalemia, elevated hepatic transaminases, and heparin-induced thrombocytopenia (HIT) in 3% to 5% of patients.

Low-molecular-weight heparin (LMWH) is theoretically advantageous because of increased antithrombotic activity and decreased hemorrhagic risk. However, disadvantages include a prolonged half-life (approximately doubled in AKIN stage 3, with no significant clearance during ARRT), incomplete reversal with protamine, and limited availability of appropriate monitoring by serial anti–factor Xa determinations (recommended level 0.25 to 0.35 U/ml). Meta-analyses and the American College of Chest Physicians (ACCP) guidelines conclude that the use of LMWH is associated with major bleeding in patients with a creatinine clearance below 30 ml/min, and recommend either unfractionated heparin or a reduction in LMWH dose by 50% for such patients.[6,38] LMWH dosage is not interchangeable between different drugs. If LMWH is used, most experience is with dalteparin administered as a single bolus of approximately 20 to 30 U/kg for intermittent HD, followed by an infusion of approximately 10 U/kg/h for PIRRT. Overall, evidence does not support a recommendation of LMWH over unfractionated heparin in terms of safety and efficacy in the critically ill AKI setting, although it is not contraindicated in those with a low risk of bleeding.

Other approaches to anticoagulation include direct thrombin inhibitors (e.g., argatroban), antithrombin-dependent factor Xa inhibitors (e.g., fondaparinux), and serine protease inhibitors (nafamostat mesilate). Their roles are usually limited to anticoagulation of patients with HIT. Argatroban does not cross-react with heparin antibodies and is the preferred approach because of its hepatic clearance (half-life approximately 35 minutes, no significant clearance during intermittent HD or PIRRT[39]) and ease of monitoring with APTT. It is administered as a 0.1-mg/kg bolus before intermittent HD or an infusion of 0.1 to 0.2 mg/kg/h during PIRRT, titrated according to APPT. Further management of HIT is provided in

guidelines from the ACCP and the European Best Practice Guidelines.[6,8]

For those receiving systemic anticoagulation with heparin, the incidence of significant bleeding complications is up to 25% to 30%. Alternatives to systemic anticoagulation include regional citrate anticoagulation, regional heparin anticoagulation, and prostacyclin (epoprostenol). The lowest rates of hemorrhage and greatest prolongation of filter life are associated with regional citrate anticoagulation, and it is the preferred regional technique.

Regional citrate anticoagulation involves calcium chelation in the extracorporeal blood circuit with calcium reversal. For intermittent HD and PIRRT, this most commonly involves an infusion of 4% trisodium citrate into the proximal circuit, with zero- or low-calcium dialysate and an infusion of calcium chloride into the venous blood line. A simpler approach has been described in which the citrate infusion is combined with normal calcium dialysate and no calcium infusion. The positive calcium flux through the hemodialyzer maintains calcium balance without the need for a separate infusion and provides partial chelation of the undialyzed citrate.

For CRRT, regional citrate anticoagulation may be performed with 4% trisodium citrate or with anticoagulant citrate dextrose A. The latter is preferred over sodium citrate because it is less hypertonic, potentially reducing complications from overinfusion and mixing errors. For continuous HD, a prefilter infusion of 3% to 7% of *Qb* with a postfilter infusion of calcium chloride is used. This requires dialysate that is hyponatremic and devoid of alkali because citrate metabolizes to bicarbonate in the liver in a 1:3 ratio. For continuous HF, a prefilter infusion of substitution fluid can be used that contains no calcium but citrate as buffer (Table 74-1). Frequent monitoring and titration of citrate dose have usually been advocated to keep the ionized calcium within a therapeutic range. Many centers now use a simplified fixed-dose anticoagulant citrate dextrose A protocol that minimizes the need to measure postfilter calcium or adjust the citrate infusions. Major complications of regional citrate anticoagulation include systemic hypocalcemia and metabolic alkalosis from citrate toxicity, particularly in patients with liver dysfunction.

Regional heparin anticoagulation involves neutralization of heparin by infusion of protamine into the venous blood-line. It may be complicated by rebound bleeding, occurring when neutralization with protamine wears off faster than the anticoagulation from heparin. Furthermore, protamine may cause sudden hypotension, bradycardia, or anaphylactoid reactions.

Prostacyclin is an effective alternative anticoagulant. However, it is a vasodilator, causing a variable but occasionally marked decrease in blood pressure. Moreover, there is a risk of worsening ventilation-perfusion mismatch and lactic acidosis in patients with multiorgan dysfunction, and a risk of increasing intracranial pressure in patients with combined liver and kidney failure.

MODALITY CHOICE AND OUTCOMES IN ACUTE RENAL REPLACEMENT THERAPY

On the basis of current evidence, the use of one modality of ARRT over another is unlikely to translate to overall clinical benefit if applied to all patients.[1,19] The relationship between modality choice and outcomes is being studied in specific clinical situations such as acute lung injury, sepsis, and acute cardiac decompensation. Such studies may yet yield definitive data, but in the interim, modality choice depends on the most clinically appropriate rate of solute and fluid removal for the given clinical situation. Certain patients are best treated with a lower-efficiency modality, such as those who are hemodynamically unstable, including those with cardiogenic shock.[40] Although tolerance to ultrafiltration during intermittent HD can be improved, patients still often require a change to a lower-efficiency modality as evidenced by contamination between the arms in the Continuous Venovenous Haemodiafiltration Versus Intermittent Haemodialysis for Acute Renal Failure in Patients with Multiple-Organ Dysfunction Syndrome (Hemodiafe) study.[41] Given the risks of hypotension and subsequent fresh ischemic injury, PIRRT and CRRT are more desirable for such patients. The same applies to those who are at risk for dialysis disequilibrium syndrome. Solute disequilibrium should be minimized to avoid water influx into the brain in

Comparison of Regional Citrate Anticoagulation Protocols

	Modality	Blood Flow (ml/min)	Replacement Fluid Composition (mmol/l)	Dialysis Fluid Composition (mmol/l)	Citrate Source
Mehta et al[47] (1990)	CAV-HD	52-125	Normal saline	Na 117, Cl 122.5, Mg 0.75, K 4, dextrose 2.5%	4% Trisodium citrate
Hoffmann et al[49] (1995)	CVV-HD	125	Prefilter: normal saline + KCl 4, alternate with 0.45% saline + KCl 4 Postfilter: 0.45% saline + $MgSO_4$ + $CaCl_2$	—	4% Trisodium citrate
Palsson and Niles[48] (1999)	CVV-HD	180	Citrate 13.3, Na 140, Cl 101.5, Mg 0.75, dextrose 0.2%	—	Customized citrate solution
Tolwani et al[50] (2001)	CVV-HD	125-150	—	Normal saline + $MgSO_4$ 1.0, KCl 3	4% Trisodium citrate
Tobe et al[51] (2003)	CVV-HDF	100	Normal saline	Normocarb	ACD-A
Mitchell et al[52] (2003)	CVV-HD	75	—	Variable Ca 1.75-1.78	ACD-A
Swartz et al[53] (2004)	CVV-HD	200	—	Na 135, HCO_3 28, Cl 105, $MgSO_4$ 1.3, glucose 1 g/l	ACD-A
Gupta et al[54] (2004)	CVV-HDF	150	Normal saline ± $MgSO_4$ and KCl	PD fluid: Na 132, Ca 1.25, Cl 95, Mg 0.5, lactate 360 mg/dl, 1.5% dextrose	ACD-A

Table 74-1 Comparison of regional citrate anticoagulation protocols. *ACD-A,* Anticoagulant citrate dextrose form A; *CAV-HD,* continuous arteriovenous hemodialysis; *CVV-HD,* continuous venovenous hemodialysis; *CVV-HDF,* continuous venovenous hemodiafiltration; *PD,* peritoneal dialysis. Number behind electrolytes are concentrations in mmol/l.

those with cerebral edema or high intracranial pressure, and influx into the abdomen in those with compartment syndrome.[40]

An important determinant of modality choice is cost, and the complex extracorporeal circuits and requirement for replacement fluids generally make CRRT more expensive than intermittent HD or PIRRT. Pharmacoeconomic studies comparing ARRT modalities are all limited by wide variation in ICU cost and reimbursement structures. The modality that is the easiest to organize and least expensive to perform will be the most successful, if all outcomes are equivalent. Ultimately, the skill and experience of the staff providing ARRT probably influence patient outcomes as much as the choice of modality itself.

ACUTE RENAL REPLACEMENT THERAPY DURING MECHANICAL CIRCULATORY SUPPORT

There has recently been an increase in the use of mechanical circulatory support devices. Two are particularly important to ARRT providers: extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VADs). ECMO is used for refractory acute cardiac and/or respiratory support. Its use was largely limited to pediatrics, but recent advances have resulted in renewed interest in adults. ECMO can be either venoarterial, in which the blood is drawn from the venous system, oxygenated, and returned into the arterial circulation (providing cardiorespiratory support), or VV, in which the oxygenated blood is returned into the venous circulation (providing only respiratory support).

Ventricular assist devices are blood pumps that assist the left and/or right ventricles in patients with refractory heart failure or cardiogenic shock. They are used as a bridge to recovery, as a bridge to transplantation, or for long-term therapy in patients ineligible for transplant. Early VADs had pulsatile flow, but the limitations of these pumps led to the development of axial and centrifugal pump VADs that create nonpulsatile flow.[42] The improved reliability and results obtained with VADs, together with the increasing prevalence of severe heart failure, have caused a rapid increase in their use.

Acute kidney injury is common in patients with circulatory and/or respiratory failure. If the cause of AKI is simply hypoperfusion, initiating mechanical circulatory support may improve the renal

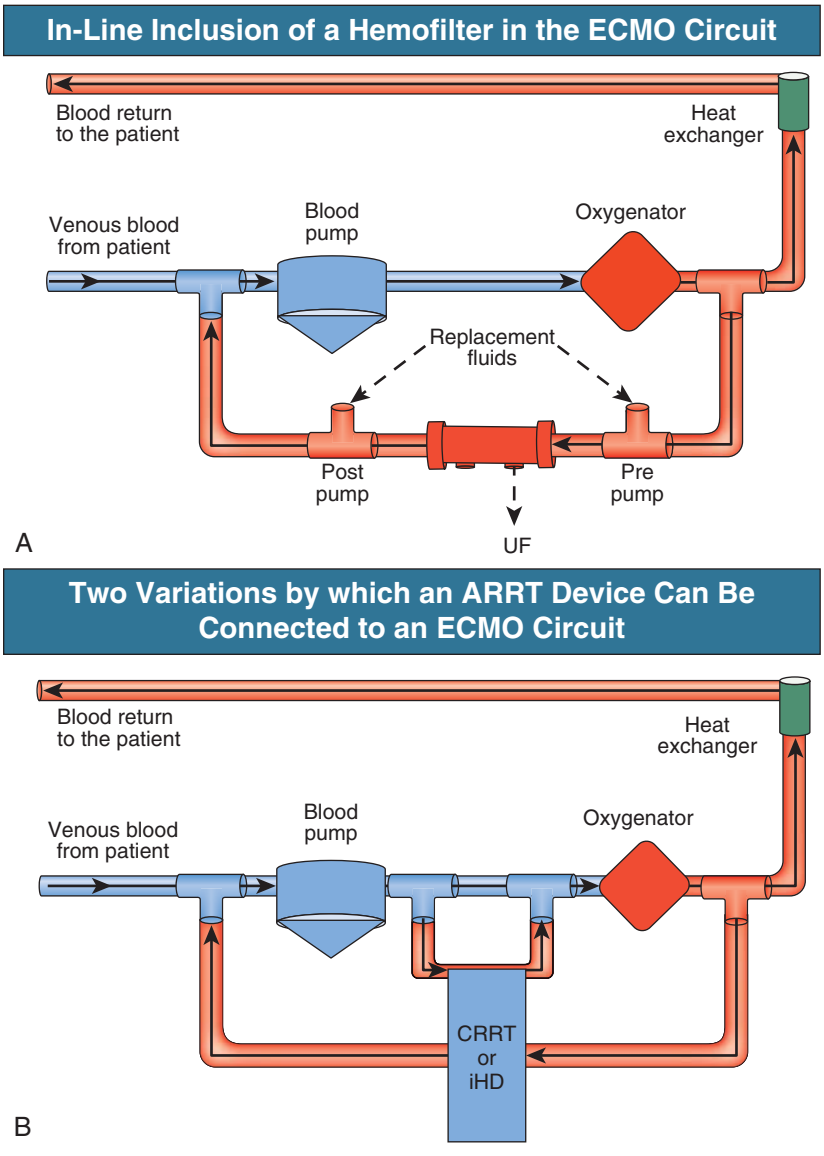


Figure 74-6 Techniques used to incorporate AART into ECMO and VAD circuits. A, In-line inclusion of a hemofilter in the ECMO circuit. Note that inclusion into an RVAD circuit would be similar except simplified in that blood comes from the body to the pump and then goes back to the body without passing through an oxygenator. **B,** Two variations by which an ARRT device can be connected to an ECMO circuit. Note that flow in the mechanical circulatory support circuit is high enough that recirculation is not a concern even when the arterial access port is distal to the venous return port. *ARRT,* Acute renal replacement therapy; *CRRT,* continuous renal replacement therapy; *ECMO,* extracorporeal membrane oxygenation; *iHD,* intermittent hemodialysis; *RVAD,* right ventricular assist device; *UF,* ultrafiltration.

function.[43] However, it can also be associated with mechanisms that induce AKI, including periprocedural hypotension, inflammation, thromboembolism, hemolysis, and medications. Consequently, AKI remains a common complication of mechanical circulatory support and frequently requires ARRT. Although few data are available to guide the use of ARRT in this situation, the general principles are similar to those for other ICU patients. However, special consideration should be given to volume management in these patients, not only because volume overload is associated with worse outcomes, but also because volume management facilitates weaning of mechanical circulatory support and allows for better delivery of nutrition.[44,45] Consequently, even though all forms of ARRT have been successfully used in patients with mechanical circulatory support, prolonged or continuous modalities are generally advantageous. Monitoring volume status in patients on continuous flow mechanical circulatory support devices can be particularly challenging. Patients have minimal pulses, so specialized blood pressure cuffs with low pulsatility modes are needed, or blood flow is monitored with flowmeters or Doppler. Because continuous flow pumps are dependent on preload, hypovolemia leads to left ventricular collapse with subsequent fall in mechanical circulatory support flow, pump overdrive, hypotension, and ventricular arrhythmias. This should be corrected by gentle volume administration while other causes of preload reduction (e.g., bleeding, sepsis) are considered. Decreasing the pump speed and treating arrhythmias should usually be performed only after detailed consultation. Chest compressions should not be performed.

Technical Aspects of Acute Renal Replacement Therapy During Mechanical Circulatory Support

Patients on mechanical circulatory support present several access options. The first is via standard HD catheters, which have the advantage of maintaining the two circuits independent of each other. The risks are the same as in other patients, but infections are especially hazardous as they are an important cause of death.

An alternative method of accessing the circulation is directly via the mechanical circulatory support circuit. This method is only for ECMO or right ventricular assist device (RVAD) circuits, not left ventricular assist devices (LVADs), because of the unacceptable risk of thromboembolism. Two three-way taps are placed along the mechanical circulatory support circuit to create a shunt for ARRT. The placement sites depend on the type of ARRT that will be used. In the first method, a hemofilter is directly placed in the circuit shunt. Blood flow through the filter is determined by the pressure gradient between the arterial port (located postpump, where the pressure is positive) and the venous port (located prepump, where the pressure is negative). The ultrafiltrate, dialysate, and/or replacement fluid volumes are regulated via infusion pumps (Fig. 74-6, *A*). This method is simple, adds little expense, and does not require another specialized machine. However, the infusion pumps are a source of errors; thus the accuracy of the infused and removed volumes should be confirmed (especially in infants).

In the second method, the three-way taps are used to connect a dialysis or CRRT machine to the mechanical circulatory support circuit. Modern ARRT machines can accommodate positive arterial access pressures; thus numerous access sites have been successfully used (Fig. 74-6, *B*).[46] This setup uses commercially available ARRT machines that control the renal replacement therapy procedure. It requires the use of an ARRT machine and can be labor intensive. The technique used should be determined by the availability of appropriate equipment and the skill and experience of the staff.

DRUG DOSAGE IN ACUTE RENAL REPLACEMENT THERAPY

For patients undergoing CRRT, 20 liters of daily filtrate correspond to a glomerular filtration rate (GFR) of approximately 14 ml/min, and the dose of drugs should be calculated accordingly. Any drug with a low therapeutic index that can be readily measured should be measured frequently early in the course of ARRT, until a stable pattern appears. One day of CRRT is in general comparable to one intermittent HD treatment with regard to drug removal.

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CHAPTER 75

Management of Refractory Heart Failure

Edward A. Ross and Kevin Damman

Nephrologists are being increasingly consulted regarding fluid management in patients with refractory heart failure. Renal expertise extends beyond diuretics and electrolyte homeostasis and now includes recent advances in acute and chronic fluid removal by extracorporeal dialysis machines or isolated ultrafiltration (UF) devices, as well as peritoneal modalities.

DEFINITION AND SCOPE OF THE PROBLEM

Heart failure and renal dysfunction may coexist, but each disease can also cause or exacerbate the other. Poor cardiac output results in reduced renal perfusion and may result in kidney ischemia and progressive chronic kidney disease (CKD).[1] Conversely, CKD may result in salt and water retention with subsequent venous congestion, hypertension, activation of the renin-angiotensin-aldosterone system (RAAS), and vascular calcification that cause cardiac dysfunction, accelerated atherosclerosis, and left ventricular hypertrophy and remodeling. These conditions subsequently may exacerbate heart failure, which results in a vicious cycle of reduced cardiac output and kidney dysfunction.

Of the 100,000 patients in the Acute Decompensated Heart Failure National Registry (ADHERE) 57% had CKD stages 3 or 4, 7% were at stage 5 (68% receiving dialysis), and only 9% had normal kidney function. In patients with heart failure who presented with CKD at the time of admission, there was greater use of diuretics and inotropes, less angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) administration, and a 5% higher in-hospital mortality rate.[2]

The cardiorenal syndrome has been classified[3] into several categories, including cardiorenal (heart causing kidney disease), renocardiac (CKD leading to heart failure), and syndromes in which both are primary disorders or secondary to systemic conditions, although the significance of this classification for treatment strategies is unclear.

PATHOGENESIS

Figure 75-1 illustrates the pathogenesis of refractory heart failure.

In the cardiorenal syndrome low cardiac output is the most important aspect of heart failure. Low cardiac output worsens renal perfusion and function, activating the RAAS and other systems, leading to salt and water retention with a subsequent and paradoxical further worsening of cardiac function. Central to this vicious cycle is tubuloglomerular feedback (TGF; described in Chapter 2), which is maladaptive in heart failure and in the case of some drugs that alter tubular sodium delivery. Secondary (hyper)aldosteronism (resulting in increased sodium retention), increased systemic vascular resistance (thereby putting more strain on the heart), and higher cardiac filling pressures may reduce cardiac output as described by the Frank-Starling mechanism, wherein further increase in preload reduces stroke volume. This further activates the sympathetic nervous system (SNS), which in turn worsens vasoconstriction, cardiac function, and renal perfusion. Excessive activation of both the RAAS and SNS pathways has long been considered the hallmark of worsened heart failure. However, other pathophysiologic mechanisms that could have important therapeutic implications have now been elucidated and are discussed in the following paragraphs.

Venous Congestion

There has been a growing appreciation that through multiple pathways right-sided congestion and renal venous hypertension cause kidney dysfunction.[4] In this regard, heart failure would be analogous to such disorders as the abdominal compartment syndrome, portal hypertension, or renal venous thrombosis; however, some of these conditions differ in whether there is extravascular versus intravascular hydrostatic pressure transmitted to the kidneys. Venous hypertension is thought to trigger neuromyogenic changes that decrease renal perfusion, raise kidney interstitial pressure, narrow the arterial-to-venous pressure gradient, lower renal blood flow and glomerular filtration rate (GFR), trigger maladaptive autoregulatory responses, and exacerbate neurohumoral pathways already problematic in heart failure. Furthermore, there is also a direct effect of higher renal venous pressure that transmits to the renal parenchyma. This higher pressure directly opposes filtration in the Bowman capsule, causes collapsing of tubules, and may be the first initiating trigger for tubulointerstitial fibrosis.[5] These mechanisms are consistent with a critical role of the adrenergic system in modulating venous tone and thus capacity. In that veins contain 70% of the circulatory volume, changes to venous capacitance (and pressure) can decompensate or ameliorate heart failure, without changes to total body salt, fluid, or weight.[6] This variation in the venous reservoir volume reconciles how approximately a third of outpatients have heart failure decompensation with minimal change in weight, and how 16% of heart failure inpatients can symptomatically improve despite no weight loss. If validated, this pathway could potentially lead to pharmacologic treatments based on modulation of adrenergic tone. Changes in reservoir capacity would also confound interpretation of simultaneous changes in volume by extracorporeal UF. The importance of congestive renal failure is highlighted by studies in which kidney function in decompensated heart failure correlated better with right-sided pressures than the ejection fraction or cardiac index. In addition, elevated central venous pressures correlated with mortality.[7] Better kidney function resulted when central venous pressures below 8 mm Hg were achieved.[8]

Adenosine Mediators

Adenosine receptors are involved with TGF signaling and maintain intrarenal vascular tone via a number of complex pathways; these

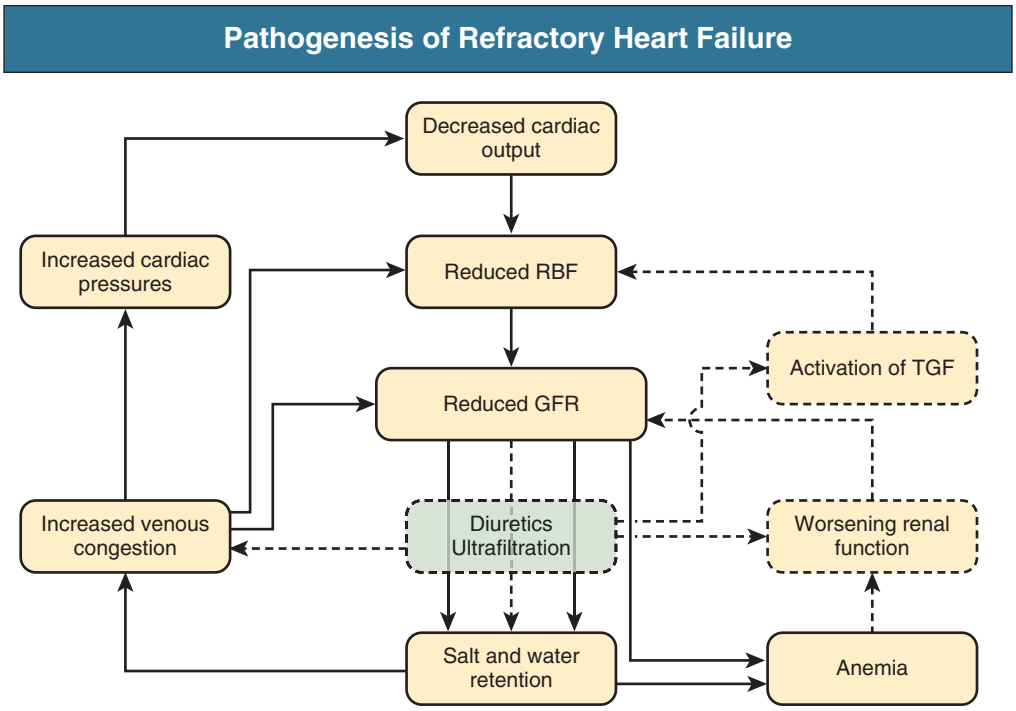

Figure 75-1 Pathogenesis of refractory heart failure. *GFR,* Glomerular filtration rate; *RBF,* renal blood flow; *TGF,* tubuloglomerular feedback. Dashed lines indicate treatment and its effects.

include A_1 receptors (A_1Rs), which cause afferent arteriolar vasoconstriction, and A_2 receptors, which induce efferent vessel dilation. Actions of adenosine at the macula densa and mesangium depend on angiotensin, renin, nitric oxide, and prostaglandin levels. A_1R antagonists could thereby not only restore diuretic sensitivity but also allow appropriate aquaresis in severe heart failure.

Inflammatory Cytokines

Chronic as well as acute exacerbations of heart failure are associated with widespread inflammation and high levels of proinflammatory cytokines, which may further boost cardiac, renal, and other tissue dysfunction.

Anemia

Anemia may be caused by chronic disease or coexistent CKD, or it may be the consequence of hemodilution by venous congestion. The term *cardiorenal anemia syndrome* emphasizes this pharmacologically remediable aspect of heart failure.

Diuretic Tolerance and Adverse Effects

Many patients with heart failure develop tolerance to chronic diuretic therapy, fail to have appropriate natriuresis despite escalating doses, and have worsening of neurohumoral mediator levels—that is, diuretic resistance.[9] Thus some of the cardiac benefits from ACE inhibitors might be from blocking diuretic-induced RAAS activation. Consistent with this paradigm and data from the ADHERE registry, morbidity and mortality in advanced heart failure increased up to fourfold with higher doses of diuretics, despite the fact that there were no clinical or echocardiographic parameters to suggest that the high-dose group had any worse cardiac function.[10] However, when differences in baseline characteristics were controlled for, outcomes with respect to diuretic therapy were similar in a large French registry of patients with acute heart failure.[11] In a multicenter analysis, patients on high-dose diuretics had worsening of GFR compared with the control group on alternative medications, despite equivalent fluid losses.[12] Finally, in the Diuretic Optimization Strategies Evaluation (DOSE) trial (see later), there was no difference in outcome in high- versus low-dose diuretic therapy, despite a higher incidence of (transiently) worsening GFR in the high-dose diuretic group.[13]

TREATMENT

General Approach and Limitations

A pragmatic approach is to first address potentially treatable problems such as valvular disease, conduction disorders and arrhythmias, pericardial effusion, or coronary ischemia (e.g., by angioplasty and stenting) (Box 75-1). The clinician can then approximate the volume of excess fluid and can craft a daily therapeutic goal concurrent with salt restriction. Medication-naive patients can then be cautiously treated as described in the following sections, with serial monitoring because hypotension or renal dysfunction commonly limits the use of pharmaceuticals. Determining to what degree a particular patient may be able to tolerate drug-induced hypotension (e.g., from afterload-reducing agents) is clinically challenging. If there is marked sensitivity of the blood pressure or GFR to low doses of RAAS blockade, bilateral renal artery stenosis should be considered (see Chapter 39).

Pharmacologic Therapeutic Strategies

The pharmacologic management of heart failure is summarized in Box 75-1 and includes traditional approaches for arrhythmias (e.g., for atrial fibrillation) and afterload reduction, SNS blockade, and mineralocorticoid receptor antagonism. Although diuretics remain the front-line treatment for heart failure patients, adequate salt and water clearance in acute heart failure is often difficult; registry data

Treatment Modalities for Refractory Heart Failure

Traditional Treatment
Diuretics: loop diuretics, long-acting thiazides
Digoxin
ACE inhibitors and ARBs
Mineralocorticoid receptor antagonists
β-Blockers
Vasodilators
Blood transfusions

Pharmaceuticals
Inotropes—for example, milrinone, dobutamine*
Synthetic natriuretic peptides*
Aquaretics: vasopressin antagonists*
Erythropoietic-stimulating agents*
Adenosine receptor blockade*

Mechanical Treatment
Biventricular pacing
Ventricular assist devices

Ultrafiltration
Peritoneal dialysis
  Manual (CAPD) and automated using a cycler (APD)
Extracorporeal therapies
  Intermittent short-duration ultrafiltration
  Slow continuous ultrafiltration (SCUF)

Box 75-1 Treatment modalities for refractory heart failure. *ACE,* Angiotensin-converting enzyme; *APD,* automated peritoneal dialysis; *ARB,* angiotensin receptor blocker; *CAPD,* continuous ambulatory peritoneal dialysis. *No clinical benefit established.

indicated that of patients admitted with acute heart failure, approximately 16% were discharged at a higher body weight.[14]

Diuretics

Despite the concerns described previously, most patients initially respond to escalating doses of diuretics. Loop diuretics need to be administered at frequent intervals at a high enough dose to achieve adequate drug levels within the glomerular filtrate. Coadministering a long-acting thiazide diuretic may help maintain natriuresis. In severe heart failure, continuous low-dose infusion of a loop diuretic may be required. In the DOSE study,[13] high versus low doses and continuous versus bolus infusion of loop diuretics were tested in acute heart failure. None of the dosage regimens was associated with superior outcome. Although higher dosages of diuretics resulted in more frequent transient decreases in GFR, this did not affect the long-term outcomes. Based on the recently completed Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial, in which there was worsened renal function in decompensated heart failure, efficacious and safe algorithms can be crafted for stepped pharmacologic care wherein inotropes are added to diuretics.[15]

Renin-Angiotensin-Aldosterone System Antagonists

Although low GFR is a marker for increased mortality with heart failure, a further fall in GFR after initiation of RAAS blockade does not necessarily portend a worsened outcome.[16] ACE inhibitors and ARBs, however, may worsen GFR in patients undergoing diuresis or in those with advanced CKD to the extent that there needs to be a temporary decrease in dose or withdrawal. Alternatively, diuretic dosage may need to be reduced before the ACE inhibitor dose is adjusted. Hyperkalemia may also limit the use of RAAS blockers.

Adenosine Receptor Antagonists

Despite encouraging findings in an early study of the selective A_1R antagonist rolofylline for acute heart failure with renal dysfunction, no clinical benefits were noted in the more than 2000 patients in the PROTECT investigation (Placebo-Controlled Randomized Study of the Selective Adenosine A_1 Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function).[17]

Erythropoiesis-Stimulating Agents

In a large registry 25% of patients with heart failure exhibited hemoglobins of 5 to 10.7 g/dl, and anemia (hemoglobin < 12.1 g/d,) was associated with higher in-hospital mortality, longer length of stay, and more readmissions at 90 days.[18] In small series, correction of severe anemia (hemoglobin < 10 g/dl) improved heart failure and clinical outcomes. However, in a recent large randomized controlled trial studying the Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) in 2278 patients, there was no benefit from raising the hemoglobin from as low as 9.0 to a target of 13.0 g/dl. We believe the most prudent course for pharmacologic anemia correction is to follow guidelines based on coexistent chronic kidney disease (see Chapter 83).[18a]

Antidiuretic Hormone Antagonists

Release of vasopressin by (nonosmotic) low cardiac output results in water retention and hyponatremia. Vasopressin (V_2) selective antagonists, such as tolvaptan and lixivaptan, or a nonselective oral V_{1a}/V_2 antagonist increased urine output and serum sodium. However, in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST), in which tolvaptan was used for a minimum of 60 days, there was no effect at 10 months on all-cause mortality or heart failure–related morbidity.[19] For now, vasopressin antagonists are not indicated in patients with cardiorenal failure.

Natriuretic Peptides

Early clinical trials were encouraging for a cardiac benefit, but there was no improvement in renal function. The Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure (ASCEND-HF), including more than 7000 acute heart failure patients, showed no beneficial effect of nesiritide when compared with placebo.[20]

Nonrenal Salt and Water Removal

Nonrenal methods for salt and water removal have been proposed to be advantageous because they avoid TGF-mediated neurohumoral pathway activation and are effective in patients whose condition is refractory to pharmaceutical treatment. However, establishing their outcome benefits and determining the optimal use (as summarized in Box 75-2) have been controversial.

Paracentesis

In a subset of patients, intra-abdominal hypertension may cause renal venous hypertension and kidney congestion. In five patients, removal of approximately 3 liters of ascites decreased intra-abdominal pressure and improved GFR.[21] Repeated paracentesis, however, causes significant protein losses, often the need for albumin repletion, and the possibility of subsequent fluid leakage and/or infection. Nevertheless, the role for this approach in selected patients needs to

Stepwise Treatment Approach for Symptomatic Heart Failure (HF) and the Cardiorenal Syndrome

Step 1

1. Compliance: Optimize adherence to medication regimen and salt restriction.
2. Electromechanical: Evaluate and treat arrhythmias and dyssynchrony
3. Anatomic, with imaging (cardiac catheterization, echocardiogram) as appropriate for:
   a. Ischemic: Angioplasty, stents, or surgery when appropriate for coronary artery stenoses
   b. Other remediable disorders such as valvular heart disease, pericardial effusions, constrictive pericarditis
4. Anemia control, following CKD guidelines (see Chapter 83)
5. Pharmacologic, with dose reductions for hypotension:
   a. ACE inhibitors and ARBs
   b. β-Blocker therapy
   c. Mineralocorticoid receptor antagonists
   d. Diuretics if volume overloaded, congestion, symptoms are present
   e. Other agents: Afterload-reducing medications (e.g., hydralazine), digoxin

Step 2: For Worsened Renal Function, Ineffective Diuresis, Persistent HF

1. Begin stepped approach to escalate pharmacologic treatment, preferably algorithm-based. Focus on dose adjustments to avoid hypotension and further renal impairment
2. Reevaluate for concurrent renal disease (i.e., renocardiac syndrome)
   a. Consider primary nephrologic disorders (e.g., parenchymal, obstruction)
   b. Consider evaluation for unilateral or bilateral renal artery stenosis
   c. If necessary, paracentesis or other specific therapies to reduce intra-abdominal hypertension, relieve renal venous hypertension and renal congestion

Step 3: For Persistent Hypotension, Renal Dysfunction and Acute Decompensated HF

1. Reassess to further optimize pharmacologic care with diuretics and inotropes.
2. Consider ultrafiltration but acknowledge risks of renal deterioration, catheter- and/or anticoagulation-related complications.
3. Begin cautious extracorporeal ultrafiltration, especially if patient's condition is refractory to pressors:
   a. Intermittent slow ultrafiltration, when hypotension does not preclude adequate fluid removal over typically 4- to 6-hour sessions
   b. Continuous ultrafiltration, when equipment is available and patient becomes hypotensive or has worsening renal function with intermittent treatment sessions

Box 75-2 Stepwise treatment approach for symptomatic heart failure and the cardiorenal syndrome. *ACE,* Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker.

be better defined, especially in those settings in which the more elaborate and costly nonpharmacologic methodologies are not available.

Ultrafiltration: Peritoneal Dialysis

Most of the experience with using peritoneal dialysis (PD)–based UF to treat heart failure has been in small series.[22] There are specific issues with regard to PD use for heart failure. Apart from volume and sodium clearance, other potential advantages include the removal of heart failure–induced ascites (thereby lowering the risk of spontaneous bacterial peritonitis and intra-abdominal hypertension). Compared with rigorous PD exchange prescriptions in end-stage renal disease (ESRD) patients, there can be simplified lower-frequency regimens crafted for just fluid removal using nonabsorbable osmotic agents such as icodextrin. The literature is, however, confounded by a wide range in patients' underlying CKD, as well as the fact that many individuals have had initial care with hemofiltration, and in these patients it has been difficult to prove improved heart failure survival. In practice, PD for heart failure is most commonly advocated as a chronic treatment, with advanced pharmaceutical and extracorporeal methods used as initial strategies for acute decompensation.

Concerning potential adverse outcomes, as with any rapid use of newly placed PD catheters, acute heart failure patients have increased risk of early fluid leaks and peritoneal infection. In addition, PD-induced electrolyte disturbances (e.g., hypokalemia or hypomagnesemia) may worsen rhythm control. Notably, approximately half of PD ultrafiltrate occurs through aquaporins. Thus, fluid losses are hypotonic and accomplish less sodium removal than the isotonic extracorporeal blood-based hemofiltration modalities. Large peritoneal fluid volumes can also potentially compromise respiration, which might already be tenuous in heart failure; this could be avoided by frequent lower-volume exchanges via automated cyclers. The albeit limited literature has described efficacy of PD in cardiorenal (apart from renocardiac) patients for fluid removal; its use has restored diuretic responsiveness, reduced body weight, resulted in better echocardiographic or other objective cardiac hemodynamic parameters, improved heart failure biomarkers (e.g., brain natriuretic peptide and aldosterone), improved New York Heart Association (NYHA) class, increased 6-minute walk capacity, provided a bridge to cardiac transplantation, decreased hospitalization days, and improved quality of life.[23] Several of these studies used simple PD regimens such as one to three exchanges per day[24] or treatments performed in-center (thrice weekly for 12-hour sessions).[24] Overall the studies have shown that chronic PD in heart failure has had an acceptably low rate of complications and has been well tolerated, but PD has to date not been associated with improved mortality in heart failure patients.[24]

Extracorporeal Ultrafiltration: Conventional Hemodialysis or Hemofiltration

There is extensive experience with intermittent hemodialysis techniques for fluid removal in heart failure. Acute temporary or tunneled dual-lumen catheters are inserted (see Chapter 91). Permanent vascular access (as used for ESRD patients) is often precluded because these arteriovenous fistulas or grafts may shunt a liter or more of blood per minute. Technical approaches include "isolated UF" (see Chapter 93) or traditional dialysis techniques when electrolyte disorders are already present. Even with careful setting of the UF rate, many unstable heart failure patients will not tolerate removal of 2 or more liters during typical 2- to 4-hour treatment times. It is important to note that episodes of hypotension will not only prevent further fluid removal but can also induce acute kidney injury (AKI) and potentially make the patient dialysis dependent.

The key to hemodynamic stability may be to dramatically slow the UF rate (see later), and this approach has led to longer and then continuous treatment modalities: slow extended-duration isolated UF, and continuous venovenous hemofiltration (CVVH). However, the literature lacks larger groups of patients treated with such techniques, homogenous patient populations, appropriate control groups, well-defined outcome measures, and strict treatment protocols.

Ultrafiltration: Setting the Rate of Fluid Removal

The key concept is to avoid intravascular fluid depletion by ensuring that the UF rate does not exceed the rate at which the vascular plasma compartment is being refilled from interstitial spaces. The plasma refill rate can vary over the course of fluid removal, as it is dependent on Starling forces (generated by the plasma oncotic pressure and the gradient between interstitial and vascular hydrostatic pressures) and the permeability of vascular basement membranes. If the UF rate exceeds the plasma refill rate, hemoconcentration, hypovolemia, hypotension, and decreased renal function develop. Equipment has been developed for hemodialysis machines that optically monitors hemoconcentration, and this approach can also be used as a guide for UF in patients with refractory heart failure. In addition, body fluid determination can be done by bioimpedance vector analysis, although its role in guiding heart failure treatment has yet to be established.

Effect of Extracorporeal Ultrafiltration on the Pathophysiology of Heart Failure

In a report of 24 patients with refractory heart failure, removal of up to 4 liters of fluid in a few hours[25] did not affect plasma volume—that is, UF matched the plasma refill rate. Even at 24 hours postprocedure the patients had reduced right atrial, pulmonary artery, and wedge pressures; increased stroke volume; stable heart rates and systemic vascular resistance; and improved responsiveness to diuretics.

Ultrafiltration in heart failure patients decreases levels of norepinephrine, aldosterone, and renin.[26] In contrast to diuretics alone, UF also reduced systemic levels of inflammatory cytokines. Some patients reportedly also have improved exercise capacity and pulmonary function. Last, when comparing UF with diuretics, it is important to appreciate that salt losses vary between these therapies. Part of the benefit from UF may be a result of the convection of isotonic fluid, compared with less sodium being removed in the diuretic-induced hypotonic urine.

Effect of Extracorporeal Ultrafiltration on Renal Function

It has been proposed that the benefits of UF for renal function occur predominantly in patients with low urine output (<1 l/day), in whom UF reverses the RAAS and SNS activation, thereby improving renal perfusion and GFR and restoring sensitivity to diuretics.[27] In contrast, in heart failure patients with a mean baseline GFR of 48 ml/min and preserved diuretic sensitivity, there were no significant differences in the kidney parameters before or after 2 days of either UF or intravenous diuretic therapy.[28]

Although there are encouraging (but not unanimous) reports of renal function improving with UF when compared with diuretics, it is important that cautious fluid removal be accomplished without a significant fall in GFR or in a manner that is detriment to renal hemodynamics.[29,30] Determining a safe rate of UF, however, can be difficult, and excessive fluid removal can unquestionably lead to a rise in serum creatinine in more patients.[31]

Ultrafiltration: Recent Advances in Extracorporeal Techniques

The barriers of extended treatment times and the need for 1 : 1 supervision by nurses have been overcome with commercially available modern devices dedicated to isolated UF. These now have small extracorporeal blood volumes (<100 ml), allow blood flows low enough (<50 ml/min) to permit use of temporary peripheral vein catheters, and have preassembled tubing for one-step loading, computerized simple user interfaces with embedded help screens, remote monitoring capabilities, and miniaturization for portability. Treatment times range from 6 h/day to continuous treatment over multiple days. A first feasibility study[32] demonstrated that 16- to 18-gauge catheters could deliver blood at up to 40 ml/min, resulting in 2.6 ± 1.0 liters (up to 3.7 liters) of UF over approximately 7 hours. In another study[29] of 20 patients with decompensated heart failure and serum creatinine levels of at least 1.5 mg/dl (132 µmol/l) and/or diuretic resistance, more than 8 liters fluid were removed. Patients were discharged earlier without changes in GFR and had improved heart failure scores; some had resolution of hyponatremia and fewer readmissions. In the Relief for Acutely Fluid-Overloaded Patients with Decompensated Congestive Heart Failure (RAPID-CHF) trial on 40 patients, UF did not significantly affect weight loss but did improve fluid removal and symptoms compared with usual care.[33]

Two large prospective studies, however, subsequently had opposite conclusions. In the UNLOAD trial (Ultrafiltration Versus Intravenous Loop Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure), 200 heart failure patients were randomized to early UF or intravenous diuretics and followed for 90 days.[30] The UF achieved by the study was 241 ml/h for 12.3 ± 12 hours, which led to a weight reduction of 5.0 ± 3.1 kg over the 2 days, approximately 2 kg more than those in the control diuretic group. Although dyspnea was improved in those undergoing UF at 8 hours, this was not different at 48 hours. Renal end points also were not different. At 90 days the UF group had fewer total rehospitalizations (18% vs. 32%), rehospitalization days (1.4 vs. 3.8 days), and unscheduled office and emergency room visits (21% vs. 44%), but the study was not powered to allow conclusions on these clinical endpoints. Potential weaknesses of the study design included sponsorship by the manufacturer, submaximal medical therapy in the diuretic group, and uncertainties regarding posthospitalization care and readmission. In the CARRESS-HF trial[34] 188 patients were compared at 96 hours after randomization to a protocol of stepped drug therapy (diuretics with intravenous inotropes) or extracorporeal UF at 200 ml/h. There was no difference in weight loss (approximately 5.6 kg), dyspnea, or well-being scale scores, or diuretic dose; however, the UF group but not the pharmacologic group experienced a decline in GFR. At 60 days there were no differences in mortality, emergency visits, or rehospitalizations for heart failure or any cause. It remains unclear whether these disappointing findings for UF can be extrapolated to all such patients and methodologies. This trial had limitations in that the inclusion criteria necessitated that patients were in acutely decompensated heart failure and already had AKI with a rise in creatinine of at least 0.3 mg/dL, which could indicate that the initial renal injury had already occurred. Notably, most UF was accomplished early in the protocol, with a mean duration of only 40 hours compared with the pharmacologic care over 96 hours. Thus it remains unknown whether alternative protocols with slower or more prolonged UF might have had different heart failure or renal function outcomes. Furthermore, a large proportion of patients in the UF group (10%) did not receive the randomized treatment for various reasons, and 30% in this group also received intravenous diuretics after UF had ceased. Thus, crossover between therapies was

an important confounder, and it is unclear what the implications of these limitations are.

Safety and Risks to Extracorporeal Therapies

Although newer simplified devices for isolated UF have improved the ease of patient care, these modalities are not risk free. In a small, outpatient, 1-year study of 14 patients, two deaths were attributed to complications of the UF procedure.[35] In the CARRESS-HF trial,[34] such UF-related complications included catheter exit-site hemorrhage and systemic infection. In the UNLOAD trial,[30] however, the UF therapy proved very safe. The recently developed machines dedicated to isolated UF have an added margin of safety conferred by low rates of filtration and blood flow, as well as more robust automated monitoring software. Nevertheless, all complications that can occur in hemodialysis therapies are of course also relevant for heart failure patients receiving isolated UF (see Chapter 95).

SUMMARY

Despite longstanding evidence concerning the pathophysiology of fluid overload in heart failure and adverse neurohumoral effects from diuretics, it has been difficult to reach a consensus on the benefits or techniques of UF or diuretic therapy. PD appears to have a role in chronic heart failure care, especially for individuals whose management is complicated by CKD. For acutely decompensated heart failure, recent evidence suggests that protocolized stepped pharmacologic care can be efficacious and safer than rapid UF; however, it remains to be determined whether there can be benefits from alternative extracorporeal protocols.

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CHAPTER 76

Hepatorenal Syndrome

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DEFINITION

Hepatorenal syndrome (HRS) is a potentially reversible functional renal failure that occurs in patients with acute or chronic liver disease, advanced hepatic failure, and portal hypertension. Although it may occur in patients with acute liver failure or severe acute alcoholic hepatitis, it is mainly observed in patients with advanced cirrhosis. HRS is characterized by impaired renal function and marked abnormalities in the arterial circulation and endogenous vasoactive systems. In the kidney, there is pronounced vasoconstriction resulting in low glomerular filtration rate (GFR). In the splanchnic circulation, there is marked arteriolar vasodilation resulting in reduction of systemic vascular resistance and arterial hypotension.[1-3] Two forms of HRS can be identified on the basis of the progression of the disease (Box 76-1). The acute form (type 1 HRS) is characterized by an acute and rapid deterioration in renal function that occurs in the setting of multiorgan failure (acute-on-chronic liver failure), whereas the chronic form (type 2) has an insidious onset and is characterized by moderate renal failure that follows a steady or slowly progressive course.[1-3]

PSEUDOHEPATORENAL SYNDROME

Pseudohepatorenal syndrome describes concurrent hepatic and renal dysfunction secondary to a wide variety of infectious, systemic, circulatory, genetic, and other diseases and after exposure to a variety of drugs and toxins (Table 76-1).[4] All these entities must be excluded before the diagnosis of HRS can be established. In all these conditions, the liver does not play a causative role in the pathogenesis of renal failure. Pseudohepatorenal syndrome is usually easy to exclude because the causative agent is frequently known and both renal and liver functional abnormalities are often found at first clinical presentation, when there is no evidence of advanced liver failure and portal hypertension. In contrast, HRS invariably occurs after liver failure and portal hypertension are fully established and frequently develops when the patient is undergoing treatment for these conditions or their complications.

PATHOPHYSIOLOGY AND PATHOGENESIS

Circulatory Dysfunction: Renal and Systemic Hemodynamic Changes

In HRS, reduction in GFR occurs mainly as a result of renal cortical hypoperfusion after intense cortical renal vasoconstriction, which can be demonstrated angiographically as marked beading and tortuosity of the interlobular and proximal arcuate arteries and the absence of a distinct cortical nephrogram and vascular filling of the cortical vessels (Fig. 76-1).[5] Intense renal vasoconstriction is the final consequence of marked systemic circulatory dysfunction, characterized by progressive splanchnic arterial vasodilation, reduction of the effective arterial blood volume, hypotension, and homeostatic activation of the vasoconstrictor systems.[3] This further compromises renal perfusion because intense renal vasoconstriction results in blunting of the autoregulation of renal blood flow, so that renal perfusion becomes more pressure dependent. In HRS, filtration fraction is also reduced, reflecting a dominant increase in afferent arteriolar tone and a decrease in the ultrafiltration coefficient. Serial systemic hemodynamic studies showed that HRS occurs in the setting of reduced mean arterial pressure (MAP), cardiac output, and wedge pulmonary pressure without change in systemic vascular resistance. These findings suggest that the inability of the heart to increase its output to compensate for a decrease in cardiac preload (secondary to the accentuation of splanchnic arterial vasodilation) also contributes to the pathogenesis of HRS.[6] Vasoconstriction is not confined to the renal vascular bed. In HRS it is also observed in other extrasplanchnic territories, including the liver, brain, muscle, and skin.[2,3]

Neurohumoral Abnormalities

The renal and systemic hemodynamic changes that characterize HRS are a direct consequence of neurohumoral disturbances.[2,3] Activation of the vasoconstrictor systems (the renin-angiotensin-aldosterone system [RAAS], the sympathetic nervous system, and vasopressin) is the cause of renal vasoconstriction; meanwhile, activation of the vasodilator systems occurs mainly in the splanchnic circulation and leads to splanchnic vasodilation. Increases in the serum and urinary levels of vasoconstrictors and in the plasma level of vasodilators are observed in patients with HRS. The vasoconstrictors include renin, norepinephrine, neuropeptide Y, arginine vasopressin, endothelin and F_2 isoprostanes, and urinary cysteinyl leukotrienes; the vasodilators include plasma endotoxin, nitrite and nitrate (end product of nitric oxide metabolism), and glucagon. The sympathetic discharges through the renal nerves are also markedly increased.

In contrast to increased plasma and urinary levels of vasoconstrictors and plasma level of vasodilators, decreased levels of urinary vasodilators have been observed in HRS. These include prostaglandin E_2, 6-keto-prostaglandin F_1 (a stable metabolite of renal prostacyclin), and kallikrein. Because the level of these urinary vasodilators is normal in compensated cirrhosis and higher than normal in decompensated cirrhosis with ascites and normal renal function, it is postulated that a reduction in the renal synthesis of renal vasodilators is the final event that leads to the development of HRS.[3]

Most of these neurohumoral abnormalities found in HRS are also detected, albeit to a lesser extent, in decompensated cirrhosis (with ascites) with normal renal function and in compensated cirrhosis (without ascites). These findings support the hypothesis that HRS most likely represents one end of the spectrum of homeostatic abnormalities that occur in liver failure and portal hypertension.

Causes of Pseudohepatorenal Syndrome		
Potential Causes	**Predominantly Tubulointerstitial Involvement**	**Predominantly Glomerular Involvement**
Infections	Sepsis, leptospirosis, brucellosis, tuberculosis, Epstein-Barr virus, hepatitis A virus	Hepatitis B and C viruses, HIV infection, *Schistosoma mansoni,* liver abscess
Drugs	Tetracycline, rifampin, sulfonamide, phenytoin, allopurinol, fluroxene, methotrexate (high dose), acetaminophen overdose	
Toxins	Carbon tetrachloride, trichloroethylene, chloroform, elemental phosphorus, arsenic, copper, chromium, barium, amatoxins,* raw carp bile toxins†	
Systemic diseases	Sarcoidosis, Sjögren syndrome	Systemic lupus erythematosus, vasculitis, cryoglobulinemia, amyloidosis
Circulatory failure	Hypovolemic or cardiogenic shock	
Malignancy	Lymphoma, leukemia	
Congenital and genetic disorders	Polycystic liver and kidney disease, nephronophthisis, congenital hepatic fibrosis	
Miscellaneous	Fatty liver of pregnancy, Reye syndrome	Eclampsia, HELLP syndrome,‡ cirrhotic glomerulopathy

Table 76-1 Causes of pseudohepatorenal syndrome. *Accidental poisoning after ingestion of mushrooms of the *Amanita* genus. †Accidental poisoning after ingestion of the raw gallbladder or bile of the grass carp (a common practice in rural East Asia). ‡Hemolysis, elevated liver enzymes, low platelet count. *(Data from reference 10.)*

Main Clinical Characteristics of Type 1 and Type 2 Hepatorenal Syndrome (HRS)

Type 1 HRS

- Acute and rapid deterioration in renal function (serum creatinine ≥ 2.5 mg/dl or 220 μmol/l in less than 2 weeks)
- Occurs in parallel with the failure of other organs or systems (e.g., coagulopathy, hepatic encephalopathy)
- In cirrhosis, is a form of acute-on-chronic liver failure
- Frequently follows a precipitating event, mainly bacterial infection
- Rapidly fatal without treatment: mean survival 2 to 3 weeks

Type 2 HRS

- Moderate stable renal impairment (average serum creatinine 2 mg/dl [176 μmol/l])
- Mainly causes refractory ascites
- Mean survival without treatment: 6 months

Box 76-1 Main clinical characteristics of type 1 and type 2 hepatorenal syndrome.

Summary of Pathogenetic Events

Figure 76-2 shows the pathogenetic events that lead to HRS. Liver failure and portal hypertension through endotoxemia and increased shear stress increase vascular production of vasodilators, including nitric oxide, carbon monoxide, and glucagon in the splanchnic circulation, leading to the initiating event of splanchnic arteriolar vasodilation (the peripheral arterial vasodilation hypothesis). Splanchnic vasodilation leads to a decrease in systemic vascular resistance, but MAP is initially maintained by an increase in cardiac output, resulting in a hyperdynamic circulation. Splanchnic vasodilation also decreases arterial filling and reduces the effective arterial blood volume. The subsequent stimulation of the central volume baroreceptors leads to compensatory activation of the vasoconstrictor systems, in particular the arginine vasopressin system, RAAS, and sympathetic nervous system (including its hormones norepinephrine and neuropeptide Y), which help restore effective arterial blood volume. This restoration is achieved in patients with compensated cirrhosis but not in patients with decompensated cirrhosis, in whom progressive splanchnic arteriolar vasodilation leads to increased splanchnic capillary pressure, resulting in an increase in lymph formation that exceeds reabsorption capacity. In parallel, further contraction of the effective arterial blood volume leads to reduction of systemic MAP and further stimulation of the vasoconstrictor systems, resulting in sodium and water retention. The net result of these combined effects is continuous ascites formation (the forward theory of ascites formation).[2,3]

The splanchnic circulation is resistant to the effects of vasoconstrictors because of local release of vasodilators; progressive splanchnic vasodilation continues to occur as liver failure and portal hypertension progress. This leads to continued contraction of effective arterial blood volume, which, in combination with the progressive inability of the cirrhotic heart to respond to reduced preload consequent to splanchnic vasodilation, results in further reduction of MAP and more intense stimulation of the vasoconstrictor systems. Normally, the effect of vasoconstrictors on the renal circulation is counterbalanced by the reactive production of intrarenal vasodilators. It is postulated that HRS develops when the balance of activities between the renal vasoconstrictors and intrarenal vasodilators finally breaks down. The likelihood that this will occur increases with progressive or acute deterioration in liver function or increasing severity of portal hypertension (e.g., after acute alcoholic hepatitis) and is precipitated by events that lead to further volume contraction and reduction of the effective arterial blood volume (e.g., spontaneous bacterial peritonitis; see later discussion).

EPIDEMIOLOGY

The possibility for development of HRS in the cirrhotic patient is estimated to be 18% at 1 year and 39% at 5 years.[7] Neither the cause nor the Child-Pugh score or the model for end-stage liver disease (MELD) score (http://www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality/) predicts the incidence of HRS. Rather, independent predictors of HRS include dilutional hyponatremia, impairment in systemic hemodynamics (high plasma renin activity and noradrenaline concentration and low cardiac output),[6,7]

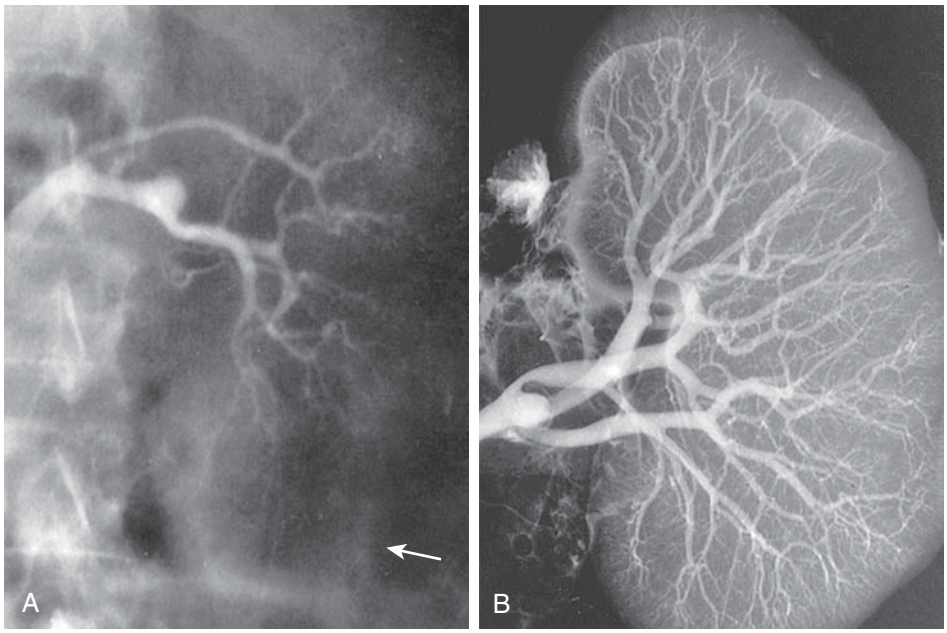

Figure 76-1 Renal arteriography of a patient with hepatorenal syndrome (HRS). A, Renal angiogram (the arrow marks the edge of the kidney). **B,** The angiogram carried out in the same kidney at autopsy. Note complete filling of the renal arterial system throughout the vascular bed to the periphery of the cortex. The vascular attenuation and tortuosity seen previously **(A)** are no longer present. The vessels are also histologically normal. This indicates the functional nature of the vascular abnormality in HRS.[4]

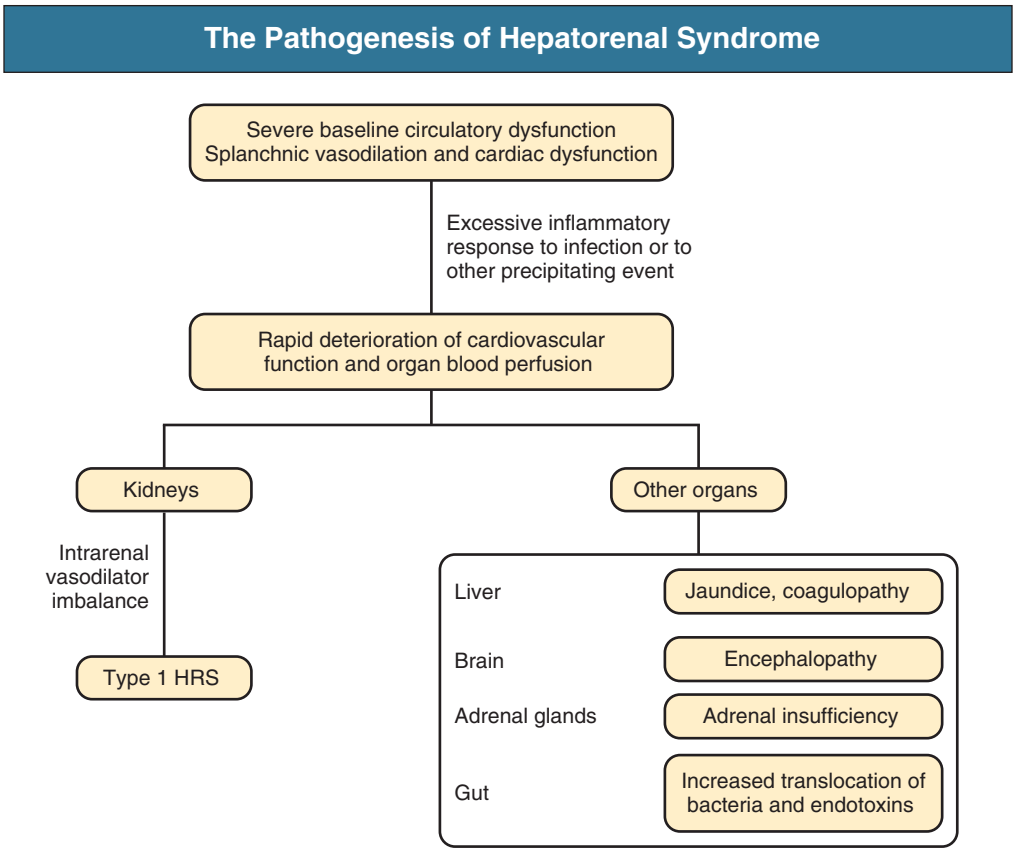

Figure 76-2 The pathogenesis of hepatorenal syndrome (HRS). Mechanisms leading to type 1 HRS and multiorgan failure. Patients with cirrhosis and ascites present a severe cardiocirculatory dysfunction that may be further aggravated by infection. Although circulatory dysfunction predominantly affects the kidneys and leads to the development of type 1 HRS, it also decreases the perfusion of other organs and systems such as the liver, with marked impairment in hepatic function and aggravation of portal hypertension; the brain, with the development of hepatic encephalopathy; the adrenal glands, with the development of relative adrenal dysfunction; and the gut, decreasing intestinal motility and promoting intestinal bacterial overgrowth and bacterial translocation.[2,3]

abnormal renal duplex Doppler ultrasound study findings (resistive index >0.7),[8] and low GFR.[3]

CLINICAL MANIFESTATIONS

Type 1 and type 2 HRS are considered to be different syndromes rather than different expressions of a common underlying disorder.[2,3] Type 1 HRS is characterized by a rapid decline in renal function (see Box 76-1) and is observed in patients with acute decompensation of advanced cirrhosis, severe acute alcoholic hepatitis, or acute liver failure. In addition to developing a rapidly progressive acute kidney injury (AKI), patients also develop multiorgan dysfunction including severe hepatic failure (jaundice, coagulopathy), brain failure (hepatic encephalopathy), and frequently relative adrenal insufficiency. Hyponatremia is almost always present, and arterial blood pressure is usually low. Type 1 HRS may be precipitated by bacterial infections (especially spontaneous bacterial peritonitis), gastrointestinal bleeding, or total paracentesis without albumin administration. Left untreated, type 1 HRS tends to run a rapid and progressive downhill course, resulting in death of the patient within 2 to 3 weeks.[7]

Type 2 HRS is characterized by insidious onset and slowly progressive deterioration of renal function. This is most often observed in patients with cirrhosis and portal hypertension. These patients tend to be less severely jaundiced and mainly present with refractory ascites caused by poor response to diuretics. Low-normal arterial blood pressure, modest prolongation of prothrombin time, and moderate or marked hypoalbuminemia and hyponatremia are usually present. Type 2 HRS tends to run a slowly progressive downhill course over months, which most likely reflects the natural course of the disease because additional precipitating factors are not usually identified.[2,3,7] Mean survival time after onset of type 2 HRS is 6 months.

PATHOLOGY

Hepatorenal syndrome is, by definition, a functional renal disorder, and the presence of significant glomerular and/or tubular disease excludes the diagnosis. However, glomerular abnormalities, including mesangial expansion, capillary wall thickening, mesangial and capillary wall electron-dense deposits, and immune deposits of C3 and IgA, IgM, and IgG, are frequently found in cirrhotic patients with normal renal function and minimal urinary abnormalities. The presence of such glomerular abnormalities in a cirrhotic patient, therefore, does not exclude the diagnosis of HRS. Protrusion of the proximal tubular epithelium into the Bowman space (glomerulotubular reflux) is not specific for HRS and is found in other conditions associated with profound renal ischemia and terminal hypotension. Although early autopsy studies demonstrated normal tubular morphology in patients who had died of HRS, detailed light and electron microscopic studies have documented proximal tubular lesions consistent with ischemic injury. However, these lesions do not explain the renal failure and reduction in GFR observed in patients with HRS.[3]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnostic criteria for HRS were established by the International Ascites Club in 1996[1] and have recently been revised (Box 76-2).[9] The main differences between the new and old criteria include the exclusion of creatinine clearance as a measure of renal function because of the difficulty in obtaining accurate urine collection data, the removal of ongoing bacterial infection as an exclusion criterion so that treatment of HRS is not delayed in these patients, the substitution of saline with albumin as the preferred fluid for plasma volume expansion, and the removal of the minor criteria because they are not thought to be essential.

Diagnostic Criteria of Hepatorenal Syndrome According to the International Ascites Club

- Cirrhosis with ascites
- Serum creatinine >1.5 mg/dl (133 μmol/l).
- No improvement in serum creatinine (decrease to a level of 1.5 mg/dl or less) after at least 2 days of diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day.
- Absence of shock.
- No current or recent treatment with nephrotoxic drugs.
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria, and/or abnormal renal ultrasound findings.

Box 76-2 Diagnostic criteria of hepatorenal syndrome according to the International Ascites Club.[9]

The diagnosis of HRS is mainly one of exclusion and should be suspected in any patient with acute or chronic liver disease with advanced liver failure and portal hypertension who develops progressive renal impairment. Serum creatinine concentration and blood urea nitrogen are poor markers of GFR in cirrhosis.[3] Cirrhotic patients may have significant renal impairment despite normal serum creatinine or blood urea nitrogen concentration values because they are frequently malnourished, with reduced lean body mass, and often have a low urea generation rate because of liver failure and low protein intake. Severe hyperbilirubinemia, which is often present in patients with HRS, interferes with the Jaffe reaction for creatinine quantification and may cause falsely low results. Enzymatic creatinine assays are less susceptible to high bilirubin levels. In cases of uncertainty, GFR may be assessed with use of ^{125}I-iothalamate or chromium 51–labeled ethylenediaminetetraacetic acid (^{51}Cr-labeled EDTA). Studies involving a low number of patients suggest that serum cystatin C could be an accurate GFR marker in the cirrhotic population.[10] However, the real usefulness of serum cystatin C in the assessment of GFR in cirrhosis needs to be confirmed.

In patients with preexisting liver failure, portal hypertension, and renal failure, the use of nephrotoxic agents (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs] and aminoglycosides) must be stopped, and conditions leading to renal failure must be excluded by careful history, physical examination, urine examination, and ultrasound study before the diagnosis of HRS can be considered. The absence of shock or gastrointestinal bleeding, and excess gastrointestinal, peritoneal, or renal fluid loss must also be documented. Prerenal AKI must be excluded by withdrawal of diuretics and fluid challenge either with 1.5 liters of normal saline or preferably with albumin, 1 g/kg body weight per day up to the maximum of 100 g/day for 2 days. Absence of microhematuria and proteinuria of less than 500 mg/day help exclude significant coexisting glomerular or tubulointerstitial disease leading to renal failure and support the diagnosis of HRS.

The most important differential diagnosis for renal failure in cirrhosis is between type 1 HRS and "true" AKI with tubular damage,

because they require rapid therapeutic decisions with different treatments. The parameters traditionally used to differentiate AKI with tubular damage from functional renal failure (urinary sodium excretion and urinary-plasma osmolality ratio) are of no value in patients with cirrhosis and ascites.[3] Granular casts may be found in the urinary sediment in both HRS and AKI with tubular damage. Recent data suggest that the determination of the neutrophil gelatinase–associated lipocalin (NGAL) level, a urinary biomarker of tubular damage, could be of help to differentiate these two entities.[11] However, further studies are needed to confirm this finding because biomarkers of AKI can also be increased in pre-renal acute injury[12] and HRS can progress to AKI in final stages.

NATURAL HISTORY

The prognosis of HRS is poor. Without treatment, the median survival rate for type 1 HRS is about 2 weeks; that of type 2 HRS is about 4 to 6 months.[3,7] Patients with type 1 HRS usually die in the setting of multiple organ failure and are now considered to have acute-on-chronic liver failure, a syndrome recently redefined as characterized by the presence not only of organ failure(s) and high mortality rate but also of systemic inflammation.[13] Severe hepatic encephalopathy, gastrointestinal bleeding, and sepsis are common final events in these patients. Patients with type 2 HRS are at a higher risk of type 1 HRS after the development of a precipitating event.[3]

PREVENTION AND TREATMENT

General Principles in the Prevention of Renal Failure

In patients with cirrhosis and ascites excessive diuretic therapy results in volume contraction and renal failure. To avoid the latter, a stepwise approach to the treatment of ascites is recommended. All patients are advised to have bed rest and to follow a low-sodium diet (60 to 90 mmol/day, equivalent to about 1.5 to 2 g of salt per day). After this, spironolactone is prescribed at increasing doses (100 mg/day as initial dose; if there is no response within 4 days, 200 mg/day). When there is no response to this dose of spironolactone, furosemide is added at increasing doses every 2 days (40 to 80 mg/day). Maximum doses of spironolactone and furosemide are 400 and 160 mg/day, respectively. In patients with diuretic resistance, therapeutic paracentesis is indicated but must be combined with plasma volume expansion with use of albumin (8 g/l of ascites removed) to decrease the incidence of circulatory dysfunction after treatment and to prevent the development of HRS. The use of renin-angiotensin system (RAS) blockers as well as potentially nephrotoxic agents, including NSAIDs, aminoglycosides, and radiocontrast media, should be avoided as much as possible.[2,3] β-Blockers, used for primary or secondary prophylaxis of variceal bleeding, reduce MAP and GFR and must be used cautiously in patients with cirrhosis and ascites. Close monitoring of renal function is recommended, especially in patients with refractory ascites. β-Blockers may increase short-term mortality in this specific cirrhotic subpopulation and should therefore be replaced by band ligation of varices.[14]

Preventive Measures

Accepting the hypothesis that HRS represents one end of the spectrum of the homeostatic abnormalities in liver failure and portal hypertension and that it is precipitated by clinical events as volume contraction or bacterial infection, it follows that a major focus of treatment must be to prevent such events and to treat them promptly when they occur. There should be a low threshold for antibiotic therapy for suspected infection in cirrhosis. Spontaneous bacterial peritonitis must be excluded by regular examination of ascites whenever a patient is admitted to the hospital or clinically deteriorates. This infection must be treated not only with broad-spectrum antibiotics but also with albumin infusion (1.5 g/kg at diagnosis and 1 g/kg at day 3) because the latter has been shown to prevent the subsequent development of HRS and improves short-term survival.[15] Primary prophylaxis of spontaneous bacterial peritonitis with norfloxacin has recently been shown not only to prevent its development but also to delay the development of HRS and to improve patient survival in cirrhotic patients at high risk for complications (low ascitic protein level <15 g/l; advanced liver failure with Child-Pugh score ≥9 and serum bilirubin ≥3 mg/dl; or impaired renal function with serum creatinine ≥1.2 mg/dl or serum sodium ≤130 mmol/l).[16] Norfloxacin is thought to exert its renoprotective effect by reducing bacterial translocation from the intestine, endotoxemia, and nitric oxide generation, which in turn leads to improved hemodynamics. Prophylactic use of pentoxifylline (400 mg orally three times per day) also prevents the development of HRS in patients with acute alcoholic hepatitis, probably by inhibiting the synthesis of tumor necrosis factor α.[17]

General Approach to Treatment

As mentioned before, in patients with preexisting liver failure, portal hypertension, and renal failure, the use of nephrotoxic agents must be stopped. The absence of shock or gastrointestinal bleeding, and excess gastrointestinal, peritoneal, or renal fluid loss must also be documented. Pre-renal AKI must be excluded by withdrawal of diuretics and fluid challenge either with normal saline or preferably with albumin. Absence of microhematuria and proteinuria should also be confirmed.

Once the diagnosis of HRS has been made, patients should be assessed for orthotopic liver transplantation (OLT). Suitable candidates should be placed on the waiting list for deceased donor or if possible living donor liver transplantation. Bridge treatments are also needed. Pharmacotherapy, transjugular intrahepatic portosystemic shunt, extracorporeal liver support therapy, and, in patients with advanced uremia, renal replacement therapy are treatments that can be used in patients with HRS. They can improve renal function and the clinical condition of the patient before OLT and in some patients who are not transplant candidates can prolong survival by months.

Pharmacotherapy

At present, the most promising pharmacotherapy appears to be vasoconstrictor therapy targeted at reversal of splanchnic arteriolar vasodilation and restoration of the effective arterial blood volume with use of albumin (Box 76-3). Vasodilator therapy, which aims at reversal of renal vasoconstriction, is contraindicated in HRS because it is ineffective and can induce marked hypotension.

Vasopressin analogues exhibit preferential vasoconstrictor action on the splanchnic versus the renal vascular bed. Terlipressin (triglycyllysine vasopressin) is a synthetic analogue of vasopressin that, in addition to having a greater effect on the vascular vasopressin receptors (V_1) than the renal vasopressin receptors (V_2), is a prodrug requiring transformation to the active form, lysine vasopressin. Because of this, terlipressin has a prolonged half-life and can be given as an intravenous bolus or as continuous intravenous infusion. Continuous administration improves the probability of HRS reversal and reduces the incidence of systemic ischemic side effects.[3] Long-term

Randomized Controlled Trials of Terlipressin or Norepinephrine in Hepatorenal Syndrome						
Reference	**Treatment**	**Vasoconstrictor Dose**	**Patients (n)***	**Reversal of HRS†**	**Survival at 3 Months**	**Survival at 6 Months**
Solanki et al, 2003[24]	Terlipressin + albumin Placebo	1 mg/12 h —	12 (0) 12 (0)	42%‡ 0%	NA 0%	NA 0%
Sanyal et al, 2008[25]	Terlipressin + albumin Placebo	1-2 mg/6 h —	56 (0) 56 (0)	34%† 13%	NA NA	43% 38%
Neri et al, 2008[26]	Terlipressin + albumin Albumin	0.5-1 mg/8 h —	26 (0) 26 (0)	80%† 19%	54%† 19%	42% 15%
Martín-Llahí et al, 2008[27]	Terlipressin + albumin Albumin	1-2 mg/4 h —	23 (6) 23 (5)	39%† 4%	26% 17%	NA NA
Alessandria et al, 2007[33]	Terlipressin +albumin Norepinephrine + albumin	1-2 mg/4 h 0.1-0.7 μg/kg/min	12 (7) 10 (6)	83% 70%	67% 70%	67% 70%
Sharma et al, 2008[34]	Terlipressin + albumin Norepinephrine + albumin	0.5-2 mg/6 h 0.5-3 mg/h	20 (0) 20 (0)	50% 50%	NA NA	NA NA

Table 76-2 Randomized controlled trials on terlipressin or norepinephrine in hepatorenal syndrome. *Number of patients with type 2 hepatorenal syndrome in parentheses. †Serum creatinine ≤1.5 mg/dl. ‡$P < .05$ versus placebo or control.

Pharmacologic Options in the Treatment of Hepatorenal Syndrome

Terlipressin + albumin*: Terlipressin: 1 mg/4-6 h to start,† increasing to a maximum of 2 mg/4-6 h if serum creatinine decreases <25% at day 3. Treatment is maintained until serum creatinine has decreased below 1.5 mg/dl (133 μmol/l). Maximum duration of treatment: 14 days.

Norepinephrine + albumin*: Norepinephrine: IV infusion at 0.5 mg/h to start, increasing the dose by 0.25 to 0.5 mg/h every 4 hours up to a maximum of 3 mg/h to achieve an increase in MAP of at least 10 mm Hg. Maximum duration of treatment: 14 days.

Vasopressin + albumin*: Vasopressin: IV infusion at 0.01 U/min to start, increasing the dose upward to a maximum of 0.8 U/min to achieve an increase in MAP of at least 10 mm Hg. Maximum duration of treatment: 11 days.

Midodrine + octreotide + albumin*: Oral midodrine 2.5 to 7.5 mg/8 h + subcutaneous octreotide 100 μg/8 h to start, increasing midodrine dose to a maximum of 12.5-15 mg/8 h and octreotide dose to a maximum of 200 μg/8 h to achieve an increase in MAP of at least 15 mm Hg. Maximum duration is not defined.

Box 76-3 Pharmacologic options in the treatment of hepatorenal syndrome. *IV,* Intravenous; *MAP,* mean arterial pressure. *Albumin dose: 1 g/kg on day 1 (up to 100 g) followed by 20 to 40 g/day. Central venous pressure monitoring is advised (but not mandatory) to achieve a value of 10 to 15 mm Hg. †Terlipressin can also be administered as continuous infusion.

prospective studies[18-22] and a large retrospective study[23] in patients with type 1 and type 2 HRS have shown that terlipressin combined with daily albumin infusion improved renal function in 60% of the treated patients, with 37% surviving beyond 1 month, 60% without OLT. Reversal of HRS was associated with improved survival.[21,23] The efficacy of terlipressin in the treatment of HRS has been confirmed in four randomized trials (Table 76-2).[24-27] Terlipressin was given at a starting dose of 2 to 6 mg/day, and in two studies the dose was titrated upward on the basis of response to a maximum dose of 12 mg daily. Both treated patients and controls were given daily albumin infusion of 20 to 40 g/day. Reversal of HRS was associated with improved survival in only one study.[26] The inclusion of patients with more severe renal failure in the treated group[25] and the unexpected high response and survival rate in controls[27] may explain the inability of some of these studies to show a survival benefit of treatment despite success in reversing HRS. The latter is likely a result of the more aggressive use of albumin infusion in these studies because such an approach has been shown to reverse HRS in a high proportion of patients.[28] A meta-analysis recently published confirms that terlipressin plus albumin prolongs short-term survival in patients with type-1 HRS.[29] Response to therapy is characterized by a slowly and sustained reduction in serum creatinine and improvement in systemic hemodynamics (marked suppression of the plasma levels of renin and norepinephrine, increase in MAP), urine volume, and serum sodium concentration. Median time to reversal of HRS is 7 days and depends on pretreatment serum creatinine.[3]

Recurrence rates of HRS after successful treatment are variable and tend to be more common in type 2 (around 50%) than in type 1 HRS (20%).* Re-treatment with terlipressin is successful in most patients.[19,21,25] Younger age,[23,26] lower baseline serum creatinine level,[27] Child-Pugh score of 12 or lower,[23,26] administration of albumin,[21] serum bilirubin below 10 mg/dl, and increase in MAP over 5 mm Hg after initiation of terlipressin[30] are independent predictors for a successful response to treatment. In patients with severe alcoholic hepatitis, the absence of underlying cirrhosis increases the probability of response to medical treatment. Child-Pugh score (<12)[21,23,25,26] and MELD score[27] are independent predictors for survival. Transient abdominal pain and diarrhea after the first dose of terlipressin treatment are common. Significant ischemic side effects attributed to terlipressin occurred in an average of 4% to 12% of patients.[18-27]

Intravenous vasopressin has been used as an alternative to terlipressin in the treatment of HRS in countries where this drug is not available and was successful in reversing type 1 and type 2 HRS in 42% of patients in a retrospective study.[31] Responders had significantly lower mortality and a higher liver transplantation rate than nonresponders did. No adverse effect related to therapy was observed.

Intravenous norepinephrine combined with intravenous albumin and furosemide reversed type 1 HRS in 10 of 12 patients; three survived with OLT, and four survived for a median of 332 days without OLT.[32] With use of a similar dosage regimen, two randomized comparative studies showed that norepinephrine is as effective as terlipressin in the treatment of type 1 and type 2 HRS (see Table 76-2).[33,34] All recurrences were successfully re-treated with the original

*References 18, 19, 21, 22, 25, 27.

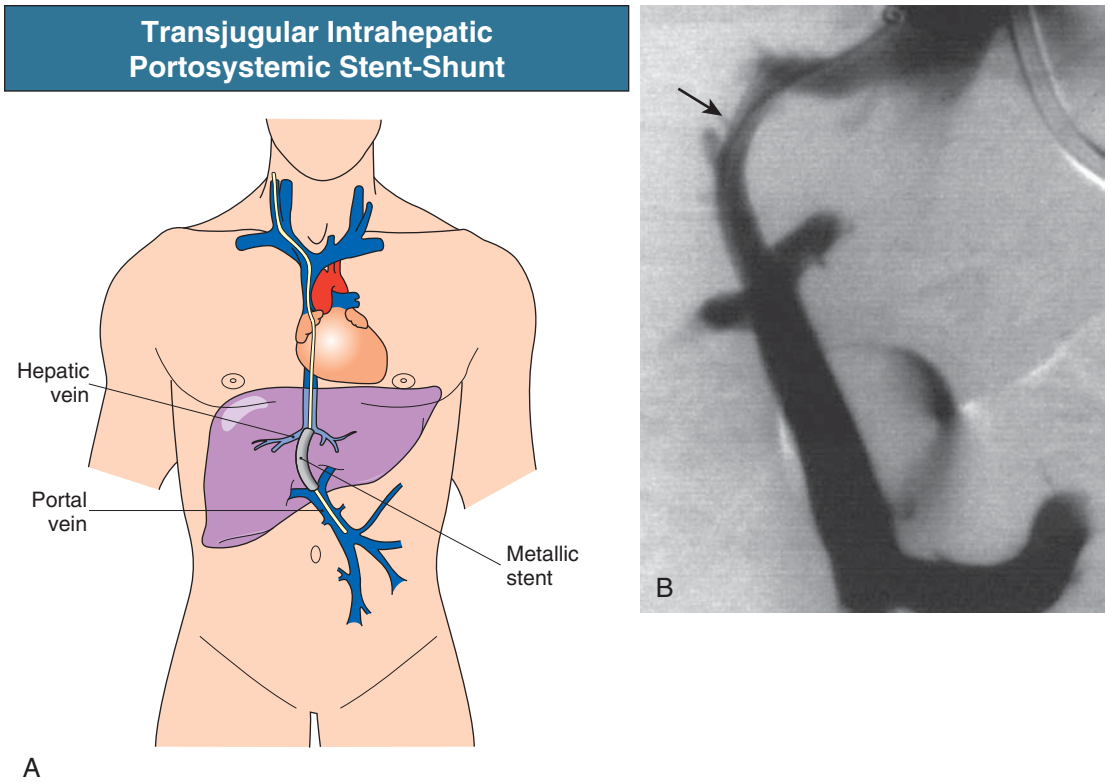

Figure 76-3 Transjugular intrahepatic portosystemic shunt. A, An intrahepatic tract has been created between the right hepatic vein and the right portal vein. **B,** The tract is dilated *(arrow)* and stented, creating a shunt as demonstrated on shuntogram. *(Courtesy Dr. W.K.Tso, Queen Mary Hospital, Hong Kong.)*

regimen. Significant treatment-related side effects were low, and the cost of treatment with norepinephrine was 3 and 15 times lower, respectively, than with terlipressin.

Administration of midodrine (an oral vasoconstrictor with α-adrenergic effect), subcutaneous octreotide, and albumin infusion has been demonstrated to improve renal function in patients with HRS in studies with low numbers of patients.[35-38] However, this treatment is less effective than the combination of terlipressin plus albumin.[3]

Transjugular Intrahepatic Portosystemic Shunt

Portal hypertension is central in the pathogenesis of the homeostatic abnormalities in HRS. The high operative mortality precludes side-to-side portacaval shunts in HRS patients. The transjugular intrahepatic portosystemic shunt (TIPS) creates a parenchymal track between branches of the hepatic and portal vein (Fig. 76-3). In experienced hands, operative mortality rates are 1% to 2%, and the morbidity rate is 10%. Procedure-related complications include intra-abdominal bleeding, cardiac arrhythmia, shunt migration and thrombosis, hemolytic anemia, fever, infection, and reactions to radiocontrast media (including nephrotoxicity). The resultant diversion of portal blood flow from the liver to the systemic circulation may result in transient deterioration of liver function. Shunt stenosis and hepatic encephalopathy are the main long-term complications of TIPS. Exceptionally, TIPS induces disabling encephalopathy. In these cases closure of the shunt should be performed.[39] In an earlier study, TIPS improved renal function in six of seven HRS patients (all with Child-Pugh score <12) and achieved a mean survival of 4.7 (0.3 to 17) months.[40] A long-term study of 31 cirrhotic patients with HRS (14 type 1 and 17 type 2) who were not transplant candidates and did not have severe liver failure confirmed that TIPS improved renal function and survival compared with controls.[41] Shunt stenosis and occlusion occurred in seven patients and could be treated in six by balloon dilation or stent prolongation, and 11 developed hepatic encephalopathy during follow-up. TIPS, therefore, could be an alternative treatment of type 1 HRS in patients without response to terlipressin/norepinephine plus albumin.

Combined TIPS and intravenous terlipressin therapy was performed in nine patients with type 2 HRS.[22] All seven patients who responded to terlipressin and relapsed after treatment cessation responded to TIPS. In another study, TIPS was performed in five patients with type 1 HRS after successful treatment with midodrine, octreotide, and albumin.[37] Complete normalization of renal function was observed in all patients 12 months after TIPS. In both studies, improvement or elimination of ascites was an added benefit.

Extracorporeal Liver Support Therapy

Extracorporeal liver support therapy, as a bridge to OLT, relies on biologic (hepatocytes from human or animal source in an *ex vivo* perfusion system) or nonbiologic methods, including plasma exchange and albumin dialysis systems. Numerous studies have suggested that albumin dialysis (molecular adsorbent recirculating system [MARS] or fractionated plasma separation and adsorption [FPSA]) may have beneficial effects in patients with type 1 HRS. In a small prospective randomized controlled trial, a mean of five treatments with MARS effectively removed albumin-bound toxic metabolites (i.e., bilirubin and bile acids), improved renal function, and prolonged survival in eight patients (mean survival, 25 ± 5 days) with type 1 HRS and severe liver failure compared with five control patients treated only with hemodiafiltration (mean survival, 5 ± 2 days).[42] In another study of eight encephalopathic patients with acute

alcoholic hepatitis (five with type 1 and two with type 2 HRS), MARS improved renal function, bilirubin, prothrombin time, grade of encephalopathy, MAP, systemic vascular resistance, and cardiac output, with four patients still alive without OLT at 3 months.[43] Three large randomized controlled trials have so far been performed evaluating albumin dialysis in patients with acute-on-chronic liver failure.[44-46] In the first study, albumin dialysis with MARS was found to be more effective than standard medical therapy in the management of patients with grade III or IV hepatic encephalopathy. Most patients had HRS, and the treatment was found to be safe.[44] The two other trials compared albumin dialysis with standard medical therapy in patients with type 1 HRS (MARS) or with type 1 and 2 HRS (FPSA). Significant beneficial effect on hepatic encephalopathy was observed in the MARS study but not on survival.[45] In the FPSA trial no effect on survival was observed in the whole group or in patients with type 1 HRS, but a significant improvement was observed in patients with high MELD score (>30 points). The administered dosage of dialysis was very low in both studies (six sessions of 6 hours in 21 days). In these studies, therapy was well tolerated.[45,46] Further studies are clearly needed to ascertain the potential role of albumin dialysis in type 1 HRS. Patients with type 2 HRS are usually treated by total paracentesis or TIPS.

Renal Replacement Therapy

Hemodialysis and peritoneal dialysis in HRS patients with advancing uremia are both difficult. Conventional hemodialysis is hampered by the invariable systemic hypotension, and the efficacy and safety of peritoneal dialysis have not been well evaluated in these patients. Continuous venovenous hemofiltration (CVVH) or continuous venovenous hemodiafiltration (CVVHDF) has been advocated for the treatment of advancing uremia in HRS.[47] This is particularly true for patients with fulminant hepatic failure in whom intermittent dialysis can increase intracranial pressure. Anticoagulation should be minimized or may be avoided totally, especially in patients with preexisting coagulopathy, by giving the replacement fluid in the predilutional mode. When anticoagulation is needed, conventional heparin is generally recommended. Regional citrate anticoagulation is not recommended in advanced cirrhosis because the liver plays a significant role in its metabolism. If used, dose adaptation and close metabolic monitoring would be required, especially after prolonged use. Close plasma calcium monitoring is mandatory because hypocalcemia is common as a result of the impaired citrate clearance. Bicarbonate should be used instead of lactate as the buffer for the replacement solution to minimize metabolic acidosis. MARS may be combined with either CVVH or hemodialysis for the treatment of HRS. This approach may be most desirable in patients who also have severe hepatic encephalopathy. In patients who could require venovenous bypass for liver transplantation, the site of dialysis catheter placement should be carefully chosen so that the right jugular and right femoral vein may be preserved for cannulation.

Liver Transplantation

Liver transplantation is the treatment of choice in patients with advanced cirrhosis, including those with type 1 and type 2 HRS.[48-51] The hemodynamic and neurohormonal abnormalities associated with HRS disappear within the first month after liver transplantation. For this reason, calcineurin inhibitors should be withheld in the first few days after OLT to give the ischemic kidney a chance to recover, thus avoiding the nephrotoxicity of these immunosuppressants. Patients with HRS who undergo transplantation have more complications, spend more days in the intensive care unit, and have a higher in-hospital mortality rate than transplantation patients without HRS. The long-term survival of patients with HRS who undergo liver transplantation, however, is good (3-year survival 60%) compared with transplantation in patients without HRS (70% to 80%).[48,49] Although renal function improves after transplantation in HRS patients, it never reaches that observed in non-HRS patients.[52] The incidence of end-stage renal disease in patients with HRS is slightly higher than that observed in transplantation patients without HRS (7% vs. 2%). Thus, OLT is associated with comparable liver outcome but inferior renal outcome in patients with HRS. This problem cannot be overcome by performing combined kidney and liver transplantation in HRS, which overall produces outcomes no better than with OLT alone.[53] However, in the very infrequent subgroup of patients with HRS who required prolonged pretransplant dialysis for more than 2 months (probably patients with combined functional and organic renal failure), combined kidney and liver transplantation did confer an advantage in patient survival and use of hospital resources. These infrequent patients usually have normal kidney size and morphology at ultrasound but develop some additional indications of organic nephropathy during follow-up (mild proteinuria or microhematuria).[54]

The main problem with liver transplantation in type 1 HRS is that because of their extremely short survival, most patients die before transplantation. The introduction of the MELD score for listing has partially solved the problem because patients with HRS are generally allocated in the first places of the waiting list. As mentioned earlier, treatment of HRS with vasoconstrictors and albumin improves survival in the group of patients with response to treatment, increasing the number of patients reaching liver transplantation. In addition, reversal of HRS before transplantation may decrease early morbidity and mortality after transplantation and prolong survival.[51]

Therapeutic Algorithm

Figure 76-4 shows the recommended algorithm for the management of HRS. Recent recommendations have also been published by the International Ascites Club.[9,55] OLT is undoubtedly the treatment of choice for patients with HRS, but other treatments described earlier must be used as a bridge to OLT, and they may improve the renal outcome after successful OLT. In patients who are not transplantation candidates, these treatments are their only chance for increased survival and in some cases may improve their condition to an extent that may allow them to be reconsidered for transplantation. The choice of therapeutic modalities depends on the availability of resources and expertise on the one hand and the severity of underlying renal and liver failure and the general condition of the patient on the other. All patients should be considered for vasoconstrictor therapy combined with albumin infusion. Among the vasoconstrictor therapies, intravenous terlipressin, combined with daily albumin infusion, is most established and is the preferred therapy.[55] In countries where terlipressin is not available, continuous intravenous norepinephrine or vasopressin may be used as alternative. Patients with a history of significant atherosclerotic or cardiovascular disease should be treated with norepinephrine plus albumin. Oral midodrine combined with subcutaneous octreotide and albumin is another alternative in the treatment of HRS, especially in patients with type 2 HRS. In patients with relatively well-preserved liver function (serum bilirubin <5 mg/dl or 85.5 µmol/l and Child-Pugh score <12) without severe hepatic encephalopathy (grade <2) or history of recurrent encephalopathy, concurrent severe bacterial infection, or serious cardiovascular or pulmonary disease, TIPS should be considered, especially in patients with recurrence after vasoconstrictor therapy, a situation more commonly observed in HRS type 2

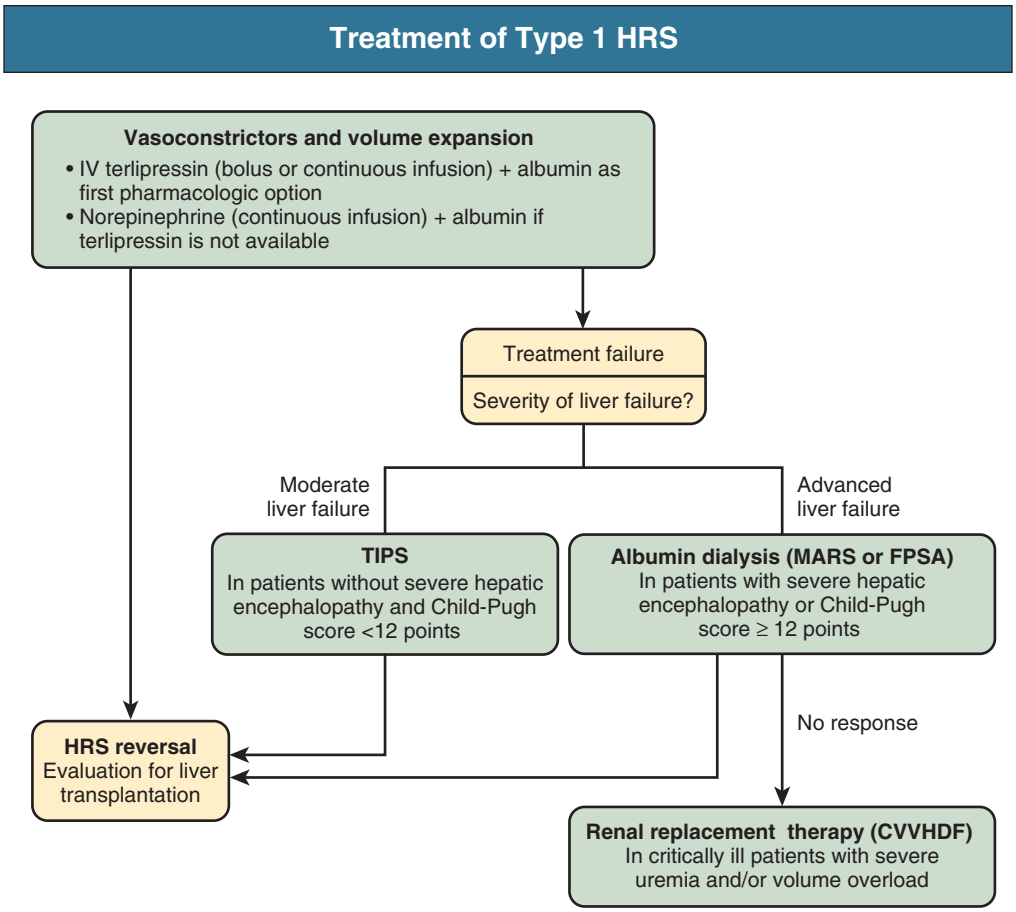

Figure 76-4 Algorithm for the management of type 1 hepatorenal syndrome (HRS). Initial treatment is based on the use of vasoconstrictor therapies plus albumin. Intravenous terlipressin is the most established and is the preferred therapy.[55] If terlipressin is not available, continuous intravenous norepinephrine should be used. Patients with history of significant atherosclerotic or cardiovascular disease should be treated with norepinephrine. If pharmacologic therapy fails, the severity of liver failure should be assessed. In patients with less severe liver dysfunction (bilirubin <5 mg/dl or 85.5 µmol/l and Child-Pugh score <12) without severe hepatic encephalopathy (grade ≤2) or history of recurrent encephalopathy, transjugular intrahepatic portosystemic shunt (TIPS) should be considered.[3] In patients with more severe liver failure (Child-Pugh score ≥12) and/or severe hepatic encephalopathy (grade >2), albumin dialysis (molecular adsorbent recirculating system [MARS] or fractionated plasma separation and adsorption [FPSA]) should be considered. In critically ill cirrhotic patients with advancing renal failure, continuous venovenous hemodiafiltration (CVVHDF) is the treatment of choice.

patients.[3] In these patients, TIPS may have the added benefit of relieving refractory ascites. TIPS also appears to achieve complete normalization of renal function in selected patients after an initial successful response to vasoconstrictor therapy. In patients with severe liver failure (Child-Pugh score ≥12) and severe hepatic encephalopathy (grade >2), MARS should be considered. In critically ill cirrhotic patients with advancing renal failure, CVVH is the treatment of choice and may be combined with other therapeutic modalities, especially MARS or FPSA.

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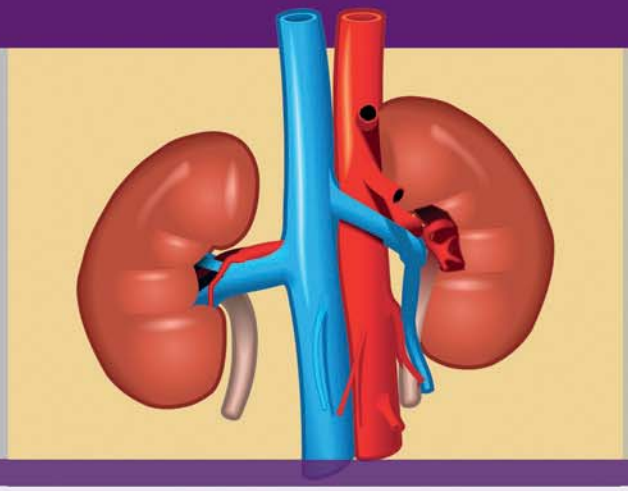

SECTION XV

Drug Therapy in Kidney Disease

CHAPTER 77

Principles of Drug Therapy, Dosing, and Prescribing in Chronic Kidney Disease and Renal Replacement Therapy

Matthew J. Cervelli and Graeme R. Russ

Renal impairment can alter drug pharmacokinetics and pharmacodynamics, and consequently patients with renal impairment are at risk of adverse effects. In addition, these patients take multiple drugs and are at high risk of drug interactions and drug-related problems.[1] To prescribe safely and effectively, clinicians should be familiar with the pharmacokinetics of drugs in varying stages of renal impairment and renal replacement therapy (RRT) and ideally rely on data from these populations. Unfortunately, such information is not always available, and exclusion of these patients from clinical studies can lead to restrictive licensed recommendations. This chapter describes pharmacokinetic principles and highlights common prescribing issues in patients with renal impairment, dialysis, and transplantation. Specific dose recommendations and pharmacokinetic data are not included but can be obtained from references developed specifically to provide concise, reliable, and practical information for prescribing the settings of renal impairment, dialysis, and transplantation.[2-5]

PHARMACOKINETIC PRINCIPLES

Pharmacokinetics describes the behavior of a drug (or metabolite) with regard to absorption, distribution, metabolism, and elimination (Fig. 77-1 and Table 77-1).[6,7]

Absorption: Bioavailability

Bioavailability *(F)* is the portion of a drug dose that appears in the systemic circulation after administration by a nonintravenous route. Whereas drugs given intravenously have 100% bioavailability, drugs given by alternative routes pass through a series of biologic membranes before entering the systemic circulation so that only a fraction may reach the circulation.

After oral administration, the liver can metabolize a drug during "first pass" when it is absorbed or later when it is delivered through systemic blood flow. First-pass metabolism can significantly reduce absorption. The gastrointestinal mucosa also acts as a barrier to absorption by metabolizing drugs or retarding absorption.[8] Renal impairment can influence absorption, although the effect is difficult to quantify and clinical examples are limited. Gastrointestinal edema can limit oral absorption, for example, of furosemide. Nausea and vomiting from uremia can impair absorption and contact time between the drug and gastrointestinal mucosa. In patients with advanced uremia, the alkalinizing effect of salivary urea may decrease absorption of drugs optimally absorbed in an acid milieu. Commonly prescribed metallic ion phosphate binders can decrease drug absorption by forming nonabsorbable complexes with drugs (Table 77-2).[9] Changes in cardiac output in renal failure can reduce the rate and extent of absorption for drugs with significant first-pass metabolism. Increased absorption in patients with renal impairment from reduced first-pass metabolism is seen with some β-blockers, dextropropoxyphene, and dihydrocodeine. Comorbidities in renal patients also have an effect; for example, absorption can be erratic because of diabetic gastrointestinal neuropathy.

Distribution

Volume of Distribution

After absorption, drugs may distribute from plasma to an extravascular compartment. Each drug has a characteristic volume of distribution (V_D), which is really an apparent V_D because it does not correspond to an anatomic space but instead relates the amount of drug in the body to its plasma concentration. V_D is used to calculate the loading dose to achieve a desired plasma concentration (V_D = dose/plasma). Water-soluble drugs tend to be restricted to the extracellular fluid space and have a relatively small V_D. Lipid-soluble drugs penetrate body tissues and have a large V_D. Increased V_D can occur with edema, ascites, or infection, particularly for water-soluble drugs. If usual doses are given, low concentrations result. Conversely, muscle wasting or volume depletion can decrease the V_D of water-soluble drugs, and usual doses produce high concentrations.

Plasma Protein Binding

Drugs can bind extensively to plasma proteins.[10] The free (unbound) fraction of a drug is usually the portion that exerts a pharmacologic effect. If protein binding is reduced, a greater free fraction is available for any given total drug concentration, which may increase drug activity. Organic acids usually have a single binding site on albumin, whereas organic bases have multiple binding sites on glycoproteins. Protein binding can be altered in patients with renal impairment, especially when serum albumin is low (e.g., nephrotic syndrome) or when uremic toxins displace drugs from binding sites (Table 77-3). Predicting the effect of changes in protein binding is difficult because even though more free drug is available at the site of action, more is available for metabolism or renal excretion. Hence, lower plasma concentrations can occur and drug half-life may decrease rather than increase. Phenytoin, for example, has marked decreases in protein binding in patients with renal impairment, and toxicity can occur despite normal or low total plasma concentrations because of an increase in free fraction. With albuminuria, bound drug may also be lost, which may partially explain the refractoriness of nephrotic patients to diuretics. In patients with chronic kidney disease (CKD), high plasma levels of α_1-acid glycoprotein are induced in acute and chronic inflammation, which can increase drug binding.

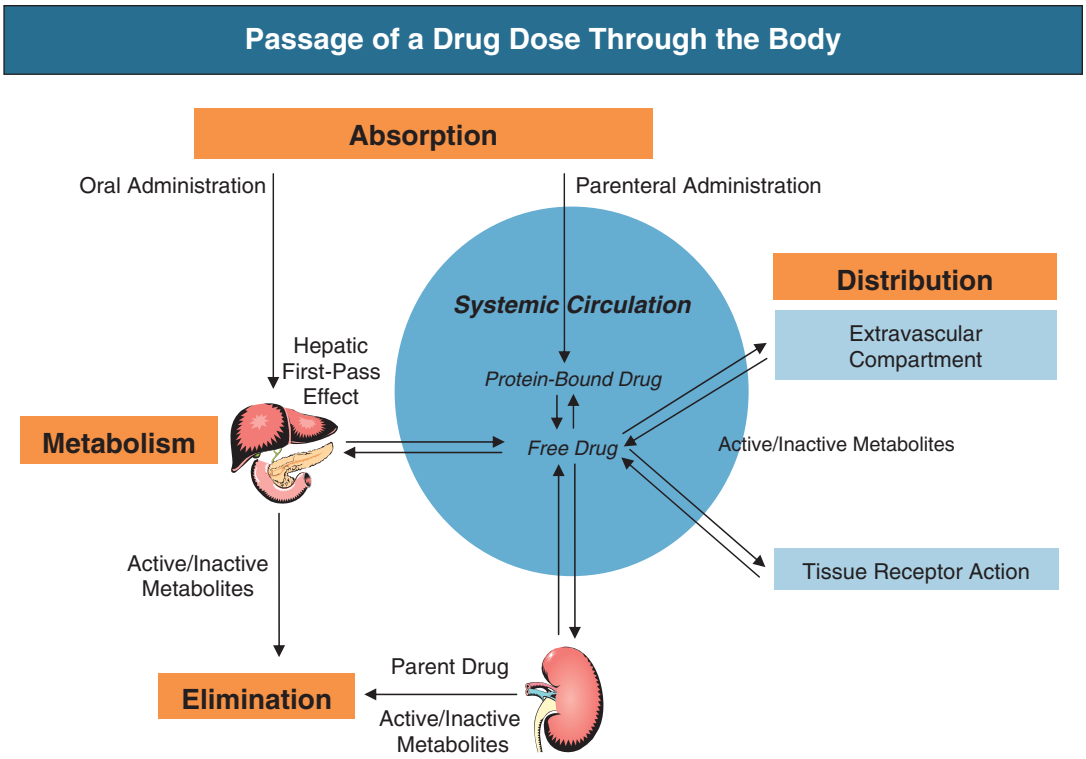

Figure 77-1 Passage of a drug dose through the body.

Pharmacokinetic Parameters

Parameter	Definition	Application
Bioavailability (*F*)	Percentage of a dose that appears in the systemic circulation after administration by a nonintravenous route	Determines the amount of drug reaching the systemic circulation
Volume of distribution (V_D)	Proportionality constant relating the amount of drug in the body at a given time to a simultaneously occurring drug concentration in plasma, blood, or other reference fluid at an identical time	Determines the size of loading doses
Clearance (Cl)	Proportionality constant between rate of drug elimination from the body (units = mass/unit time) and the concentration of the drug in plasma or blood at the same point in time	Determines the maintenance dose
Half-life ($t_{1/2}$)	Time taken for the drug concentration in plasma to fall to half its current value	Determines frequency of administration and time to steady state

Table 77-1 Pharmacokinetic parameters.

Effect of Food and Phosphate Binders on Oral Drug Absorption

Drug	Effect of Food
Captopril	Decreases serum drug levels
Bisphosphonates (oral)	Significantly reduces drug absorption
Cinacalcet	Significantly increases drug absorption
Iron (oral)	Decreases absorption
Ketoconazole or itraconazole	Increases absorption with reduced pH
Sirolimus	High-fat meals increase absorption
Tacrolimus	Reduces drug absorption
Drug	**Effect of Metallic Phosphate Binders**
Bisphosphonates (oral)	Calcium-containing binders significantly reduce absorption
Fluoroquinolones	Reduction in absorption
Tetracycline	Reduction in absorption
Thyroid hormones	Reduction in absorption

Table 77-2 Effect of food and phosphate binders on oral drug absorption.

Metabolism

Drug metabolism is primarily a hepatic function by which drugs are converted to more water-soluble entities to promote elimination by the kidneys and bile. Despite the assumption that nonrenal clearance is unchanged, renal impairment can alter and slow drug metabolism.[11] It is important to note that some drugs have renally cleared active or toxic metabolites that, although insignificant in normal renal function, can accumulate in patients with renal impairment.

Elimination

The kidney is the most important organ for drug and metabolite elimination. Terms to describe drug clearance are shown in Box 77-1. Total drug clearance equals the apparent volume of blood or plasma from which the drug is cleared per unit of time and is expressed as the dose divided by the area under the drug concentration curve (AUC). *Half-life* describes the time taken for plasma

Protein Binding of Drugs in Renal Disease	
Major Effects	**Minor Effects**
Albumin: Binding Sites for Acidic Compounds	
Barbiturates (↓)	Ascorbic acid
Benzodiazepine	Valproate (↓)
Carbamazepine	Fatty acids
Fibrates	Nafcillin
Furosemide (↓)	Phenylbutazone (↓)
Mycophenolate mofetil	Probenecid
Penicillins	Thiopental (↓)
Phenytoin (↓)	Warfarin (↓)
Sulfonamides (↓)	Thyroxine (↓)
Globulins: Binding Site for Basic Compounds	
Digoxin (↓)	Adenosine
Methadone	Amitriptyline
Propranolol	Chloramphenicol

Table 77-3 Protein binding of drugs in renal disease. ↓ indicates reduced protein binding in renal impairment. For all other drugs listed, protein binding is increased. The therapeutic effect is, however, not easily predicted (see text).

Mathematics of Drug Elimination

Total body clearance = Drug dose / AUC

Renal clearance = Total amount of drug in urine/plasma drug concentration

Total amount of drug in urine = Drug × volume of the sample collected in a fixed time

Drug half-life ($t_{1/2}$) = $V_D \times 0.693$ / Clearance

Box 77-1 Mathematics of drug elimination. *AUC,* Area under the concentration-time curve; V_D, volume of distribution (dose/blood concentration).

concentrations to halve and is related to V_D and clearance. Quantitation of drug elimination by the kidney is expressed as renal clearance, which depends on renal blood flow and the ability of the kidney to remove the drug. Renal drug clearance is the balance of its glomerular filtration rate (GFR), renal tubular secretion, and tubular reabsorption. Glomerular filtration depends on molecular size (<10 kd), charge, and protein binding (increased when binding decreases). Secretion of drugs eliminated by tubular transport may change with renal disease, but measurement of tubular function is difficult. Practically, as GFR decreases, drugs dependent on tubular secretion are also excreted more slowly. Assuming no change in nonrenal clearance, as GFR falls, clearance of drugs (and metabolites) eliminated by the kidney decreases, and their half-life is prolonged.

PRESCRIBING PRINCIPLES FOR CHRONIC KIDNEY DISEASE AND RENAL REPLACEMENT THERAPY

Ideally, dose modification recommendations should be made by comparing the pharmacokinetics of a drug at varying stages of renal impairment relative to normal function. However, lack of reliable data and individual patient factors limit such generalities, and clinical judgment about a patient's ability to handle a drug is vital.[12] Dose nomograms, tables, and computer recommendations are helpful but not necessarily associated with better outcomes. Physicians should use clinical judgment to evaluate every situation individually, choose a dosage regimen based on factors in that patient, and continually reevaluate response to therapy.

Initial Assessment and Laboratory Data

A targeted history is important in assessing dose in patients with renal impairment. Previous drug efficacy or toxicity should be determined and the current drug list reviewed for potential interactions or nephrotoxins. Physical and laboratory parameters indicate volume status, height, weight, and extrarenal disease (e.g., liver).

Estimating Renal Function for Drug Dosage

Estimating renal function is essential in renal drug dosage. The greater the degree of renal impairment, the greater the potential for dose modification. With exceptions, dose modification is usually not clinically necessary until GFR is below 30 ml/min. Assessment of renal function for drug administration is not a precise science, and what is essential for clinical decision making is awareness that renal function is impaired, and approximately to what extent, rather than knowledge of the precise GFR.[13] For drug prescribing, renal impairment is usually graded as mild (30 to 60 ml/min), moderate (10 to 30 ml/min), or severe (dialysis). For drug dosage calculation, methods of estimating GFR are sufficient (see Chapter 3). The Cockcroft-Gault equation has been the most widely used and accepted method for drug dosage calculation. The Modification of Diet in Renal Disease (MDRD) formula, if not corrected for body surface area, can lead to recommendations different from those obtained by the Cockcroft-Gault equation. An important limitation of many renal function estimates is inaccuracy of single-point estimates when renal function is rapidly changing. This may lead to overestimation or underestimation of renal function and underdose or overdose. In patients with severe acute kidney injury (AKI), the decline in GFR is so rapid that patients should receive dosages appropriate for a GFR below 10 ml/min. The opposite is true in rapidly improving renal function after AKI or early post-transplant.

Activity and Toxicity of Metabolites

It is essential to consider the activity (or toxicity) of drug metabolites in addition to that of the parent drug itself. Renally cleared metabolites can accumulate, leading to enhanced drug action or toxicity (Table 77-4).

Fraction of Active Drug (and Active or Toxic Metabolite) Excreted Unchanged in Urine

The greater the fraction of active drug or metabolite excreted unchanged by the kidneys (fe), the greater the need for dose modification. It is usually clinically necessary to modify doses only if the fe is greater than 25% to 50%. The reported fe is often determined from studies that do not distinguish between parent drug and metabolites. The contribution of inactive nontoxic metabolites to overall renal drug elimination may exaggerate the potential for harm. Active or toxic metabolites should be assessed separately for

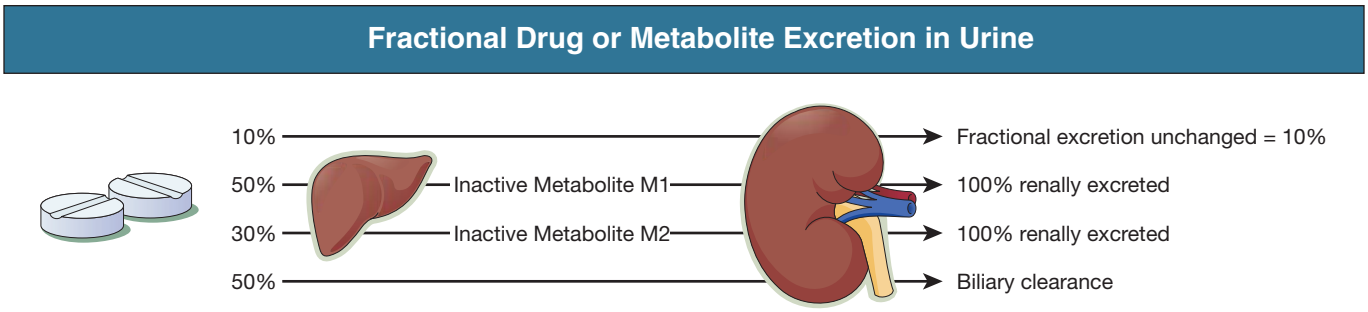

Figure 77-2 Fraction of drug or metabolite excreted in urine. In this hypothetical example, 10% of the dose is excreted unchanged in urine (fe = 10%); 50% of the dose is metabolized to inactive metabolite M1, which is then all renally excreted; 30% of the dose is metabolized to inactive metabolite M2, which is all renally excreted; and the remaining 10% is excreted unchanged in bile. For this drug, the total excretion of drug dose in urine is 90%. However, this 90% comprises 10% as parent drug and 80% as inactive metabolites, and dose modification is probably not essential even in severe renal impairment. Total renal excretion of the dose is 90%; however, the clinically significant fraction of active drug excreted in urine is 10%.

Drugs with Active or Toxic Metabolites That Accumulate in Subjects with Reduced GFR

Drug	Active Metabolite	Consequence
Allopurinol	Oxypurinol	
Cefotaxime	Desacetylcefotaxime	
Glyburide	4-*trans*-Hydroxyglibenclamide 3-*cis*-Hydroxyglibenclamide	Hypoglycemia
Morphine	Morphine-6-glucuronide	CNS side effects
Tramadol	*O*-Desmethyltramadol	CNS side effects
Venlafaxine	*O*-Desmethylvenlafaxine	CNS and cardiovascular side effects
Drug	**Toxic Metabolite**	**Consequence**
Dapsone	Monoacetylated metabolite	
Meperidine (pethidine)	Normeperidine (norpethidine)	CNS (seizures)
Nitroprusside	Thiocyanate	Cyanide toxicity
Procainamide	*N*-Acetylprocainamide (NAPA)	Arrhythmia
Propoxyphene	Norpropoxyphene	Cardiac toxicity

Table 77-4 Drugs with renally cleared active or toxic metabolites. *CNS,* Central nervous system.

their dependence on renal elimination in the same way as the parent drug (Fig. 77-2).

Therapeutic Index of the Drug or Metabolites

The decision to modify dosage for patients with renal impairment is influenced by the therapeutic window or index of the drug. The therapeutic window is the range of plasma drug concentrations spanning the minimum concentration for clinical efficacy and toxicity. The therapeutic index is the ratio of these concentrations (Fig. 77-3). If the therapeutic window is wide (e.g., many penicillins), there may be no clinical need for dose modification despite significant renal elimination. If the therapeutic window is narrow (e.g., digoxin), dose modification is more critical. Clinicians should judge the clinical relevance of increased exposure to drug or metabolites.

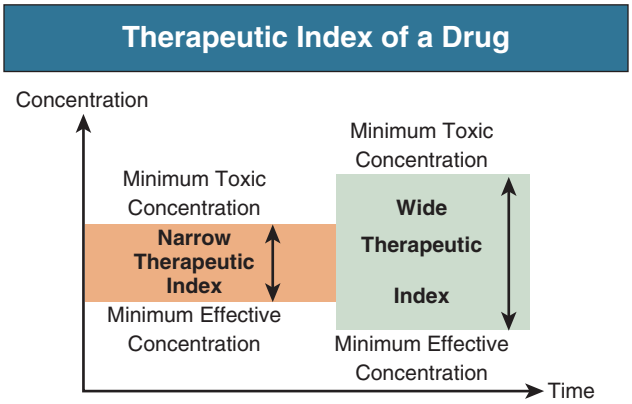

Figure 77-3 Therapeutic index of a drug. Two examples of drugs with, on the left, a narrow therapeutic index, and on the right, a wide therapeutic index.

Avoid Nephrotoxic Drugs

A wide range of drugs can cause nephrotoxicity (Table 77-5). Idiosyncratic nephrotoxicity (e.g., interstitial nephritis) is unpredictable and independent of dose. Predictable hemodynamic-related nephrotoxicity can occur with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, antihypertensives, and laxatives. Direct tubular nephrotoxins include aminoglycosides, vancomycin, amphotericin, cisplatin, calcineurin inhibitors (CNIs), and radiographic contrast media. Obstructive uropathy can occur with tubular crystallization of acyclovir, statin-induced rhabdomyolysis, or tricyclic antidepressant use. In dialysis patients with no significant residual renal function, use of nephrotoxic drugs may be acceptable. Drug nephrotoxicity is discussed further in Chapter 69.

Drugs That Aggravate the Metabolic Effects of Renal Impairment

Some drugs have no direct adverse effect on renal function but when used in patients with renal impairment can aggravate the metabolic consequences of renal failure. Hyperkalemia is worsened with potassium supplements, potassium-sparing diuretics, aldosterone antagonists, and blockers of the renin-angiotensin system. The catabolic effects of tetracycline can exacerbate uremia. Sodium-containing drugs and those that promote sodium and water retention should be used cautiously because they may provoke fluid overload and hypertension.

Nephrotoxic Drugs		
Examples	**Mechanism**	**Prevention and Management**
ACE inhibitors, ARBs	Impairment of angiotensin II–mediated afferent arteriole dilation during renal hypoperfusion	Withdraw in renal hypoperfusion
Aminoglycosides Amikacin Gentamicin Tobramycin	In proximal tubules, aminoglycosides bind to anionic phospholipid, are delivered to megalin, are taken up into the cell, accumulate, and cause direct toxicity	Alternative if possible Monitor drug concentrations Avoid multiple daily doses Withdraw if creatinine rises
Antifungals Amphotericin	Afferent vasoconstriction and direct action to reduce GFR Distal tubular injury via creation of pores that increase membrane permeability leading to hypokalemia, hypomagnesemia, metabolic acidosis caused by tubular acidosis, polyuria from nephrogenic diabetes insipidus	Avoid use Administer slowly with hydration Use liposomal preparation
Antivirals		
Acyclovir	Deposition of drug crystals → intratubular obstruction and foci of interstitial inflammation	Avoid bolus dose Reduce dose in renal impairment Hydrate during therapy
Cidofovir	Induces apoptosis in proximal tubule → tubular dysfunction, diabetes insipidus, renal failure	Oral probenecid and hydration
Foscarnet	Direct tubular toxicity → acute tubular necrosis, nephrogenic diabetes insipidus Crystals in glomerular capillary lumen and proximal tubular lumen	Hydration
Indinavir	Crystal neuropathy, nephrolithiasis → obstructive AKI	Hydration
Calcineurin inhibitors Cyclosporine Tacrolimus	↓ PG and ↑ 20-HETE acid production → vasoconstriction, generation of H_2O_2 resulting in depleted glutathione → decreased GFR, ischemic collapse or scarring of the glomeruli, vacuolization of the tubules, and focal areas of tubular atrophy and interstitial fibrosis	Measure plasma concentrations Avoid interacting drugs Withdraw drug (switch to mTOR inhibitor)
Chemotherapeutics		
Cisplatin	*Cis* chloride replaced by H_2O → highly reactive OH radical → DNA injury, tubular cell death Nephrogenic diabetes insipidus, hypomagnesemia (may be persistent)	Forced diuresis and hydration
Ifosfamide	Direct tubular injury and mitochondrial damage → renal tubular acidosis, Fanconi-like syndrome, nephrogenic diabetes insipidus hypokalemia	
Intravenous immunoglobulin (sucrose-containing products)	Accumulation of sucrose in proximal convoluted tubules, ↑ osmolarity → cell swelling, vacuolization, and tubular luminal occlusion	Infusion rate <3 mg sucrose/kg/min Avoid radiocontrast Avoid sucrose-containing product Hydration
Lithium	Impairment of collecting duct concentrating ability → diabetes insipidus Chronic tubulointerstitial nephropathy (tubular atrophy and interstitial fibrosis)	Measure plasma concentrations Prevent dehydration Avoid thiazides
NSAIDs	Hemodynamically induced AKI caused by vasoconstriction via reduced prostaglandin production Recruitment and activation of lymphocytes → acute and chronic tubulointerstitial nephritis, with or without nephrotic syndrome	Avoid use Withdraw during hypoperfusion Withdraw (add corticosteroids)
Proton pump inhibitors	Interstitial nephritis	Withdraw (add corticosteroids)
Radiocontrast media	High osmolarity, medullary vasoconstriction, ↑ active transport in thick ascending loop of Henle → ↑ O_2 demand	Hydration preprocedure and postprocedure Acetylcysteine
Sulfonamides	Intrarenal precipitation → Kidney stone formation	Fluid intake >3 l/day; monitor urine for crystals Alkalinize urine to >7.15 if crystal seen

Table 77-5 Some examples of nephrotoxic drugs. *ACE,* Angiotensin-converting enzyme; *AKI,* acute kidney injury; *ARBs,* angiotensin receptor blockers; *GFR,* glomerular filtration rate; *20-HETE acid,* 20-hydroxyeicosatetraenoic acid; *H_2O_2;* hydrogen peroxide; *mTOR,* mammalian target of rapamycin; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *PG,* prostaglandin.

Effect of Renal Impairment on Pharmacodynamic or Physiologic Mechanisms

Renal disease may alter a pharmacodynamic response or physiologic process, which in turn affects clinical response. For example, the inability of impaired kidneys to activate vitamin D precursors means that vitamins D_2 and D_3 may be less effective. Patients with renal impairment often have a coagulopathy from the effects of uremia on platelet function and may be more prone to the bleeding complications of anticoagulant and antiplatelet therapy.

Effect of Renal Impairment on the Concentration of Drug at the Site of Action

Renal impairment can alter drug concentration at the site of action. Some diuretics and antibiotics become ineffective in patients with renal impairment because they do not achieve adequate concentrations at their site of action in the renal tubules or bladder. This may preclude the use of drugs such as thiazide diuretics and nitrofurantoin or may require increased doses of others (e.g., loop diuretics).

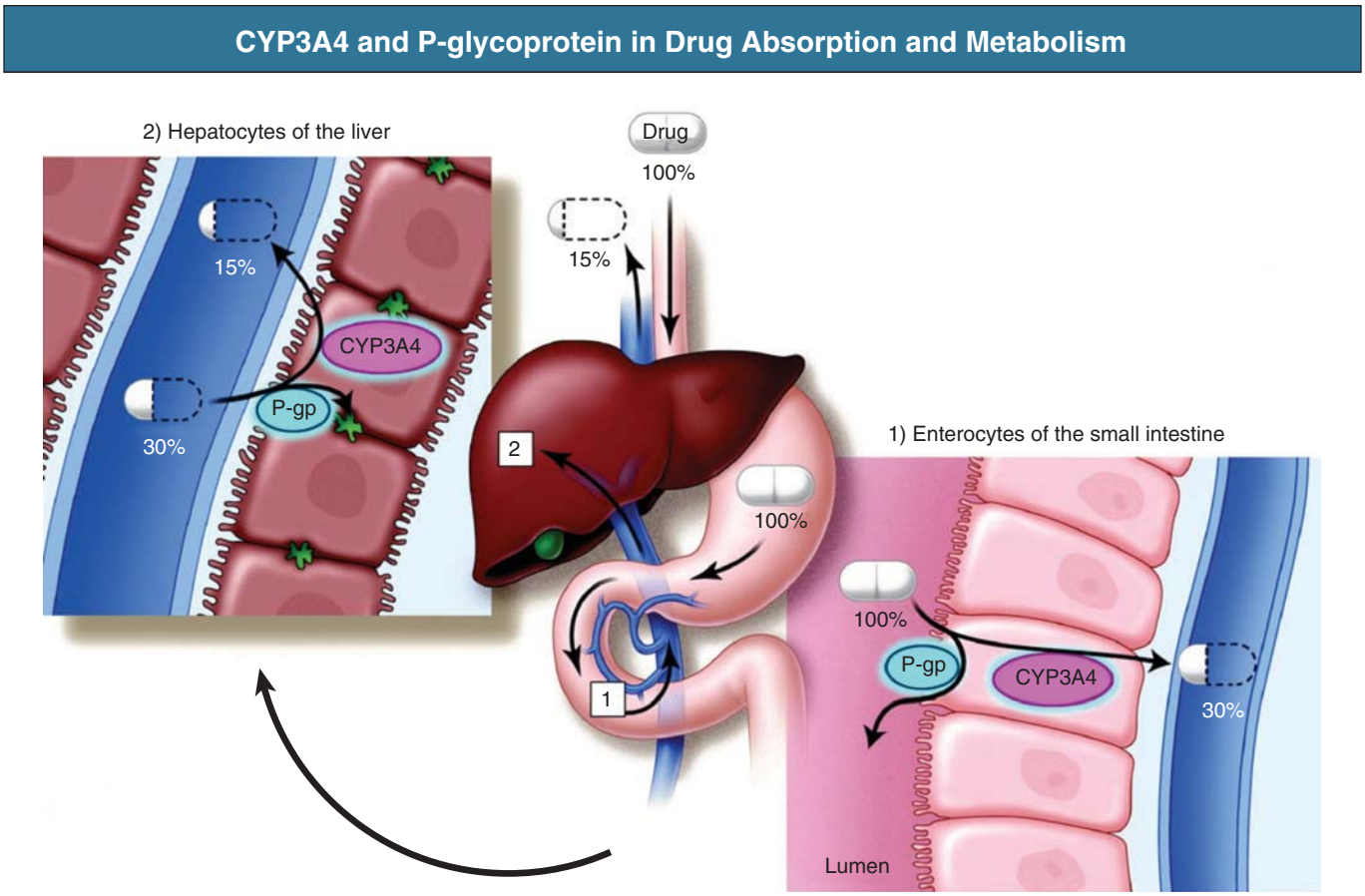

Figure 77-4 CYP3A4 and P-glycoprotein in drug absorption and metabolism. Schema for absorption and metabolism of drugs that are substrates for CYP3A4 and P-glycoprotein. Overall, approximately 15% of ingested drug reaches the systemic circulation. *1),* Enterocyte: P-glycoprotein on the apical surface of enterocytes prevents drug absorption, maintaining drug in the gastrointestinal lumen; CYP3A4 in enterocytes metabolizes drug. The net effect is that approximately 30% of ingested drug reaches the portal circulation. *2),* Hepatocyte: P-glycoprotein on the cell surface prevents drug entry into hepatocytes; CYP3A4 in hepatocytes metabolizes drug. The net effect is that drug entry to the systemic circulation is further reduced.

Location of Drug Action

Drugs that have negligible bioavailability and that are used for a local or topical effect may be given safely at normal dose despite toxicity with systemic doses. These include topical NSAIDs, nebulized gentamicin, and oral vancomycin.

Method of Administration

In fluid-restricted patients, administration of intravenous drug infusions with approved fluid volumes may be undesirable. When administration exceeds daily fluid restrictions, consider alternatives or more concentrated solutions if physiochemical parameters allow. Similarly, oral drug administration with large fluid volumes (e.g., bisphosphonates) may not be advisable. In patients with severe nausea and vomiting, essential immunosuppressants should be administered intravenously.

Drug Interactions

Pharmacokinetic drug interactions are frequently problematic, and awareness of clinically significant interactions is essential, especially with regard to patients receiving transplant immunosuppressants. The most important of these are cyclosporine, tacrolimus, everolimus, and sirolimus, which are substrates of both the CYP3A4 enzyme system and P-glycoprotein expressed in gastrointestinal mucosa and liver.[14] Co-prescription of drugs that inhibit these systems (e.g., some azole antifungals, calcium channel blockers (CCBs), macrolides, and grapefruit juice) can increase absorption and reduce metabolism of the immunosuppressant, causing toxicity. Conversely, drugs that induce these systems (e.g., barbiturates, phenytoin, carbamazepine, rifampin, and St John's wort *[Hypericum]*) can reduce absorption and increase metabolism and therefore increase the risk of rejection (Fig. 77-4 and Table 77-6). All drug changes in patients receiving transplant immunosuppression should be considered for their potential to interact, and appropriate dose modifications or alternatives used.

Clinical Condition of the Patient

The patient's welfare should override theoretical concerns. Higher-than-recommended doses may be appropriate when there is a strong clinical indication. For example, excessive reduction in initial antibiotic doses based on renal function may be inappropriate in patients with life-threatening infection when the consequences of failed therapy are greater than potential toxicity.

Methods of Dose Reduction

Loading Doses

For most drugs, steady-state concentrations are achieved after five drug half-lives. Hence, for some drugs, a loading dose is given to reduce time to steady state. Because renal impairment may prolong the half-life, simply reducing drug doses could be a therapeutic error

Common CYP3A4/P-gp–Mediated Interactions with Transplant Immunosuppressants (Cyclosporine, Tacrolimus, Sirolimus, and Everolimus)

Drug Class	Examples	Relative Potency
Drugs That Inhibit CYP3A4 and P-gp		
Macrolide antibiotics	Azithromycin	–
	Clarithromycin	+++
	Erythromycin	+++
	Roxithromycin	+
Azole antifungals	Fluconazole	+/–
	Itraconazole	++
	Ketoconazole	+++
	Voriconazole	+++
Calcium channel blockers	Amlodipine	+/–
	Nifedipine	+/–
	Felodipine	+/–
	Diltiazem	++
	Verapamil	+++
Herbals, foods	Grapefruit juice	++
Drugs That Induce CYP3A4 and P-gp		
Antiepileptics	Carbamazepine	++
	Phenytoin	+++
	Phenobarbitone	++
Antibiotics	Rifampin	+++
Herbals, foods	St John's wort	+++

Table 77-6 Common CYP3A4/P-gp–mediated drug interactions with transplant immunosuppressants (cyclosporine, tacrolimus, sirolimus, everolimus). *P-gp,* P-glycoprotein.

because this would further delay achievement of steady state. The loading dose (mg/kg) is equal to the product of the desired plasma concentration (mg/ml) and V_D (ml/kg) and is independent of clearance. Provided the desired concentration and V_D are unchanged, loading doses do not require modification in patients with renal impairment. In some instances, V_D is altered, especially with hypoproteinemia or fluid overload, and hence some clinicians alter the loading dose of drugs with a narrow therapeutic index such as digoxin. Aminoglycoside doses may need to be increased in patients with fluid overload or sepsis who have an increased V_D.

Maintenance Doses

When specific pharmacokinetic information is not available, and assuming no change in nonrenal clearance, maintenance doses should be reduced in proportion to the extent of renal impairment and renal drug elimination. For example, if renal function is 50% of normal and the drug is 100% renally excreted, a maintenance dose of 50% is required. If the drug is 50% renally cleared and the patient has 20% renal function, the dose should be 60% of normal. The dose reduction factor is estimated from first principles or the following formula:

$$\text{Dose rate in renal impairment/Dose rate in normal renal function} = (1 - \text{fe}) \times (1 - \text{Fraction of remaining renal function})$$

where fe is the fraction of active drug excreted unchanged in urine.

Once a dose reduction factor has been determined, the clinician must decide on a dose reduction method. Two methods are used, either alone or in combination (Fig. 77-5).

Interval Method Because drug clearance is reduced, a reduction in delivered dose is achieved by administering the same dose less frequently. This method is particularly useful when the size of the dose and peak blood concentrations are important for efficacy (e.g., aminoglycosides). If this method is used, practical dose intervals should be recommended rather than inconvenient or complex intervals.

Dose Method An alternative method is to administer a smaller dose at the usual interval. This method is common, especially when the size of a dose and peak concentrations are less critical for efficacy. If this method is used, clinicians should consider the availability of smaller dose formulations and the ability of the patient to accurately and safely divide available dosage forms.

Combination Method Sometimes, especially for drugs with a narrow therapeutic index, for which tight control of concentrations is required (e.g., digoxin), a combination of the dose and interval methods is used.

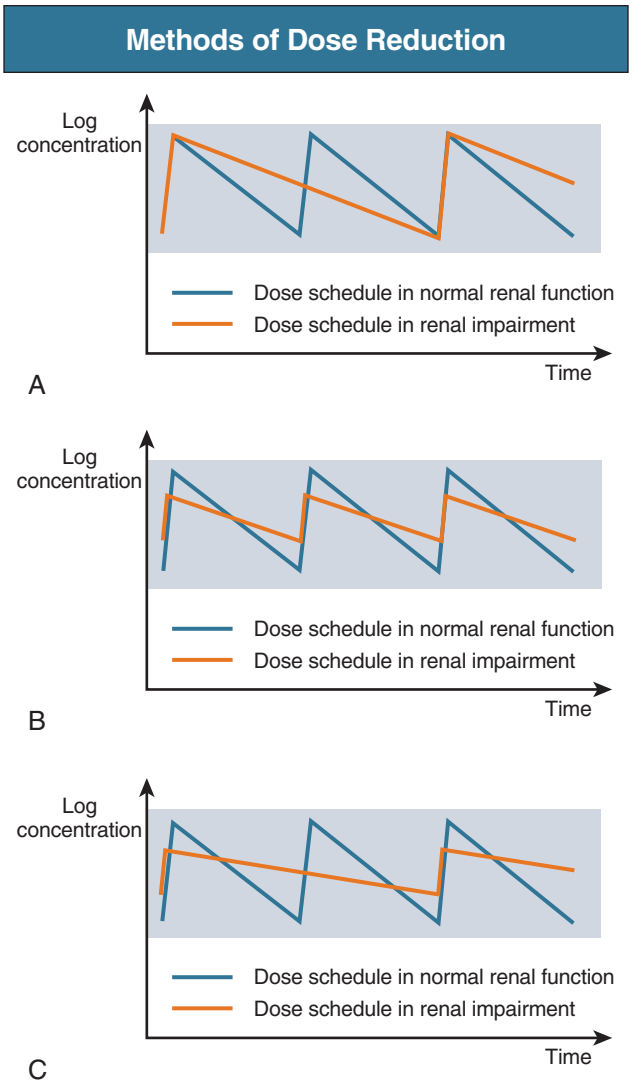

Figure 77-5 Methods of dose reduction. A, Interval method. **B,** Dose method. **C,** Combination method.

Ongoing Assessment

Even with appropriate dose modification in patients with renal impairment, clinicians should always remain vigilant and closely monitor the response to therapy to guide dose titration.

Therapeutic Drug Monitoring in Renal Impairment

Drug	Therapeutic Range and When to Draw Sample
Aminoglycosides	Peak (30 min after a 30-min infusion)
(24-h dosing)	Trough (6-12 h after dose)
Gentamicin	Peak: >10 mg/l
Tobramycin	Trough: depends on time after dose 0.5-2 mg/l
Amikacin	Peak: >30 mg/l Trough: depends on time after dose 1.5-6 mg/l
Immunosuppressants	
Cyclosporine	C_0 (trough): 150-250 µg/ml C_2 (2 h after dose): 1200-1500 µg/ml AUC_{0-4} >4400 µg/ml/h
Tacrolimus	C_0 (trough): 4-12 µg/ml
Sirolimus	C_0 (trough): 5-15 µg/ml
Antiarrhythmics	
Digoxin	0.8-2.0 µg/ml (trough at least 6 h after dose)
Lidocaine	1-5 µg/ml 8 h after IV infusion starts or is changed
Antipsychotics	
Lithium	Acute: 0.8-1.2 mmol/l (trough) Chronic: 0.6-0.8 mmol/l (trough)
Antiepileptics	
Carbamazepine	4-12 µg/ml (trough before administration)
Phenytoin	10-20 µg/ml (trough before administration)
Free phenytoin	1-2 µg/ml (trough before administration)
Phenobarbital	15-40 µg/ml (trough before administration)
Valproic acid	40-100 µg/ml (trough before administration)
Vancomycin	Trough: 10-20 mg/l

Table 77-7 Therapeutic drug monitoring in renal impairment. Target levels are dependent on assay methodology and clinical context. *IV,* Intravenous.

Therapeutic Drug Monitoring

Therapeutic drug monitoring can provide objective information to guide dosage calculation and is valuable for drugs such as aminoglycosides, glycopeptides, digoxin, lithium, antiepileptics, and immunosuppressants (Table 77-7). Assays usually measure total blood concentrations and may significantly underestimate plasma levels of the active or free form of the drug.

Clinical Response

Ultimately, clinical response should influence the need to modify doses. Doses should be carefully titrated according to response and adverse effects. For example, blood pressure for antihypertensives, blood glucose concentration and hemoglobin A1c (HbA1c) for oral hypoglycemics, and renal function for toxicity from CNIs, ACE inhibitors, and ARBs.

Extracorporeal Drug Losses

Failure to consider dialysis drug clearance may significantly reduce drug efficacy.[5,7] Alternatively, dialysis may be used in overdose to assist drug removal (see Chapter 98). Studies of drug clearance with RRT modalities have often used variations in dialysis technique that make it difficult to compare results. Many studies before the 1990s report data from standard hemodialysis (HD) with low-flux membranes, which are less efficient at drug removal than the high-flux membranes now widely used. Many recommendations report the need for supplemental doses. Clinically, supplemental doses are rarely used, especially if less than 30% of the drug is cleared or the drug has a wide therapeutic index. Rather, drugs known to be significantly cleared by dialysis should be administered after dialysis (Table 77-8). When drugs are given in multiple daily doses, at least one of the daily doses should be administered soon after the completion of dialysis.

Hemodialysis

Hemodialysis drug clearance occurs mainly by passive diffusion along a concentration gradient but also by convectional movement of soluble drug with ultrafiltrated plasma water.[7,15] The efficiency of drug removal depends on physiochemical drug properties. As molecular size decreases (<500 d) and water solubility increases, drug removal increases. Conversely, as protein binding and V_D increase, dialysis clearance decreases. HD factors influencing drug removal include membrane type and surface area, blood flow rates, and dialysis frequency and duration. HD can remove drug from plasma faster than it can redistribute from tissue, so drug concentrations determined from samples drawn soon after beginning or completion of HD may be low. Samples should preferably be drawn before dialysis or about 1 to 2 hours after to allow drug redistribution.

Peritoneal Dialysis

Many drug properties that affect removal by HD also apply to peritoneal dialysis (PD), but PD is usually less efficient.[16] For significant removal by peritoneal PD, the drug must have a very low V_D and low protein binding. For most drugs, there is little evidence of significant removal during chronic PD. A few studies have examined drug clearance from automated PD that uses large volumes of short dwells at night, often accompanied by one or more longer daytime dwells. Clearance of some drugs on automated PD is increased because of the increased drug concentration gradient between blood and dialysate. Increased drug dialyzability may occur with increased peritoneal dialysate flow rates or during peritonitis.

Continuous Renal Replacement Therapy

Drug clearance by continuous RRT (CRRT) with hemofiltration, HD, or hemodiafiltration differs from intermittent HD.[17] Relying on continuous ultrafiltration of plasma water, CRRT can remove large quantities of ultrafilterable drug. CRRT generally uses membranes with larger pore sizes and involves convective transport of solute. Hence, CRRT allows the passage of larger molecules (up to 5000 d). A large V_D and protein binding still prevent removal by CRRT. Protein binding and the device filtration rate determine the rate of removal. A series of sieving coefficients is available that allows calculation of the amount of drug actually lost if the ultrafiltration flow rate is known.[5] The sieving coefficient is the ratio of drug concentration in the ultrafiltrate to the prefilter plasma water drug concentration. The closer the sieving coefficient is to 1.0, the more it passes across the filter. There are few detailed studies of drug clearance with use of these methods, and clinicians must rely on estimates from HD, known physiochemical properties, and clinical response.

COMMON PRESCRIBING ISSUES IN CHRONIC KIDNEY DISEASE AND RENAL REPLACEMENT THERAPY

Anemia

Erythropoiesis-Stimulating Proteins

The pharmacokinetics of erythropoiesis-stimulating agents (ESAs) are not affected by renal function *per se.* However, as renal function

Dialysis Clearance of Commonly Prescribed Drugs

Drugs Significantly Cleared by Hemodialysis That Require Administration After Dialysis or a Supplement After Dialysis	Drugs Not Significantly Cleared by hemodialysis and That Do Not Require Administration After Dialysis or a Supplement After Dialysis or That Must Be Administered at Specific Times Independent of Hemodialysis
Analgesics	**Anemia**
Morphine 6-glucuronide (in toxicity)	Erythropoietins
Aspirin, high dose (contraindicated)	Iron
Antibiotics	**Analgesics**
Aminoglycosides	Morphine
Amikacin	Paracetamol
Gentamicin	Fentanyl
Tobramycin	Oxycodone
Cephalosporins	NSAIDs
Cefotaxime	**Antibiotics**
Cefazolin	Penicillins
Ceftazidime	Amoxicillin
Carbapenems	Flucloxacillin
Imipenem	Fluoroquinolones
Meropenem	Moxifloxacin
Metronidazole	Rifamycins
Penicillins	Rifampin
Amoxicillin	Rifabutin
Ticarcillin	Glycopeptides
Piperacillin	Vancomycin (oral or "low flux")
Fluoroquinolones	Tetracyclines
Ciprofloxacin	Tetracycline
Glycopeptides	Doxycycline
Vancomycin (high-flux dialyzers)	Minocycline
Teicoplanin	**Antifungals**
Miscellaneous antibiotics	Amphotericin
Ethambutol	Voriconazole
Cotrimoxazole	Ketoconazole
Antifungal	Itraconazole
Fluconazole	**Antiviral**
Antivirals	Amphotericin
Acyclovir	**Antiepileptic**
Cidofovir	Carbamazepine
Famciclovir	**Cardiovascular Agents**
Foscarnet	Amiodarone
Ganciclovir	Perhexiline
Ribavirin	Nitrates
Valganciclovir	**Anticoagulants**
Zidovudine	Heparin
Antineoplastics	Warfarin
Cyclophosphamide	LMWHs
Methotrexate	**Antiplatelet Drugs**
Anticoagulant	Low-dose aspirin
Lepirudin	Clopidogrel
Antiepileptics	Dipyridamole
Gabapentin	**Immunosuppressants**
Pregabalin	Azathioprine
Levetiracetam	Cyclosporine and tacrolimus
Cardiovascular Agent	Mycophenolate
Sotalol	Prednisolone
Antidiabetic	Sirolimus and everolimus
Metformin (in overdose)	T cell–depleting antibodies
Vitamins	Rituximab
Water-soluble B, C, and folate	Anti-CD25 antibodies
Psychotropic	**Antidiabetics**
Lithium	Sulfonylureas
	Musculoskeletal Agents
	Bisphosphonates
	Antiepileptics
	Sodium valproate
	Carbamazepine
	Antidepressants
	SSRIs (administer in morning)
	Vitamins
	Fat-soluble vitamins A, D, E, K

Table 77-8 Dialysis clearance of drugs. *LMWHs,* Low-molecular-weight heparins; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *SSRIs,* selective serotonin reuptake inhibitors.

decreases, their dose may need to be increased to account for reduced endogenous erythropoietin production. The use of ESAs is discussed further in Chapter 83.

Iron Therapy

Oral supplements may be sufficient in the early stages of CKD or in PD patients who do not have the same degree of regular blood loss as HD patients. Maximum absorption of oral iron occurs with frequent administration of small doses away from food, although gastrointestinal intolerance limits therapy. It is important to avoid interactions with drugs whose absorption is affected by oral iron. Patients with severe iron deficiency and those on HD often require intravenous supplementation (see Chapter 83).

Analgesics

Various analgesics (or their metabolites) undergo renal excretion or are nephrotoxic, and dose modification or avoidance is required.[20,21] Fear of adverse effects often prevents use of sufficient doses to manage pain appropriately. Adequate initial doses should be followed by careful assessment and dose titration.

Acetaminophen (Paracetamol)

Despite suggestions that acetaminophen may be nephrotoxic, lack of platelet inhibition and gastrointestinal irritation makes it a safer base analgesic in the settings of CKD and RRT than NSAIDs and opioids. Acetaminophen is hepatically metabolized and does not require dose adjustment.

Opioid Analgesics

Opioids have metabolites with variable activity and dependence on renal excretion.[22,23] Metabolite accumulation in patients with renal impairment prolongs drug action and predisposes to central nervous system (CNS) toxicity (sedation, respiratory depression, confusion, hallucinations, and seizures), which is often difficult to distinguish from uremic symptoms. Regular opioid use in fluid-restricted renal patients can exacerbate constipation. Opioids should be used cautiously in patients with renal impairment, with adequate doses given to establish control and titrated to the smallest effective dose for the shortest period.[24] Morphine is metabolized to two renally cleared active metabolites (morphine 3-glucuronide and morphine 6-glucuronide). Their accumulation in patients with renal impairment may be responsible for CNS toxicity, respiratory depression, and sedation.[25] Morphine is best avoided, but if it is essential, then significant dose reduction is recommended. Meperidine (pethidine) is metabolized to a renally cleared metabolite (normeperidine) that can cause CNS toxicity (seizures, myoclonus, mental state changes, respiratory depression, and psychosis).[26] It should be avoided in patients with moderate to severe renal impairment. Dextropropoxyphene should be avoided because it is metabolized to the renally cleared metabolite norpropoxyphene, which can cause cardiac toxicity. Hydromorphone is metabolized to hydromorphone 3-glucuronide, which has minor activity and does not accumulate substantially. Buprenorphine is metabolized to relatively inactive metabolites, which are excreted in bile, and is relatively safe. Weaker opioids (codeine, dihydrocodeine, and hydrocodone) can still cause CNS and respiratory depression. They should be avoided or used cautiously in patients with severe renal impairment. With appropriate titration, alfentanil, fentanyl, sufentanil, methadone, and oxycodone are relatively safer choices because they do not have significantly active metabolites. The partial opioid tramadol is metabolized to a renally cleared active metabolite, *O*-desmethyltramadol; its half-life doubles in patients with renal impairment and it predisposes patients

to seizures, respiratory depression, and other CNS adverse effects. In patients with opioid intoxication, naloxone may be used at normal dose for reversal.

Nonsteroidal Anti-inflammatory Drugs

The most frequent nephrotoxic effect of NSAIDs is to cause acute renal impairment by preventing renal prostaglandin-mediated afferent arteriolar vasodilation (see Chapter 69). In healthy individuals, cyclooxygenase (COX) inhibition has little effect on renal function. Nephrotoxicity is more likely in those with a high renin state or renal hypoperfusion, in whom renal prostaglandins are upregulated and play a supportive role in maintaining glomerular filtration. Use of NSAIDs with ACE inhibitors, ARBs, diuretics, or antihypertensives increases the potential for nephrotoxicity, and these combinations should be prescribed cautiously. When essential, NSAIDs should be used at the lowest effective dose for the shortest period with monitoring of renal function. Increases in potassium, sodium, and fluid retention may also occur.

Nonsteroidal anti-inflammatory drugs can cause a rare idiosyncratic nephritis that may present with acute interstitial nephritis or nephrotic syndrome with minimal change disease.[27] NSAIDs have also been associated with renal papillary necrosis and other pathologic changes during long-term administration. Because COX-2 is expressed in the kidney, COX-2–selective agents offer no advantage in renal toxicity over nonselective inhibitors.[28] The potential for cardiovascular complications of COX-2 inhibitors is also undesirable in renal patients at high risk for cardiovascular disease.

Drugs for Neuropathic Pain

Low-dose tricyclic antidepressants are used at normal doses, although renal patients may be more sensitive to anticholinergic side effects. Low-dose valproate and carbamazepine are used at normal doses. Extreme caution is required with gabapentin[29] and pregabalin[30] because they are extensively renally cleared and can cause significant CNS adverse effects (somnolence, lethargy, dizziness, and ataxia).

Antihistamines

Normal doses of sedating antihistamines can be used initially with titration based on response and typical cholinergic side effects to which renal patients may be more susceptible. Sedating antihistamines should be used cautiously in patients with bladder outflow obstruction because they may cause or aggravate urinary frequency or retention. Newer, less sedating antihistamines are better tolerated and have a wider therapeutic index, and accumulation rarely causes significant complications during short-term treatment. Cetirizine relies more on renal clearance, and dose reduction is suggested. Loratadine and desloratadine have active metabolites but are safe. Fexofenadine is safe; however, terfenadine should be avoided because of the risk of arrhythmias.

Anti-infective Agents

The kidneys excrete many anti-infectives, and dose reduction is often required in patients with severe impairment or who are undergoing extended therapy. Many anti-infectives have a wide therapeutic index, and dose adjustment is clinically unnecessary despite their reliance on renal excretion. An important principle of anti-infective dosage in patients with renal impairment is to initiate effective drugs at sufficient doses. Excessive dose reductions may fail to achieve effective drug concentrations. Normal doses or doses larger than expected on the basis of renal function may be appropriate in treating less susceptible organisms and when drug distribution to the site of infection is reduced (e.g., in meningitis). Normal loading doses may be appropriate to achieve therapeutic concentrations. More severe infection, particularly in severely immunocompromised patients, may require extended therapy. In patients with urinary tract infection, if GFR is below 30 ml/min and the drug does not undergo tubular secretion, inadequate renal tract concentrations may result and systemic accumulation could lead to toxicity. Nitrofurantoin becomes ineffective in patients with advanced renal impairment,[31] and accumulation causes peripheral neuropathy. Anti-infective prescribing for urinary tract infection is discussed further in Chapter 53.

Antibacterials

Variations in pharmacokinetics of antibiotics in patients with impaired renal function have significant impacts on clinical care.[32]

Aminoglycosides

Aminoglycosides are extensively excreted unchanged by the kidneys and can cause nephrotoxicity and ototoxicity.[33] When use is essential, the total daily dose should be reduced, treatment courses kept to a minimum, and serum concentrations and renal function monitored closely. Because aminoglycosides undergo tubular secretion, high urine concentrations are achieved even in patients with advanced renal impairment, and lower doses may be appropriate for uncomplicated urinary tract infections.

Aminoglycoside Dosage Schedules Despite short half-lives (2 to 3 hours with normal renal function), aminoglycosides are usually given once daily rather than in divided daily doses for most indications. This is based on data showing that their action is dependent on peak concentration and that once-daily regimens have reduced toxicity. The required dose regimen depends on V_D and renal clearance. Dosage calculation in renal impairment first involves reducing the normal daily dose (5 to 7 mg/kg for gentamicin and tobramycin or 15 mg/kg for amikacin) according to renal function (e.g., with 25% remaining renal function, reduce the total daily dose to 25% of normal). Because of their peak concentration–dependent activity, aminoglycosides should be administered at a minimum effective dose (≥2.5 mg/kg for gentamicin and tobramycin; ≥7.5 mg/kg for amikacin) to achieve target peak serum concentrations (>10 μg/ml for gentamicin and tobramycin; >30 μg/ml for amikacin). The calculated reduced normal daily dose might be lower than the minimum individual dose required to achieve target peak concentrations. If this is true (e.g., with moderate to severe renal impairment), it may be necessary to administer the minimally effective dose at an extended interval (e.g., every 36 or 48 hours) rather than reducing the size of the individual dose. Although use of longer administration intervals (>48 hours) is a common practice, its efficacy relies on a postantibiotic effect, and it is uncertain whether this effect lasts for extended dosage schedules.

Aminoglycoside Concentration Monitoring Because of pharmacokinetic variability in patients with infection and renal impairment as well as toxicity, monitoring is essential to guide calculation of aminoglycoside dosage. It is particularly important at the initiation of therapy or when significant changes occur in renal function or clinical condition. Routine monitoring is not required for short treatment (less than 48 hours). Graphic methods that use a single-point concentration 6 to 14 hours after administration are valid only with relatively normal renal function. They do not provide information on attainment of peak concentrations and are not recommended in patients with renal impairment. Trough concentrations can be measured but must be interpreted in the context of the time after the dose when the sample was drawn. Trough monitoring does not

provide information on the attainment of peak concentrations and may be below the limit of quantification of some assays. Some patients, especially those with severe sepsis and renal impairment, may have altered (usually higher) V_D, which results in lower peak concentrations. Measuring peak concentrations (30 minutes after dosing) is the only certain way to determine if adequate peak concentrations have been achieved and to assist in determining the size of subsequent doses. Combining peak and trough monitoring provides information on both V_D and clearance and can therefore be used to determine both the size of individual doses and the administration interval. Provided the relationship between the time of administration and blood sampling is known, simple dose modifications are made on first principle estimates (see the earlier discussion of methods of dose reduction).

Carbapenems

Ertapenem, doripenem, imipenem,[34] and meropenem[35] are significantly excreted in urine but with appropriate dose modification can be used safely. Imipenem can cause significant neurotoxicity (myoclonic activity, seizures, and confusion), especially in high doses in those with underlying CNS disorders or renal impairment. Meropenem and doripenem may be preferable because they appear less neurotoxic. Imipenem is inactivated by renal dehydropeptidase 1 and is combined with cilastatin to prevent this.

Cephalosporins

Despite the fact that cephalosporins are predominantly renally cleared, the relative safety of many of them means that normal doses are used for short-course therapies even in dialysis patients (e.g., ceftriaxone, cefaclor, and cephalexin). High-dose parenteral therapy and prolonged courses of some agents require dose reduction in patients with severe impairment. Reduction is suggested in patients with severe impairment for cefepime,[36] cefotaxime,[37] ceftazidime,[38] cefoxitin, and cefazolin.[39] Therapeutic concentrations of cefazolin are maintained after doses of 20 mg/kg (approximately 2 g) after dialysis three times weekly.[40] Some cephalosporins cause a creatinine-like reaction in assays based on the picrate method. This can falsely elevate serum creatinine and be mistaken for nephrotoxicity.[41]

Fluoroquinolones

Renal excretion is significant with ciprofloxacin, norfloxacin, and gatifloxacin, and doses should be halved if GFR is below 30 ml/min.[42,43] Moxifloxacin is 20% renally excreted, and dose reduction is not required. Norfloxacin is well secreted by kidneys and useful in urinary tract infections. Quinolones are generally well tolerated but can cause CNS effects (headache, dizziness, insomnia, depression, restlessness, and tremors), interstitial nephritis, and crystalluria. Fluids should be encouraged (if tolerated) and excessively alkaline urine avoided to prevent crystalluria. Quinolone absorption is reduced when the drug is coadministered with compounds containing metals such as magnesium, calcium, aluminum, and iron, and therefore they should be administered away from meals and metallic phosphate binders.[9]

Glycopeptides

Glycopeptides (vancomycin and teicoplanin) are extensively renally excreted. Because of potential nephrotoxicity and ototoxicity, dose modification is essential even in mild to moderate impairment. Nephrotoxicity is greater in those with renal impairment, prolonged therapy, high doses, and concomitant nephrotoxins. Nephrotoxicity may be less common with teicoplanin. Ototoxicity may involve sensorineural deafness and tinnitus. Permanent deafness is more likely with previous auditory compromise or impaired renal function. If glycopeptides are essential, duration of therapy should be minimized, with regular monitoring of serum concentrations and renal function. Glycopeptides demonstrate time-dependent antibacterial activity, so dosage calculation should be repeated once serum concentrations have fallen below minimum inhibitory concentrations. In dialysis patients, single doses (e.g., 1 g) of vancomycin maintain therapeutic concentrations (>15 μg/ml) for 3 to 5 days.[44] Vancomycin is removed more extensively with high-flux than with low-flux dialysis membranes.

Lincosamides

Lincosamides (e.g., clindamycin and lincomycin) are relatively safe and are not significantly excreted by the kidneys. A significant adverse effect is pseudomembranous colitis. If this occurs, the drug should be stopped. Fluid management and treatment with oral metronidazole or vancomycin are required to prevent hypovolemia and electrolyte disturbances.

Macrolides

Macrolides are mostly hepatically cleared, and dose modifications are usually not required even in patients with end-stage renal disease (ESRD). Dose reduction is required with high-dose or intravenous erythromycin,[45] which may prolong the QT interval and cause ototoxicity. Various macrolides are potent inhibitors of CYP3A4 and P-glycoprotein, so there may be major interactions with and increased exposure to coadministered drugs that rely on CYP3A4- or P-glycoprotein–mediated absorption and metabolism (cyclosporine, tacrolimus, sirolimus, everolimus, and statins). Erythromycin and clarithromycin are the most potent inhibitors, and dose modification of the concomitant drug is required. Roxithromycin is a much weaker inhibitor and usually causes little or no clinically significant interactions. Azithromycin does not interact.

Penicillins

Most penicillins have a short half-life and are rapidly eliminated by renal filtration and secretion. Most have a relatively wide therapeutic window and are used at normal doses for short courses of oral therapy. High-dose parenteral therapy or prolonged high-dose oral therapy may require dose reduction to prevent electrolyte disturbances and neurotoxicity in patients with advanced renal failure. Because most penicillins exert little or no postantibiotic effect, the amount of time above the minimum inhibitory concentration is more important than the maximum concentration. Severe reductions in frequency of administration are not advised. Dose reduction of ticarcillin-clavulanate[46] and piperacillin is advised.

Rifamycins

Rifamycins are mainly hepatically metabolized and used at normal doses. Orange-red coloration of body fluids (e.g., urine and PD fluid) is common. Infrequently, these agents cause hepatotoxicity and blood dyscrasias. Rifampin is a potent enzyme inducer and significantly increases metabolism of drugs, including immunosuppressants. Although structurally similar, rifabutin does not induce CYP450 enzymes to the same extent.

Tetracyclines

Tetracycline depends more on renal excretion than do doxycycline and minocycline. In patients with renal impairment, tetracycline is antianabolic causing uremia, hyperphosphatemia, and metabolic acidosis; it may also aggravate preexisting renal failure.[47] Tetracycline should be avoided in renal impairment; however, doxycycline, minocycline, and tigecycline are not antianabolic and may be used as usual. Nephrotoxicity has occurred in association with acute fatty

liver with high-dose tetracyclines. Degraded tetracycline (anhydro-4-epitetracycline) may result in renal tubular damage and a Fanconi-like syndrome.

Sulfonamides and Trimethoprim

Most sulfonamide use is accounted for by cotrimoxazole (sulfamethoxazole in a 5:1 combination with trimethoprim). Sulfonamides are eliminated by acetylation followed by renal excretion. Acetylated metabolites may cause crystalluria and tubular damage. Sulfamethoxazole and trimethoprim display similar renal excretion except at extremes of urine pH. Alkaline urine promotes sulfamethoxazole excretion, whereas acidic urine promotes trimethoprim excretion. Accumulation of both occurs in renal impairment,[48] and dose reduction is advisable except perhaps in the initial treatment of *Pneumocystis jiroveci* infection, in which the risk of toxicity is balanced against the seriousness of infection. Trimethoprim inhibits tubular secretion of creatinine, resulting in a reversible increase in serum creatinine[49] that can be misinterpreted as trimethoprim nephrotoxicity.

Other Antibiotics

Linezolid is used at a normal dose. Metronidazole has a partially active, renally cleared metabolite, although only 15% of the parent drug is renally cleared. It is usually given in usual doses or reduced to twice-daily doses with dialysis.[50]

Antimycobacterials

Antimycobacterial treatment (see also Chapter 54) requires dose modification according to renal function and avoidance of drug interactions.[51] Ethambutol is significantly renally cleared (80%) and has a prolonged half-life in patients with renal impairment. Dose reduction is essential to avoid visual toxicity. Isoniazid, pyrazinamide, and rifampin-rifabutin can be given in usual doses. Rifampin causes induction of hepatic enzymes and severe drug interactions with transplant immunosuppressants. Of the second-line agents, amikacin, kanamycin, streptomycin, capreomycin, and gatifloxacin are extensively renally cleared, are nephrotoxic, and require significant dose reduction.

Antifungals

Amphotericin

Amphotericin use is limited by nephrotoxicity (see Chapters 55 and 69). Nephrotoxicity with crystalline amphotericin may be minimized with prehydration and administration by continuous infusion. Newer liposomal formulations have fewer infusion-related problems and are less nephrotoxic[52] but more expensive. In maintenance dialysis patients who do not have potential for further clinically significant loss of renal function, liposomal or lipid preparations offer no major advantage except a lower incidence of infusion reactions. Oral amphotericin is not absorbed and does not contribute to nephrotoxicity.

Azole Antifungals

Most azole antifungals (ketoconazole, itraconazole, and voriconazole) are extensively metabolized and do not require dose reduction. Fluconazole[53] is renally excreted; after an adequate loading dose, maintenance doses should be reduced in patients with moderate to severe renal impairment, and it should be given after dialysis. Fluconazole is significantly excreted in urine and therefore preferred for fungal urinary tract infections. The manufacturer recommends avoiding intravenous voriconazole because of possible accumulation of the intravenous vehicle (sulfobutyl betadex sodium). Ketoconazole and itraconazole require an acidic environment for absorption. Given the widespread use of acid suppressants in renal impairment, this is a clinically important interaction. Voriconazole, ketoconazole, and itraconazole are potent inhibitors of CYP3A4 and P-glycoprotein, which are involved in the metabolism and absorption of a variety of drugs, including cyclosporine, tacrolimus, sirolimus, everolimus, and statins. A twofold to 10-fold reduction of the concomitant drug may be required with drug monitoring; however, the magnitude of interaction may restrict the ability to use the concomitant drug. Interactions between ketoconazole and CNIs or mammalian target of rapamycin (mTOR) inhibitors have been exploited as a cost-reducing, "immunosuppressant-sparing" strategy. Increased exposure to statins (except pravastatin) increases the risk of rhabdomyolysis-induced renal impairment. Fluconazole is a weak enzyme inhibitor, and although caution should be exercised, the need for preemptive dose reduction of concomitant drugs is less certain. Topical azoles including bifonazole, clotrimazole, econazole, ketoconazole (topical), tinidazole, and miconazole are minimally absorbed and do not cause interactions.

Other Antifungals

Absorption of nystatin from topical and oral preparations is minimal and safe in patients with renal impairment. Terbinafine is hepatotoxic, and dose reduction of 50% is suggested in patients with moderate to severe renal impairment. Griseofulvin and caspofungin can be given in usual doses. Flucytosine[54] is extensively renally cleared and requires dose reduction. These agents do not interfere with CYP450 enzymes or P-glycoprotein.

Antivirals

Many antivirals (or their active metabolites) are extensively renally excreted and can cause nephrotoxicity (see Chapter 69).

Guanine Analogues

Acyclovir, its prodrug valacyclovir, and famciclovir[55] are extensively renally cleared and can crystallize in tubules, causing obstructive uropathy. High concentrations cause severe CNS toxicity (cerebral irritation, ataxia, and myoclonus). Ganciclovir and its prodrug valganciclovir are extensively renally cleared,[56] and accumulation leads to severe bone marrow toxicity. Strict dose reduction based on renal function is essential, even in mild renal impairment. All these agents are freely dialyzed and should be given after HD.

Hepatitis B and C

Pegylated interferon alfa-2a has a larger metabolic clearance than pegylated interferon alfa-2b,[57] which has higher renal clearance and requires dose reduction in patients with renal impairment. Interferons can upregulate cell surface expression of class II histocompatibility antigens, which increases the potential for transplant rejection. Ribavirin and its metabolites rely on renal excretion, and accumulation causes severe anemia; therefore ribavirin is contraindicated if GFR is below 50 ml/min. Adefovir,[58] entecavir, lamivudine,[59] and telbivudine[60] are extensively renally excreted, and significant dose reduction is essential.

Neuraminidase Inhibitors

Oseltamivir is converted by hepatic esterases to its active metabolite, oseltamivir carboxylate, which is extensively (99%) renally cleared through filtration and secretion.[61] AUC is increased 10-fold in patients with severe renal impairment (GFR <30 ml/min). Although the drug is well tolerated, doubling the dosage interval is

recommended in patients with GFR <30 ml/min. Despite the fact that intravenous doses show significant reliance of zanamivir on renal clearance, dose modification is not necessary because absolute bioavailability from inhaled doses is approximately 2% and high intravenous doses are well tolerated.[61]

Other Antivirals

Cidofovir[62] and foscarnet[63] are extensively renally cleared and require dose reduction in patients with renal impairment. Both are nephrotoxic, require close monitoring of renal function, and should be administered with hydration. Cidofovir is often administered with probenecid to slow renal secretion and to minimize nephrotoxicity.

Anticoagulants, Antiplatelet Agents, Thrombolytics, and Hemostatics

The risk of bleeding complications with anticoagulants, antiplatelet agents, thrombolytics, and hemostatics is increased in patients with CKD and ESRD.[64,65]

Unfractionated Heparin

Unfractionated heparin (UFH) clearance occurs by a rapid saturable mechanism of the endothelium and reticuloendothelial system and a slower nonsaturable mechanism through the kidneys.[64,66] Half-life is slightly prolonged (1.5-fold) in patients with renal impairment, especially at higher doses, when renal elimination is more significant. However, UFH is initially used at normal dose with titration based on activated partial thromboplastin time monitoring. In some centers, UFH is preferred in patients with severe renal impairment because its effect is shorter and more easily measured and reversed.

Low-Molecular-Weight Heparins

Low-molecular-weight heparins (LMWHs) rely more on renal clearance than UFH, and in patients with moderate to severe renal impairment they accumulate, increasing the risk of serious bleeding.[67] Strong consideration should be given to the use of UFH in this setting. Some studies suggest that enoxaparin does not need dose reduction in the first 48 hours of therapy and that tinzaparin is less likely to accumulate. If prolonged treatment doses of LMWHs are used, the dose should be reduced and, if possible, anti-Xa activity measured to guide therapy.

Other Parenteral Anticoagulants

Other anticoagulants that accumulate in patients with renal impairment and that should be avoided or used with significant dose reduction include bivalirudin,[68] danaparoid,[69] fondaparinux,[70] lepirudin,[71] ximelagatran,[72] and melagatran.[72] Argatroban may be used at normal dose.[73] Prostacyclin, used to prevent platelet aggregation in HD circuits, is rapidly hydrolyzed and not affected by renal impairment.

Oral Anticoagulants

The liver extensively metabolizes warfarin. In patients with renal impairment, it is usually commenced at normal dose and titrated according to the international normalized ratio. Warfarin is highly protein bound, and in renal patients with hypoalbuminemia there may be increased sensitivity to warfarin.[74] Similarly, hepatic metabolism may be altered with renal impairment, increasing sensitivity.[75] Warfarin dosage in patients with advanced CKD becomes difficult given that CKD is often accompanied by vitamin K deficiency. In addition, warfarin promotes vascular calcification and should be avoided in patients with advanced CKD unless absolutely necessary—for example, in the presence of a mechanical heart valve.

Antiplatelet Drugs

Commonly prescribed doses of oral antiplatelet drugs (aspirin, clopidogrel, and dipyridamole) do not require adjustment. Despite their efficacy in patients with reduced renal function, eptifibatide[76] and tirofiban are renally excreted and have been associated with bleeding in this setting. Abciximab is cleared by platelet binding and is not associated with increased bleeding risk in patients with renal impairment.

Thrombolytics

Streptokinase, anistreplase, and alteplase are used as normal, but the high risk of hemorrhage should be considered. Urokinase is also used to unclot dialysis catheters.

Hemostatics

Tranexamic acid requires dose reduction in patients with moderate to severe renal impairment. Protamine and vitamin K are used as normal, as are fresh frozen plasma and whole blood with critical bleeding.

Diuretics

Diuretics must reach the renal tubule lumen unbound to exert an effect.[77] Pharmacokinetic and pharmacodynamic properties of diuretics can change with proteinuria or renal impairment, usually causing a resistance to their effect.[77] Tubular secretion of various organic acid diuretics is reduced because of competition from uremic organic acids. Diuretics, in particular loop diuretics, must be used cautiously in patients with AKI or renal hypoperfusion to avoid nephrotoxicity. Diuretic use in the immediate post-transplantation setting may increase urine flow in native kidneys, giving a false appearance of transplant function.

Thiazide Diuretics

Thiazide diuretics generally become ineffective as diuretics when GFR is below 30 ml/min, although they may augment the effectiveness of a loop diuretic and retain their antihypertensive effects. Metolazone can maintain efficacy at a lower GFR.

Loop Diuretics

Loop diuretics (furosemide, bumetanide, torsemide, and ethacrynic acid) remain effective at low GFR and are generally the preferred diuretics in patients with renal impairment, although higher doses are usually required.

Potassium-Sparing Diuretics

Potassium-sparing diuretics are the least effective diuretics and should be used only with great caution and at low dosage in patients with moderate to severe renal impairment because of the risk of life-threatening hyperkalemia.

Antihypertensives

Antihypertensives should be used cautiously to avoid renal hypoperfusion.[78] Hypotension from HD may require that doses be withheld or delayed on dialysis days.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Although various ARBs and the active metabolites of ACE inhibitors are renally excreted, they can be used effectively in patients with CKD if initiated at moderate doses and titrated cautiously to response, renal function, and serum potassium level. An increase in

serum creatinine (up to 20% to 30% in the first 2 months) may be associated with blood pressure response. All ACE inhibitors and ARBs can cause acute renal impairment by inhibiting angiotensin II–mediated homeostatic vasoconstriction of the efferent renal arteriole during renal hypoperfusion (e.g., with dehydration, hypotension, blood loss, and infection) or preexisting renal impairment (see also Chapter 69). Nephrotoxicity is more likely with coadministration of drugs that reduce renal perfusion including diuretics, antihypertensives, and NSAIDs.[79] Hyperkalemia is more likely in those with renal impairment and those taking potassium-sparing diuretics or supplements. Rarely, ACE inhibitors or ARBs can worsen anemia.

β-Blockers

Most β-blockers (carvedilol, labetalol, metoprolol, pindolol, and propranolol) are hepatically metabolized and used at normal doses according to response. Sotalol[80] and atenolol[81] rely on renal clearance, and dose reduction and titration are essential, although atenolol can be titrated up to normal doses even in dialysis patients. β-Blockers may slightly elevate serum potassium.

Calcium Channel Blockers

Pharmacokinetic parameters of CCBs are essentially unaltered in patients with renal impairment. These drugs are generally well tolerated and used in normal doses according to response. Dihydropyridine CCBs can cause significant edema, which can aggravate the edema of renal impairment. To varying extents, CCBs inhibit CYP3A4 and P-glycoprotein, causing increased absorption and reduced elimination of various substrate drugs, including cyclosporine, tacrolimus, sirolimus, and everolimus. Verapamil and diltiazem are moderately potent inhibitors, and dose modification and monitoring of the concomitant drug are required. This interaction has been exploited so that the CCB is used as an immunosuppressant-sparing agent.[82] Other CCBs do not usually cause clinically significant changes in concomitant drug concentrations, and dose modification is usually not required.

Other Antihypertensives

Methyldopa, clonidine, prazosin, terazosin, doxazosin, and minoxidil are renally cleared but can be initiated and titrated at conventional dosage. They are often associated with a higher incidence of adverse effects in patients with renal impairment. α-Blockers cause profound orthostatic hypotension. Nitroprusside must be used cautiously because the toxic metabolite thiocyanate may accumulate with renal impairment but is hemodialyzable.[83]

Antianginal Agents

Most antianginals (nitrates, CCBs, nicorandil, and perhexiline) can be used as normal.

Antiarrhythmics

Various antiarrhythmics (digoxin, disopyramide, procainamide,[84] and sotalol[80]) rely on renal excretion and require dose modification. Digoxin is commonly used, and because of its significant reliance on renal excretion and narrow therapeutic window, dose reduction is essential even in patients with mild impairment. Because of reduced tissue protein binding and V_D, some physicians use a smaller loading dose of digoxin than in patients with normal renal function. Cautious monitoring and titration should be exercised to prevent accumulation and further toxicity. When possible, monitoring of antiarrhythmic drug concentrations and the electrocardiogram is recommended. Other agents (amiodarone, flecainide, metoprolol, mexiletine, and verapamil) are used at normal doses.

Lipid-Lowering Agents

Bile Acid–Binding Resins

Bile acid–binding resins are now rarely used. The large fluid volumes required to administer them limit their use. They can interfere with absorption and enterohepatic recirculation of various drugs, including mycophenolate.

Statins

Statins (HMG-CoA reductase inhibitors) can be used effectively in patients with renal impairment and those who have undergone transplantation.[85] Most are extensively metabolized to products with varying activity; however, normal doses may be used in the first instance and titrated to target cholesterol values. Rhabdomyolysis with acute renal impairment can occur, although the risk does not appear to be greatly increased with renal impairment. The risk increases with use of fibrates and drugs that inhibit the CYP3A4 metabolism of statins. Patients commencing therapy should have lipids, renal function, and creatine kinase monitored regularly.

Fibrates

Fenofibrate but not gemfibrozil is extensively renally excreted, and dose reduction is required. Combination of statins and fibrates significantly increases the risk of rhabdomyolysis and should be used only when benefits outweigh risks and with monitoring for muscle symptoms, creatine kinase, and alanine aminotransferase.

Diabetes

The kidney plays an important role in insulin metabolism,[86] and thus renal function influences glycemic control. Diabetes is also common after transplantation because of resumption of insulin metabolism by the functioning transplant and the effect of drugs (tacrolimus and corticosteroids). Various antidiabetic drugs (or their metabolites) depend on renal excretion, and accumulation in patients with renal impairment can cause adverse effects.[87] Patients with renal impairment are at markedly increased risk of hypoglycemia, and drugs should be initiated and titrated cautiously.[88] Management of diabetes in patients with CKD is discussed in Chapter 32.

Diabetes Management in Peritoneal Dialysis

Peritoneal dialysis patients may have higher antihyperglycemic requirements because of the glucose load in PD fluid. If intraperitoneal insulin is used, dosages may vary from intravenous requirements. Icodextrin solutions can significantly interfere with blood glucose monitoring because of metabolites (maltose, maltotriose, or maltotetraose) that falsely elevate blood glucose readings as a result of monitors that use the enzyme glucose dehydrogenase pyrroloquinoline quinone. A glucose-specific test strip is required to avoid interference.

Biguanides

Metformin is excreted almost entirely unchanged in urine, and accumulation can contribute to severe or fatal lactic acidosis (see Chapter 32).[89] Metformin should be temporarily discontinued in situations known to increase the risk of lactic acidosis or to reduce renal function (e.g., acute tissue hypoxia, dehydration, serious infection or trauma) and 24 to 48 hours before anticipated surgery or use of iodinated radiocontrast media. Although metformin is not

usually recommended if GFR is below 60 ml/min and certainly below 30 ml/min, low-dose protocols may be considered in a specialized setting. Nevertheless, stability of a patient with renal impairment receiving low-dose metformin does not abolish the risk of lactic acidosis. Lactic acidosis has occurred with doses of 500 mg/day, and any acute deterioration in renal function can result in reduced drug clearance at any time. Patients on this regimen should be advised to seek early medical advice in any cases of acute deterioration in health.

Insulin

As renal function decreases, insulin clearance decreases. Uremia, however, can cause peripheral resistance to insulin, requiring increased doses. Most insulin regimens can be used in patients with CKD or transplantation with cautious titration and monitoring. Theoretically, insulin glargine is preferable to insulin detemir because the latter is highly bound to serum albumin, and in patients with decreased or unstable serum albumin, a higher free fraction may occur.

Meglitinides

The nonsulfonylurea insulin secretagogues repaglinide and nateglinide can be used in patients with renal failure without dose adjustment.

Sulfonylureas

Sulfonylureas are metabolized and some (glibenclamide and glimepiride) have active, renally excreted metabolites. In patients with moderate to severe renal impairment, hypoglycemic risk is increased.[90] These agents should be initiated at low dose and titrated to response. Gliclazide and glipizide are preferable because they do not have active metabolites. Regardless of which agent is used, the effect of sulfonylureas may still be increased because the insulin released by the drug will itself have a prolonged duration of action in patients with renal impairment.

Thiazolidinediones

Thiazolidinediones are extensively metabolized and excreted in bile. Their pharmacokinetics are not significantly altered by renal impairment and in fact show reduced exposure, possibly because of reduced protein binding.[91,92] However, they can cause fluid retention and edema, exacerbating the difficulties of fluid management and heart failure.[87] Thiazolidinediones have been associated with dilutional anemia because of an increase in plasma volume, which may complicate management of renal anemia.

Drugs for Thyroid Disorders

Thyroid hormones generally do not require dose alteration in patients with CKD.[93] Doses should be initiated and titrated to thyroid-stimulating hormone levels and clinical effect. In circulation, thyroxine (T_4) is 99.98% protein bound (0.02% free) and triiodothyronine (T_3) is 99.8% bound (0.2% free). T_3 and T_4 bind partially, in slightly different proportions, to three different plasma proteins: thyroid-binding globulin, thyroid-binding prealbumin, and albumin. In protein-deficient states (e.g., nephrotic syndrome), there is the possibility of transient or permanent changes in thyroid hormone protein binding that may alter the free fraction of T_3 and T_4, leading to transient toxicity. Uremic toxins can also inhibit enzymes associated with conversion of T_4 to T_3. Oral absorption of thyroid hormones is affected by coadministration with metallic phosphate binders and iron. Euthyroid patients with CKD may have abnormal thyroid function test results, possibly because of decreased peripheral conversion of T_4 to T_3, decreased clearance of reverse T_3 generated from T_4, or decreased binding of thyroid hormones to proteins. Antithyroid drugs can be used at usual doses.

Mineral and Bone Disorders

Phosphate Binders

Phosphate binders should be taken with meals for maximal efficacy. Patients can be instructed to tailor phosphate binder intake to the phosphorus content and frequency of meals. Administration is not affected by renal function except that reducing function increases the need for phosphate binders. Dosage is based on phosphate levels and the need to avoid biochemical abnormalities (see Chapter 85). Acid suppression may reduce the effectiveness of phosphate binders by inhibiting hydrolysis of metallic ions in the gut. Phosphate binders may reduce gastrointestinal absorption of drugs, including thyroid hormones, fluoroquinolones, tetracyclines, digoxin, and immunosuppressants.

Vitamin D

In patients with renal impairment, inability of the kidneys to activate 25-hydroxycholecalciferol to calcitriol may produce relative vitamin D deficiency and hypocalcemia. The use of vitamin D preparations in patients with CKD mineral and bone disorders is discussed in Chapter 85.

Calcimimetics

Cinacalcet (see Chapter 85) dosage is independent of renal function except that progressive renal impairment exacerbates secondary hyperparathyroidism. When possible, cinacalcet should be administered with the evening meal to with the evening meal to minimize nausea. Morning blood samples for parathyroid hormone levels should be drawn at least 12 hours after administration.

Dyspepsia, Gastroesophageal Reflux Disease, and Peptic Ulcers

Proton pump inhibitors and H_2 receptor blockers are commonly used in patients with CKD (see Chapter 87). Acid suppression may reduce the effectiveness of phosphate binders by inhibiting the release of free metallic ions in the gastrointestinal tract.

Antacids

Alginates, magnesium trisilicate, and sodium bicarbonate are useful for symptom control but have high sodium content, which exacerbates hypertension and fluid status. Magnesium and aluminum salts can reduce the absorption of mycophenolate. Aluminum salts should be avoided in patients with advanced CKD.

H_2 Antagonists

Most H_2 antagonists are renally cleared but relatively safe, so dose reduction is not required.[94] Protein binding and V_D are unaltered; however, the bioavailability of nizatidine is reduced in patients with renal impairment. Cimetidine accumulation[95] produces CNS effects and also causes significant interactions through the CYP450 system and falsely elevates serum creatinine levels.[96]

Proton Pump Inhibitors

Proton pump inhibitors are generally safe and well tolerated and have a wide therapeutic index, although they have rarely been associated with interstitial nephritis.[97]

Antiemetics

Dopamine Antagonists

Domperidone, metoclopramide, and prochlorperazine are not significantly renally cleared; however, extrapyramidal and CNS effects may occur in patients with CKD, especially at high doses. Dosage should be cautiously titrated to effect. Domperidone does not cross the blood-brain barrier and may be preferable for long-term management. Metoclopramide and domperidone increase gastric emptying, which may alter drug pharmacokinetics.

5-HT_3 Antagonists

Most 5-HT_3 antagonists are minimally excreted in urine with a wide therapeutic window. Dolasetron, granisetron, ondansetron, and tropisetron are safe, and dose modification is not required.

Aperients and Laxatives

Common low-potency agents including docusate, bisacodyl, glycerin, lactulose, liquid paraffin, senna, and sorbitol may be used for acute or chronic constipation. Normal doses should be titrated to effect while avoiding significant dehydration, fluid shifts, or electrolyte disturbances. High-potency laxatives and bowel preparations should be used cautiously. They can cause significant fluid and electrolyte disturbances, especially in susceptible renal patients. Preparations containing high amounts of phosphate should be avoided. Despite the large fluid volumes required for administration, isoosmotic laxatives may be used for bowel preparation in patients with renal impairment and dialysis.

Antidiarrheals

Opioids or their derivatives should be used with the same caution as when they are used as analgesics. Loperamide and diphenoxylate-atropine can be given in usual doses.

Drugs for Erectile Dysfunction

Phosphodiesterase-5 Inhibitors

The AUCs of sildenafil, tadalafil, and vardenafil are increased in patients with severe renal impairment (sildenafil, twofold; tadalafil, fourfold; vardenafil, 20% to 30%) despite minimal dependence on renal excretion.[98] However, provided relevant cardiovascular and drug contraindications are excluded, they can be used safely. They should be initiated at low doses and titrated to response. Shorter-acting agents (sildenafil and vardenafil) may be preferable. Vardenafil can prolong the QT interval.

Intracavernosal Therapy

Drugs given directly by intracavernosal injection do not achieve significant concentrations in the systemic circulation and can be used in patients with renal impairment.

Immunosuppressants

Immunosuppression in renal transplantation as well as its adverse effects are discussed in Chapter 101. Initial and maintenance doses in any individual are highly variable and depend on local protocol, concomitant therapy, rejection risk, drug concentrations, and response. Immunosuppression is required for the life of the transplant and should never be withheld except in exceptional circumstance (life-threatening infection or malignancy). Regimens should preferably be limited to twice daily, spread at convenient times about 12 hours apart. In practice, the precise timing of doses or intake relative to time and food is not as important as consistency in relation to time and food. Patients should take their medications consistently, and doses can be titrated to levels and response. Most immunosuppressants are hepatically metabolized and do not require dose modification based on altered excretion in patients with renal impairment.

Immunosuppressants are prone to a range of significant drug interactions, and this should be considered whenever a patient receiving these agents has a change in drug regimen. Significant interactions can also occur with "natural" or "herbal" medicines (e.g., St John's wort; see also Chapter 78). If these products are deemed essential, it is advisable to monitor response, renal function, blood counts, and serum drug concentrations regularly. Therapeutic monitoring is recommended for several immunosuppressants[99] (tacrolimus, cyclosporine, everolimus, sirolimus, and mycophenolate). Target levels should be interpreted in the context of the patient's response, immunosuppressive regimen, time after transplantation, and assay methodology.[100] Pharmacokinetics may vary in relation to food (e.g., tacrolimus) or concomitant drugs (e.g., sirolimus with or without cyclosporine), so blood sampling should aim to reflect the patient's usual routine.

Calcineurin Inhibitors

Calcineurin inhibitors are extensively metabolized to inactive metabolites. The major adverse effect of CNIs is nephrotoxicity (acute and chronic),[101] and regular assessment of renal function is essential. Nephrotoxicity may increase with concurrent use of mTOR inhibitors. Early detection of CNI nephrotoxicity on biopsy assists in planning maintenance therapy (see Chapters 101 and 104). Lower doses or temporary withdrawal may be used when CNIs have caused or are likely to cause nephrotoxicity (e.g., delayed graft function).

Calcineurin inhibitors are substrates of P-glycoprotein and CYP3A4. Drugs that inhibit or compete as substrates for these enzymes can increase absorption and reduce metabolism of CNIs, causing increased serum concentrations and adverse effects. Drugs that induce these enzymes can reduce absorption and increase metabolism of CNIs, causing reduced serum concentrations, and increase the risk of rejection (see Table 77-6). Cyclosporine but not tacrolimus interferes with the enterohepatic recirculation of mycophenolate, and so the mycophenolate dose may need to be higher if this agent is coadministered with cyclosporine than if it were administered alone or with other immunosuppressants. Tacrolimus trough concentrations (C_0) show good correlation with drug exposure (AUC) and are used to monitor therapy. Debate continues about the optimal method of monitoring cyclosporine. Clinically, a combination of C_0 (trough), C_2 (concentration 2 hours post dose), and $AUC_{0\text{-}4}$ (multipoint AUC, 0 to 4 hours) is used. Different assay methodologies (high-performance liquid chromatography [HPLC] and immunoassays) have differing abilities to detect parent compound from metabolites. Specific HPLC methods are recommended, and results from different laboratories may not be interchangeable.[100]

Corticosteroids

Corticosteroids are predominantly cleared by hepatic metabolism to inactive metabolites. Dose modification based on impaired renal function is not required.

Antiproliferative and Cytotoxic Agents

Various antiproliferatives and cytotoxics are used to prevent rejection (azathioprine and mycophenolate) and in patients with

autoimmune and inflammatory renal disorders (azathioprine, cyclophosphamide, chlorambucil, methotrexate, and mycophenolate). Their primary dose-limiting toxicity is bone marrow suppression, which is exacerbated by combined use with other bone marrow suppressants (e.g., ganciclovir, cotrimoxazole, and mTOR inhibitors). Regular blood monitoring is needed to guide dosage.

Methotrexate relies on renal clearance and should be avoided or used cautiously at a reduced dose in patients with CKD. It can also cause obstructive uropathy. Renal clearance is significant with cyclophosphamide[102] (which also causes hemorrhagic cystitis) and chlorambucil, and dose modification is required. Accumulation of mycophenolate metabolites in patients with severe renal impairment predisposes to toxicity. Allopurinol significantly interferes with the metabolism of the active metabolite of azathioprine (6-mercaptopurine), and co-prescription can lead to life-threatening bone marrow suppression. The combination should be avoided by exchanging azathioprine with mycophenolate or by significant (75%) dose reduction of azathioprine or mercaptopurine.

mTOR Inhibitors

Although not nephrotoxic when used alone, mTOR inhibitors (sirolimus, everolimus) can potentiate the nephrotoxicity of CNIs. mTOR inhibitors are almost entirely hepatically metabolized to essentially inactive metabolites. Dosage is independent of renal function and based on response, serum drug levels, and specific toxicities (especially hematologic and lipids). mTOR inhibitors are substrates of CYP3A4 and P-glycoprotein. Drugs that inhibit or compete as substrates for these enzymes can increase absorption and reduce metabolism of mTOR inhibitors, causing increased blood concentrations and adverse effects. Drugs that induce these enzymes can reduce absorption and increase metabolism of mTORs and consequently reduce serum concentrations and increase the risk of rejection (see Table 77-6). Bone marrow toxicity (neutropenia, anemia, and thrombocytopenia) is increased when they are used in combination with other myelosuppressants (azathioprine, mycophenolate, ganciclovir, and cotrimoxazole). Trough levels show good correlation with drug exposure (AUC) and are used to monitor therapy. Different assay methodologies (HPLC vs. immunoassays) vary in their ability to detect parent drug from metabolites. Specific HPLC methods are recommended, and results from different laboratories or methods may not be interchangeable.

Immunosuppressant Antibodies

Antibodies used for immunosuppression include T cell–depleting antibodies (antithymocyte globulin [ATG], anti-CD3 antibodies [OKT3]), anti–interleukin-2 receptor (CD25) antibodies (basiliximab and daclizumab), and B cell–depleting antibodies (rituximab) (see Chapter 101). Dosage is independent of renal function, and these agents should be administered after plasma exchange[103] to avoid drug removal. They are not removed by HD.

Musculoskeletal Drugs

Nonsteroidal Anti-inflammatory Drugs

NSAIDs can cause significant nephrotoxicity (see Chapter 69) and should be avoided or used with extreme caution in patients with CKD.

Miscellaneous Arthritis Drugs

Gold salts and penicillamine[104] are now rarely used for rheumatoid arthritis. Both were associated with nephrotic syndrome caused by membranous nephropathy. Glucosamine and fish oil can been used safely.

Gout and Hyperuricemia

Gout is highly prevalent in patients with renal impairment. In acute therapy, short courses of oral corticosteroids are safe and preferable to NSAIDs. Colchicine[105] accumulation in patients with renal impairment may cause diarrhea and hypoperfusion-induced renal impairment as well as myelosuppression. In maintenance therapy, allopurinol is effective but the dose should initially be reduced in patients with moderate to severe renal impairment because of its renally cleared active metabolite (oxypurinol).[106] Despite this, some ESRD patients tolerate normal doses. Allopurinol significantly interacts with azathioprine, with a risk of severe myelosuppression. If the combination is unavoidable, the dose of azathioprine should be reduced to 75% and blood counts monitored carefully. Uricosuric agents (e.g., probenecid) inhibit secretion of acids in the proximal tubule and prevent reabsorption of uric acid from the tubular lumen. They often become ineffective with diminishing renal function and are best avoided if the GFR is below 40 ml/min.[107] Probenecid also interferes with the tubular secretion of many drugs, causing interactions.

Bisphosphonates

Bisphosphonates are extensively excreted in urine. The fraction not excreted is incorporated into bone, from which it slowly dissociates. In patients with renal impairment, impaired clearance of absorbed drug may increase the fraction available for incorporation into bone. The long terminal elimination half-life of these agents reflects rate-limiting dissociation from bone and may not be significantly altered in patients with renal impairment. Oral bisphosphonates appear to be safe in patients with CKD stages 2 and 3.[108] Their safety in patients with CKD stages 4 and 5 is less well established; they are contraindicated in adynamic bone disease. Rapid administration of intravenous bisphosphonates (pamidronate and zoledronic acid[109]) without hydration has been associated with acute nephrotoxicity. Intravenous preparations should be administered slowly with hydration, and renal function assessed regularly. Oral bisphosphonate administration may be complicated by the volumes of fluid recommended. In addition, many patients with renal impairment are taking calcium-based phosphate binders or supplements that impair the absorption of oral bisphosphonates. Once-weekly administration given at least 30 minutes before food and any calcium-based medications or supplements is preferable to daily doses to reduce the total weekly fluid load required to administer the tablets and helps ensure absorption.

Antiepileptics

Chronic kidney disease patients may be more prone to seizures (e.g., uremic encephalopathy and dialysis disequilibrium syndrome) and to the CNS effects of antiepileptics. Some antiepileptics rely on renal excretion, and dose modification is essential. Some antiepileptics (barbiturates, phenytoin, and carbamazepine) are strong inducers of drug-metabolizing enzymes. Coadministration with drugs reliant on hepatic metabolism (e.g., immunosuppressants) can reduce exposure and efficacy of the concomitant drug. Therapeutic drug monitoring is available for many antiepileptics and should be used to guide dosage.

Benzodiazepines

See the later discussion of psychotropic drugs.

Carbamazepine

Carbamazepine is initially administered as normal and titrated to response and blood concentrations. It is a potent enzyme inducer, and care must be taken to account for important drug interactions.

Phenytoin

Caution should be exercised with phenytoin in patients with renal impairment because of its erratic absorption, saturable metabolism, nonlinear pharmacokinetics, reduced protein binding, and increased V_D. The concentration of free drug may be higher than in patients with normal renal function; because most laboratories measure total drug concentration, a low serum total phenytoin level in patients with renal impairment should not be mistaken as subtherapeutic. Nystagmus, cerebellar ataxia, and seizures can occur in overdose, and small dose increases may result in disproportionate increases in serum concentrations. Physical findings such as nystagmus are helpful in deciding not to increase the dose. Cautious titration based on effect and monitoring of free plasma concentration is advised. Phenytoin is a potent enzyme-inducing agent, and care must be taken to account for drug interactions.

Other Antiepileptics

Levetiracetam, topiramate, and vigabatrin undergo significant renal excretion, and dose modification is required. Valproate and lamotrigine are not significantly renally excreted and do not cause enzyme induction or inhibition. Protein binding changes can increase the free fraction of valproic acid, predisposing to increased responsiveness.

Antiparkinsonian Drugs

In addition to their use for Parkinson disease and hyperprolactinemia disorders, dopaminergic drugs are used to treat restless legs and other limb movement disorders in patients with renal impairment. Most are hepatically cleared and safe, although dopaminergic agents may exacerbate postural hypotension. Amantadine[110] is highly dependent on renal excretion, and dose modification is essential.

Antimigraine Drugs

Simple analgesics (acetaminophen) are used as normal, although aspirin should be avoided at therapeutic doses and opioids used cautiously (see discussion of analgesics). NSAIDs are best avoided because of potential nephrotoxicity. 5-HT_1 agonists are effective in patients with renal impairment and transplantation. Naratriptan relies the most on renal excretion (50%), and a lower maximum dose is recommended. Sumatriptan and zolmitriptan are preferred because they are less dependent on renal excretion.

Psychotropic Drugs

Most psychotropics are fat soluble and nondialyzable, undergo significant hepatic metabolism, and are excreted as inactive compounds. Even so, patients with renal impairment are often more susceptible to common adverse effects (especially CNS effects).[111,112] Consequently, slow titration and dose modifications are required. Adverse effects are not easily distinguished from symptoms of uremia. Despite being metabolized extensively by CYP450 enzymes, very few psychotropics cause clinically significant inhibition or induction of CYP3A4.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors are extensively metabolized by the liver. Although they are less commonly used in current practice, normal doses of reversible monoamine oxidase inhibitors (moclobemide) are preferred, and these can be titrated cautiously up to full doses. Monoamine oxidase inhibitors can cause peripheral edema, which is not usually associated with fluid retention and is unresponsive to diuretics. Prostatic hypertrophy and urinary retention may also occur.

Selective Serotonin Reuptake Inhibitors

Most selective serotonin reuptake inhibitors (SSRIs) are extensively metabolized to compounds without significant SSRI activity.[113] Normal doses of most SSRIs (citalopram, fluvoxamine, paroxetine, and sertraline) can be used with cautious dose titration. Fluoxetine is metabolized to an active metabolite (norfluoxetine), but single- and multiple-dose studies have shown little change in pharmacokinetics even in dialysis patients.[114] Patients with renal impairment may be more prone to the CNS toxicity of SSRIs and serotonin syndrome. SSRIs can cause the syndrome of inappropriate antidiuretic hormone secretion and platelet aggregation or hemorrhagic complications, which theoretically increases the risk of bleeding in uremic patients who are already prone to bleeding complications. Although most SSRIs have some inhibitory effect on CYP3A4, this is usually not significant. Fluoxetine and fluvoxamine are more likely to interact than citalopram and sertraline, but all can be used in patients taking immunosuppressants. Cinacalcet can cause significant inhibition of CYP2D6-mediated metabolism of SSRIs and perhexiline. This may increase the possibility of serotonin syndrome or perhexiline toxicity.

Tricyclic Antidepressants

Tricyclic antidepressants are now infrequently used for depression but more for neuropathic pain and their anticholinergic properties in urinary tract disorders. They are predominantly metabolized to metabolites with varying activity. Patients with renal impairment may be more prone to the common anticholinergic adverse effects, particularly urinary retention, orthostatic hypotension, confusion, and sedation.[115] Obstructive uropathy can occur from the anticholinergic properties. Cautious initial doses and titration of tricyclic antidepressants are recommended. Depending on response, many agents can be used at up to normal or maximal doses in patients with renal impairment.

Other Antidepressants

Venlafaxine dose should be initially reduced in patients with severe renal impairment because of reduced clearance of the active metabolite *O*-desmethylvenlafaxine.[116] Nefazodone is used at a normal dose.

Antipsychotics

Conventional antipsychotics cause a variety of side effects to which patients with renal impairment may be susceptible (sedation, confusion, and postural hypotension). Caution is advised for atypical antipsychotics that prolong the QT interval (e.g., pimozide, thioridazine, mesoridazine, droperidol, and ziprasidone). Newer atypical agents are more commonly used and better tolerated. Clozapine, olanzapine, quetiapine, and aripiprazole are commenced at normal doses and titrated to response. Risperidone[117] and its active metabolite 9-hydroxyrisperidone are renally excreted, and clearance is reduced by 60% in patients with severe renal impairment. Lithium is filtered and reabsorbed mainly in the proximal tubules. It is extensively renally excreted and accumulates even in patients with mild renal impairment, causing toxicity, and should be avoided if possible. If use is essential, the dose must be reduced with monitoring of plasma concentrations. In hyponatremic patients, tubular reabsorption of lithium is increased, leading to increased plasma concentrations and toxicity. NSAID co-prescription may also increase toxicity. HD is efficient in removal of lithium and can be used in overdose; however, multiple dialysis treatments are usually required because plasma

concentrations rebound soon after HD. Chronic lithium nephrotoxicity is discussed further in Chapter 64.

Benzodiazepines

Benzodiazepines are extensively metabolized by the liver to a range of active and inactive metabolites. Enhanced CNS toxicity, especially sedation, is the main concern in renal patients.[118,119] Because of the potential for accumulation, chronic use should be discouraged. Short-acting benzodiazepines are preferred, and the dose should be titrated cautiously according to response. The dose of midazolam should be reduced because of changes in plasma protein binding. Hemoperfusion and dialysis are not useful in patients with benzodiazepine intoxication. Flumazenil may be used as normal in patients with overdose.

Vaccines

Live vaccines (bacillus Calmette-Guérin, oral poliovirus, rubella, typhoid, yellow fever, and varicella) in immunosuppressed patients are contraindicated because of the potential for causing disease. Attenuated vaccines (diphtheria-tetanus, hepatitis B, influenza, meningococcal, and pneumococcal) may be used; but impaired response in immunocompromised individuals may lead to inadequate protection (see Chapter 84). Hepatitis B may need more doses for seroconversion to be achieved in HD patients. Immunization should preferably occur at least 1 month before initiation of immunosuppression. After transplantation, the immune response may be inadequate for at least 6 to 8 months, meaning that vaccination should be withheld until then.[120]

Vitamin Supplementation

Patients with renal impairment may become vitamin deficient as a result of poor dietary intake and the effect of dialysis on removal of water-soluble vitamins. Administration of vitamin supplements (B, C, and folic acid) is recommended after dialysis.

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CHAPTER 78

Herbal and Over-the-Counter Medicines and the Kidney

Mark S. Segal and Xueqing Yu

In recent years, the use of herbal medicines and dietary supplements to promote the health and to treat various chronic diseases has increased globally. An estimated one third of adults in developed countries and more than 80% of the population in many developing countries are using herbal and folk medicines to promote health and to manage common maladies, such as colds, hay fever, inflammation, heart disease, indigestion, constipation, liver cirrhosis, cancer, acquired immunodeficiency syndrome, diabetes, and central nervous system diseases.[1] In Africa, up to 80% of the population depends on traditional medicine for primary health care; in China, herbal preparations account for up to 50% of the total consumption of pharmaceutical agents. There has been a surge in the popularity of herbal medicine in the West. For instance, the size of the U.S. herbal medicine market increased from $1.6 billion in 1994 to $5.3 billion in 2011.[1,2] In addition, European countries spent almost $5 billion (at manufacturers' prices to wholesalers) on over-the-counter (OTC) herbal medicines in 2003. Germany and France are the leaders in OTC sales and also have large markets for prescription herbal preparations (Fig. 78-1).[3] The European Union has taken steps with the Traditional Herbal Medicinal Products Directive (THMPD, also known as Directive 2004/24/EC) implemented in May 2011 to regulate herbal remedies. THMPD mandates that all herbal medicinal products be required to obtain an authorization to market within the European Union and that herbal medicines be manufactured under Good Manufacturing Practice. Complementary and alternative medicines, including Chinese herbal medicines and herbal plants, have been used by about 50% of Australians.[1]

Herbal medicine was widely recorded in ancient literature. To date, there are at least 11,000 species of plants for medicinal use, and about 500 of them are commonly used by various ethnic groups.[1,4] These herbal plants may be used either in their primary forms or in mixtures. However, the source and composition of botanical medicines vary depending on the prevalent local practices. Notably, these herbal remedies have not been tested for efficacy and safety, their ingredients are mostly unknown, and the dosage and route of administration are not standardized. Although the prevalence of toxicity of organs caused by traditional medicines is directly related to a combination of ignorance, poverty, lack of medical facilities, lack of legislation, and widespread belief in indigenous systems of medicine in rural areas, it has been realized recently that the problems and concerns regarding herbal medicines arise as a result of intrinsic toxicity, adulteration, contamination, substitution, misidentification, mistaken labeling, unfavorable herb-drug interactions, lack of standardization, or poor quality control.[1,4] Increasing evidence for both adverse drug reactions and poisoning events associated with the use of herbal medicines has been reported worldwide. Herbal medicines have been found to be adulterated with synthetic drugs and other potentially toxic compounds. On the other hand, coadministration of herbal medicines with conventional drugs raises the potential for herb-drug interactions, which may cause altered drug elimination, undertreatment, and/or toxicity.[1,4,5]

HERBAL MEDICATIONS AND THE KIDNEY

Kidneys are particularly vulnerable to toxic injury because of their high blood flow rate, large endothelial surface area, high metabolic activity, active uptake by tubular cells, medullary interstitial concentration, and low urine pH. Renal tubules are involved in active transport and urinary concentration, and therefore the local concentration of these toxins is potentially high, leading to direct injury to tubular cells. Herbal medicines may be toxic via one or more common pathogenic mechanisms. These include alterations in intraglomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy. Drug-related nephrotoxicity is becoming more common; people are more commonly requiring multiple medications for multiple comorbidities, and are being exposed to more diagnostic and therapeutic procedures with the potential to harm kidney function. Patient-related risk factors for drug-induced nephrotoxicity include age older than 60 years, underlying renal impairment and glomerular filtration rate (GFR) less than 60 ml/min/1.73 m^2, volume depletion, diabetes, heart failure, and sepsis.[6] These risk factors may also make individuals susceptible to renal toxicity from herbal medicines. An overview of the potential renal side effects of herbal medicines is shown in Table 78-1.

ARISTOLOCHIC ACID NEPHROPATHY OR BALKAN NEPHROPATHY

Aristolochic Acids

Aristolochic acids (AAs) are a family of structurally related nitrophenanthrene carboxylic acids that are primarily from herbal medicines such as *Aristolochia* species, including *Aristolochia fangchi, Aristolochia clematitis,* and *Aristolochia manshuriensis* (Table 78-2). The predominant AAs are AAI (8-methoxy-6-nitro-phenanthro-[3,4-*d*]-1,3-dioxolo-5-carboxylic acid) and AAII (6-nitro-phenanthro-[3,4-*d*]-1,3-dioxolo-5-carboxylic acid). AAs activated by human NAD(P)H:quinone oxidoreductase[7] and react with DNA to form covalent dA-aristolactam and dG-aristolactam adducts.[8] These aristolactam adducts are mutagenic.[8] After even a single dose, AAI is detectable in the kidneys for a long period of time. Human aristolochic acid nephropathy (AAN) is reproducible in rodents in which AA intoxication results in tubular atrophy and interstitial fibrosis, leading to renal failure.[9] The progressive tubular atrophy is related to impaired regeneration and apoptosis of proximal tubular epithelial cells, which is considered a possible mechanism of tubular epithelial cell deletion. The resident fibroblast

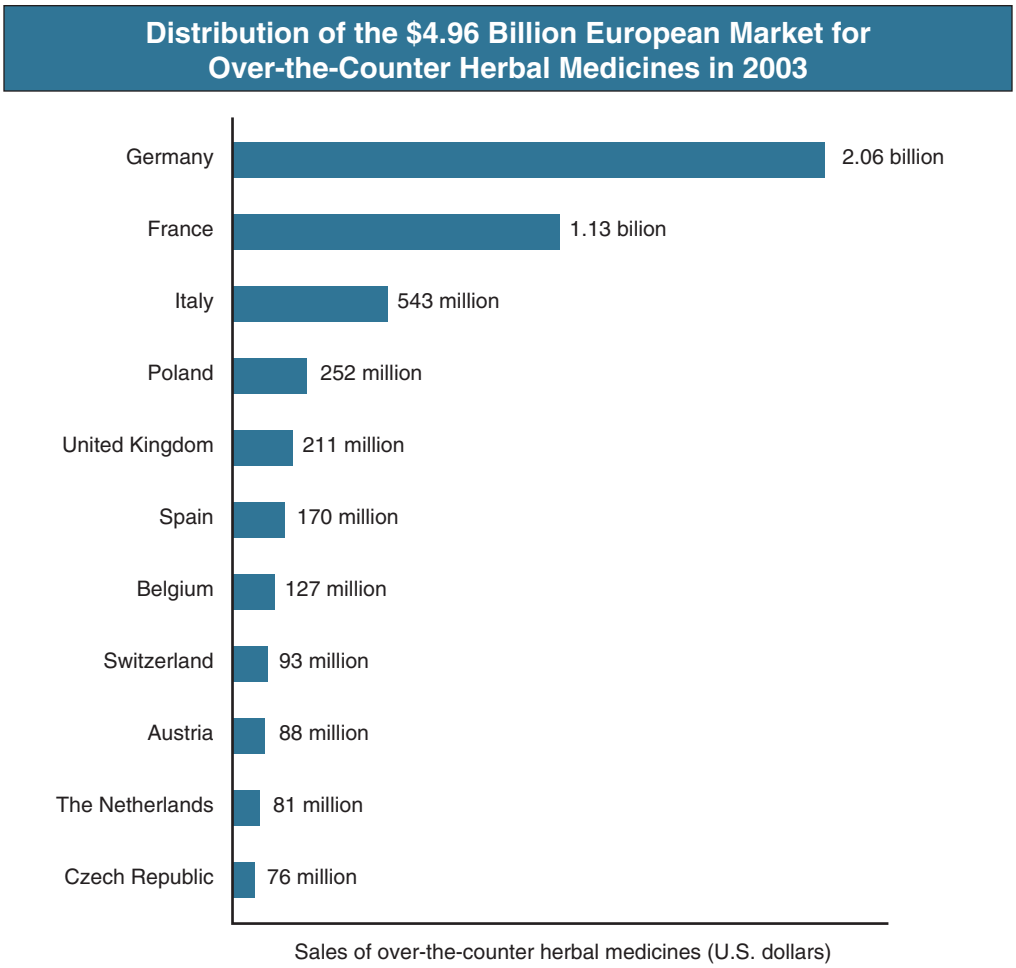

Figure 78-1 Distribution of the $4.96 billion European market for over-the-counter herbal medicines in 2003. *(From reference 3.)*

Kidney Syndromes Induced by Herbal Medicines	
Hypertension	*Glycyrrhiza* species (Chinese herbal teas, gancao, boui-ougi-tou) *Ephedra* species (ma huang)
Acute tubular necrosis	Traditional African medicine: toxic plants (*Securidaca longepedunculata, Euphoria matabelensis, Callilepis laureola,* Cape aloes), or adulteration by dichromate Chinese medicine: *Taxus celebica* Morocco: Takaout roumia (paraphenylenediamine)
Acute interstitial nephritis	Peruvian medicine *(Uno degatta)* Tung Shueh pills (adulterated by mefenamic acid)
Fanconi syndrome	Chinese herbs containing AAs (*Akebia* species, boui-ougi-tou, Mokutsu) Chinese herbs adulterated by cadmium
Papillary necrosis	Chinese herbs adulterated by phenylbutazone
Chronic interstitial renal fibrosis	Chinese herbs or Kampo containing AAs (*Aristolochia* species, *Akebia* species, Mu Tong, Boui, Mokutsu)
Urinary retention	*Datura* species, *Rhododendron molle* (atropine, scopolamine)
Kidney stones	Ma huang (ephedrine) Cranberry juice (oxalate)
Urinary tract carcinoma	Chinese herbs containing AAs

Table 78-1 Kidney syndromes induced by herbal medicines. *AA,* Aristolochic acids. *(From reference 6.)*

activation plays a critical role in the process of renal fibrosis during AA toxicity.[10] The nephrotoxic and carcinogenic effects of AAs in animals have been reported, and similar toxicities have been observed in humans. It is now known that exposure to AA causes a progressive renal interstitial fibrosis associated with urothelial malignancy.

Aristolochic Acid Nephropathy

The association of kidney disease with long-term consumption of *Aristolochia fangchi* for slimming purposes was first reported in Belgium. More than 100 young women developed chronic kidney disease (CKD) and several developed renal and urinary tract cancer

Botanicals Known to Contain or Suspected of Containing Aristolochic Acid	
Botanical Name	**Common or Other Names**
Aristolochia species	Aristolochia, Guan Mu tong, Guang Mu tong
Aristolochia acuminata (syn. *Aristolochia tagala*)	Oval leaf Dutchman's pipe
Aristolochia bracteata	Ukulwe
Aristolochia clematitis	Birthwort
Aristolochia contorta	Ma Dou Ling (fruit), Bei Ma Dou Ling (root), Tian Xian Teng (herb)
Aristolochia cymbifera	Mil homens
Aristolochia debilis (syn. *Aristolochia longa, Aristolochia recurvilabra, Aristolochia sinarum*)	Ma Dou Ling (fruit), Tian Xian Teng (herb), Qing Mu Xiang (root), Sei-Mokkou (Japanese), Birthwort, Long birthwort, Slender Dutchman's pipe
Aristolochia fangchi	Guang Fang ji (root), Fang ji, Fang chi, Makuboi (Japanese), Kou-boui (Japanese), Kwangbanggi (Korean)
Aristolochia heterophylla	Han Fang Ji
Aristolochia indica	Indian birthwort (root), Yin Du Ma Dou Ling
Aristolochia kaempferi (syn. *Aristolochia chrysops, Aristolochia feddei, Aristolochia heterophylla, Aristolochia mollis, Aristolochia setchuenensis, Aristolochia shimadai, Aristolochia thibetica, Isotrema chrysops, Isotrema heterophylla, Isotrema lasiops*)	Yellowmouth Dutchman's pipe, Zhu Sha Lian
Aristolochia macrophylla (syn. *Aristolochia sipho*)	Dutchman's pipe
Aristolochia manshuriensis (syn. *Hocquartia manshuriensis, Isotrema manshuriensis*)	Manchurian birthwort, Manchurian Dutchman's pipe (stem), Guan Mutong (stem), Kan-Mokutsu (Japanese), Mokubai (Japanese), Kwangbanggi (Korean)
Aristolochia maxima (syn. *Howardia hoffmannii*)	Maxima Dutchman's pipe, Da Ma Dou Ling
Aristolochia mollissima	Wooly Dutchman's pipe, Mian Mao Ma Dou Ling
Aristolochia moupinensis	Moupin Dutchman's pipe, Huai Tong
Aristolochia sarpentaria (syn. *Aristolochia serpentaria*)	Virginia snakeroot, Serpentaria, Virginia serpentary
Aristolochia triangularis	Triangular Dutchman's pipe, San Jiao Ma Dou Ling
Aristolochia tuberosa	Tuberous Dutchman's pipe, Kuai Jing Ma Dou Ling
Aristolochia tubiflora	Tubeflower, Dutchman's pipe, Guan Hua Ma Dou Ling
Aristolochia versicolar	Versicoloraus Dutchman's pipe, Bian Se Ma Dou Ling
Asarum canodense (syn. *Asarum acuminatum, Asarum ambiguum, Asarum canadense, Asarum furcatum, Asarum medium, Asarum parvifolium, Asarum reflexum, Asarum rubrocinctum*)	Wild ginger, Indian ginger, Canada snakeroot, false coltsfoot, colic root, heart snakeroot, Vermont snakeroot, Southern snakeroot, Jia Na Da Xi Xin
Asarum himalai(y)cum	Tanyou-saishin (Japanese)
Asarum splendens	Do-saishin (Japanese)

Table 78-2 Botanicals known or suspected to contain aristolochic acid and their vernacular names. *(From reference 16.)*

(Fig. 78-2).[11] Increasing evidence demonstrates that AAs present in the herb are the compounds responsible for this renal toxicity (Figs. 78-3 and 78-4).[12,13] The renal syndrome was initially referred to as *Chinese herb nephropathy* and later by the more specific, mechanistic name *AA nephropathy.* AAN is characterized by tubulointerstitial nephritis that rapidly progresses to fibrosis with deterioration of renal function, ultimately leading to end-stage renal disease (ESRD), sometimes within months after first exposure. The renal toxicity of AA is dependent on the dosage and the duration of administration.[14]

Epidemiology

Soon after its initial description, AAN was recognized as a global health problem.[11,12,15] Since the publication of the index cases, new cases of AAN have been reported, not only in Belgium but also worldwide[10,11,13] (see Fig. 78-2). The true incidence of AAN remains unknown and probably underestimated because numerous ingredients known or suspected to contain AA are used in traditional medicine in China, Japan, and India (see Fig. 78-3).[16]

Clinical Manifestations

The initial presentation of AAN is usually silent, and the renal disease is discovered by routine blood testing. Occasional patients present with Fanconi syndrome or with acute kidney injury (AKI) caused by acute tubular necrosis.[17] Anemia is often disproportionately severe for the degree of renal impairment. The urinary sediment is unremarkable, and the urinalysis is negative for albuminuria. However, urinary excretion of low-molecular-weight proteins (e.g., β_2-microglobulin, cystatin C) is markedly increased, and the ratio of urinary low-molecular-weight protein to albumin is higher than in glomerular diseases.[18]

Pathology

Aristolochic acid nephropathy is characterized by extensive renal interstitial fibrosis and tubular atrophy, which generally decreases in severity from the outer to the inner cortex (see Fig. 78-4). The glomeruli are relatively spared, although in the later stage of the disease there is some collapse of the capillaries and wrinkling of the

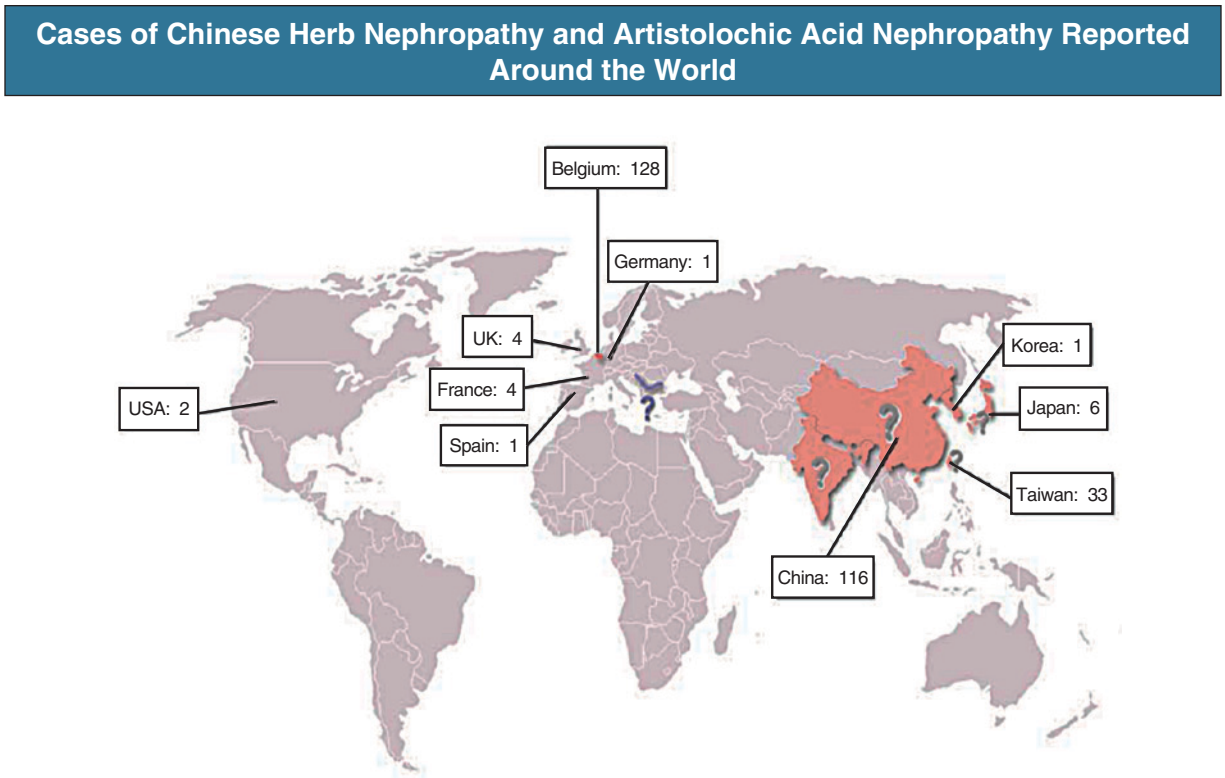

Figure 78-2 Cases of Chinese herb or aristolochic acid nephropathy reported around the world. *(From reference 16.)*

Figure 78-3 A pharmacy selling traditional herbal remedies including Fang Chi and Mu Tong. The true incidence of aristolochic acid nephropathy is largely unknown and probably underestimated because numerous ingredients known or suspected to contain AA are used in traditional medicine in India and Eastern Asia. *(From reference 16.)*

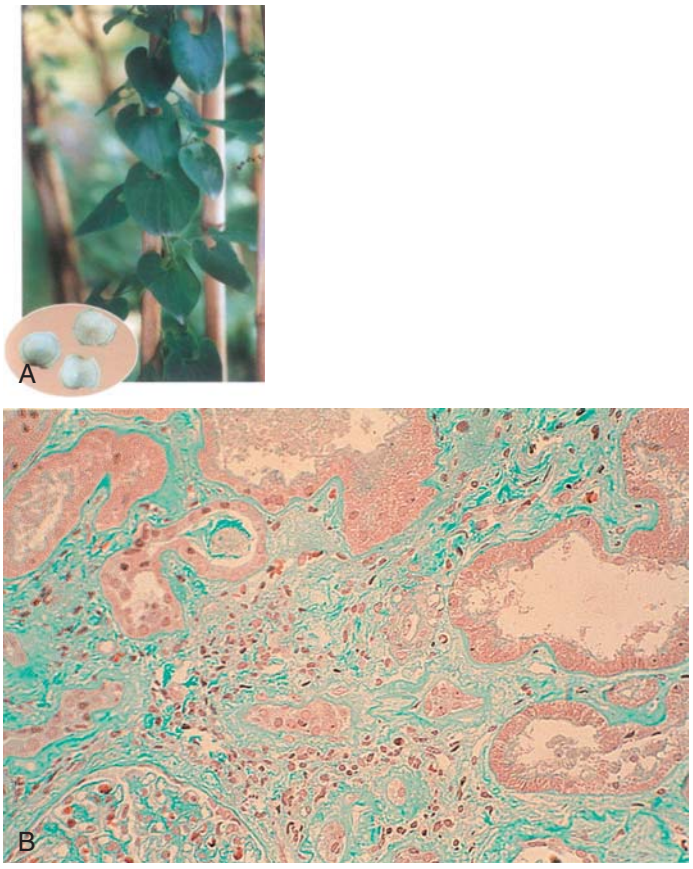

Figure 78-4 Chinese herb or aristolochic acid nephropathy. A, Guang Mu Tong, a Chinese herb that contains AAs. **B,** Extensive paucicellular interstitial fibrosis and tubular atrophy typically found in Chinese herb or aristolochic acid nephropathy. *(From reference 16.)*

basement membrane. There is endothelial cell swelling with consequent thickening of interlobular and afferent arterioles.[16,19] There are no immune deposits.

Pathogenesis

The striking association between AA exposure and urothelial abnormalities was first noted in studies showing moderate atypia and atypical hyperplasia in nephroureterectomy specimens removed at the time of transplantation from individuals with AAN (see Fig. 78-4).[21] The persistence of AA-DNA adducts in renal tissues of the Belgian women cohort is consistent with the postulated role of AA in urothelial cancer. Of AAN patients, 40% to 45% develop multifocal high-grade transitional cell carcinomas, mainly in the upper urinary tract.[13] A case series with 15-year follow-up identified upper-tract urothelial carcinoma as a potent risk factor for the subsequent development of bladder urothelial carcinoma after kidney transplantation for AAN.[22] There is a strong association between DNA adduct formation, mutation pattern, and tumor development. In animal

models, oral ingestion of AA is followed by extensive formation of AA-DNA adducts in the forestomach, accompanied by development of tumors.[22] An early and massive interstitial inflammation characterized by activated monocytes and macrophages and cytotoxic $CD8^+/CD103^+$ T lymphocytes seen in experimental AAN[23] suggests that the pathophysiology includes an immunologic element. In 2002 the International Agency for Research on Cancer Working Group concluded that there is sufficient evidence in humans to identify the carcinogenicity of herbal remedies containing plant species of the genus *Aristolochia.*[24]

Treatment

No treatment for AAN has proven to be effective in randomized trials. However, a pilot study with corticosteroids in 35 AAN patients with CKD demonstrated a significant reduction in the number of patients reaching ESRD after 1 year of corticosteroid therapy.[25] Corticosteroid therapy was later confirmed, in a larger cohort with historical controls, to slow down the progression of renal failure[26]; however, there has been no randomized controlled trial. Corticosteroids, when used for AAN, are initiated in those with an estimated GFR (eGFR) of greater than 20 ml/min at 1 mg of prednisone per kilogram.

Because patients with AAN are at increased risk for uroepithelial malignancies, they should at least be regularly screened with cystoscopy. In addition, prophylactic removal of the native kidneys and ureters should be performed in all patients with ESRD caused by AAN who are going to receive a kidney transplant and thus will be immunosuppressed.[27]

Balkan Endemic Nephropathy

Another manifestation of AAN is Balkan endemic nephropathy (BEN).

Definition

Balkan endemic nephropathy[28] is a slowly progressive condition that causes chronic interstitial fibrosis leading to ESRD and also to urothelial malignancy. BEN affects thousands of people living in Bulgaria, Bosnia, Croatia, Romania, and Serbia along the Danube River basin (Fig. 78-5).[29]

Figure 78-5 Areas where Balkan nephropathy is present. The endemic areas are in *red*.

Clinical Manifestations

Balkan endemic nephropathy typically presents in the fourth or fifth decade of life and is only rarely seen in individuals younger than 20 years. When there is prospective monitoring, tubular proteinuria is usually the first sign. Proteinuria is usually mild or intermittent but may increase in the advanced stages. The urinary sediment is usually unremarkable. Other manifestations of tubular dysfunction include impaired acidification, decreased ammonia and increased uric acid excretion, and urine-concentrating defects with renal salt wasting, which may precede the decrease in GFR. The disease slowly progresses to ESRD. There is anemia disproportionate to the degree of renal impairment. Blood pressure is usually normal until ESRD is reached. There is an increased incidence of uroepithelial carcinomas.

Pathogenesis

The clinical features closely parallel those of AAN, and there is now strong evidence for the role of AA in the pathogenesis of BEN.

In endemic regions, bread is a dietary staple and is traditionally prepared from flour made from locally grown wheat. The seeds of *A. clematitis,* a plant native to the region, have been found interspersed with the harvested wheat grain. dA-aristolactam and dG-aristolactam DNA adducts are found in the renal cortex of patients with BEN but not in those with other chronic renal diseases.[30] Transitional cell cancers from patients with BEN contain aristolactam adducts and also contain a characteristic pattern of tumor protein 53 *(TP53)* mutations: 89% occur at A:T pairs, and 78% of these are A:T to T:A transversions. A:T to T:A transversions are rare events, found in 0% of transitional cell carcinomas of the renal pelvis in an international *TP53* mutational database. Molecular, epidemiologic evidence relates urothelial carcinoma in patients with BEN to dietary exposure to AA.[31] Aristolactam-DNA adducts have been found in 70% of people in the endemic areas with dietary exposure to AA, and in 94% of patients with specific A:T to T:A mutations in *TP53*. Neither aristolactam-DNA adducts nor specific mutations were detected in tissues of those from nonendemic regions. Because BEN occurs only in a fraction of those individuals exposed to AA, there is assumed to be a genetic susceptibility that puts individuals with a dietary exposure to AA at risk for BEN and its resultant urothelial carcinomas.

Diagnosis

Diagnostic criteria for BEN in endemic areas are shown in Box 78-1. Recent analysis of 182 patients in Serbia showed that proteinuria, urine α_1-microglobulin, and kidney size are significant predictors of BEN, whereas renal failure as well as several tubular disorders (urine specific gravity, fractional sodium excretion, and tubular phosphate reabsorption) had an insignificant predictive value.

Treatment

As in AAN, there have been no randomized trials performed for treatment of BEN. Based on the nonrandomized studies of corticosteroids in AAN, a trial of corticosteroids is reasonable in those with BEN in addition to blood pressure control and management of electrolyte abnormalities.

ACUTE KIDNEY INJURY CAUSED BY HERBS

The most frequently reported nephrotoxicity caused by medicinal herbs is from southern Africa and Asia. The use of traditional herbal remedies has been implicated in 37% of all cases of acute renal failure in Nigeria.[32] Herbal plants reported as the cause for renal damage include *Securidaca longepedunculata* (or violet tree), which contains

Diagnostic Procedures for Balkan Endemic Nephropathy

Diagnosis of Balkan nephropathy is made in inhabitants from endemic settlements using the following:

1. Epidemiologic criteria
2. Demonstration of
   - GFR decrease
   - Proteinuria generally below 1 g/24 h
   - Microalbuminuria
   - Little urinary sediment
   - Tubular markers (renal glucosuria, increased urinary excretion of β_2-microglobulin or α_1-microglobulin, and *N*-acetyl-β-D-glucosaminidase)
   - Typical renal histology showing hypocellular cortical interstitial fibrosis decreasing from the outer to the inner cortex (if renal biopsy feasible)
3. Exclusion of other known kidney disease (e.g., chronic pyelonephritis [obstructive and atrophic], adult dominant polycystic kidney disease, glomerulonephritis)

Box 78-1 Diagnostic procedures for Balkan endemic nephropathy. *(Modified from reference 30.)*

methyl salicylate and saponin; *Euphorbia matabelensis,* which contains latex; *Crotalaria laburnifolia,* which contains hepatonephrotoxic alkaloids; *Uncaria tomentosa* (cat's claw); *Lepidium meyenii* (common name: maca); *Tripterygium wilfordii* (Lei Gong Teng); licorice *(Glycyrrhiza glabra)* root; and *Callilepis laureola* (Impila). The following section describes some of the important examples of nephrotoxicity caused by herbal remedies.

T. wilfordii Hook F (TWHF) is a Chinese herbal medicine used for over 2000 years. As a cream, it was used externally for treatment of arthritis and inflammatory tissue swelling for many years. Extracts of TWHF are also given orally for rheumatoid arthritis, lupus, minimal change disease, and other inflammatory conditions. The adverse effects of TWHF include gastrointestinal upset, infertility, and *in vitro* suppression of lymphocyte proliferation. In rats, daily intragastric ingestion of an effective compound extracted from TWHF for 16 days led to proximal tubular dysfunction.[33]

Cat's claw, or *Uno degatta,* is a Peruvian herbal preparation made from *Uncaria,* a woody vine found in the Amazon basin. It has been used for treatment of cirrhosis, gastritis, gonorrhea, cancers of the female genital tract, and rheumatism. The oxindole alkaloids from the root bark of cat's claw are thought to invoke its most widely sought-after medicinal effects as an herbal remedy against inflammation, but it appears that other unknown substances contribute to the overall effect of cat's claw extracts. A case of reversible acute interstitial nephritis after the use of this preparation has been reported, likely an idiosyncratic allergic reaction to the remedy.[34]

The majority of renal problems associated with mushrooms are a consequence of renal failure resulting from mushroom-induced hepatic failure. However, throughout Europe and North America there are a variety of nephrotoxic mushrooms that can be confused with edible mushrooms and can directly cause AKI. The *Cortinarius* species (*Cortinarius callisteus, Cortinarius cinnamomeus* group, *Cortinarius gentilis, Cortinarius orellanus, Cortinarius rainierensis, Cortinarius speciosissimus, Cortinarius splendens,* and *Cortinarius semisanguineus* group) are the most notorious. The most common nephrotoxic mushroom is probably *C. gentilis.* In 2011, there were 6818 mushroom exposures reported in the United States, American Samoa, Federated States of Micronesia, Guam, Puerto Rico, and the U.S. Virgin Islands with two fatalities, but only eight exposures were attributed to the *Cortinarius* group. However, the type of mushroom is unknown in over 80% of the cases, so *Cortinarius* exposures are almost certainly higher.[35] The history of mushroom ingestion may be remote, particularly with *Cortinarius.* Although gastrointestinal symptoms are usually noted at the time of ingestion, they may not be severe enough for patients to seek medical attention, and symptoms of renal failure may not present until 1 to 3 weeks after exposure. Presentation with a shorter latent period suggests a more severe toxicity and greater risk of severe renal failure. Improvement in renal function may occur within several weeks to months, but patients may require chronic dialysis or renal transplantation.

A more recently described mushroom syndrome involves *Amanita smithiana* or *Amanita proxima.* It is thought that the toxin is 2-amino-4,5-hexadienoic acid.[36] Although it causes acute tubular necrosis within hours of the time of ingestion, the clinical outcome is usually good.

OTHER RENAL COMPLICATIONS OF HERBAL REMEDIES

Hypertension

Ma huang is an ephedra-containing herbal preparation used in the treatment of bronchial asthma, cold and flu symptoms, fever and chills, headaches and other aches, edema, and lack of perspiration. In Western countries, ephedrine and herbal ephedra preparations have been used to promote weight loss and to enhance athletic performance. Dietary supplements that contain ephedra alkaloids have been reported to induce hypertension, palpitations, tachycardia, and stroke. Prescribed ephedrine was not associated with a substantially increased risk of adverse cardiovascular outcomes in a registry-based case-crossover study.[37,38] However, ephedra may pose a serious health risk to some users, such as renal patients who are particularly prone to hypertension.

The dried roots of the licorice plant *(G. glabra)* have been consumed for over 6000 years and are used as flavoring and sweating agents, as demulcents and expectorants in the Western world, and as antiallergic and anti-inflammatory agents in Asian countries, including China, Japan, and Korea. Licorice contains glycyrrhizin. After oral administration of licorice preparations, glycyrrhizinic acid is hydrolyzed by intestinal bacteria into glycyrrhetic acid. Glycyrrhetic acid can inhibit 11-β-hydroxysteroid dehydrogenase-2 (11-BOHD-2), which is found in the distal tubule and converts the corticosteroid hormone cortisol to cortisone. Decreased activity of 11-BOHD-2 leads to an excess of cortisol and an overstimulation of this mineralocorticoid receptor, leading to sodium and water retention and increased excretion of potassium. Large doses of glycyrrhizinic acid over a prolonged period can cause hypokalemia, hypernatremia, edema, pseudoaldosteronism, hypertension, arrhythmia, and other cardiac disorders.[1] To minimize the adverse effects, it is recommended that licorice not be ingested for longer than 4 to 6 weeks.[39]

Crystalluria and Nephrocalcinosis

Many health drinks that are well tolerated by individuals with normal renal function can cause serious problems in patients with limited renal function. One example of this is oxalate crystalluria. Star fruit (carambola) juice can contain as much as 800 mg of oxalate in 100 ml. Sour carambola juice is a popular beverage in Taiwan, and although preparation of commercial carambola juice by pickling and dilution markedly reduces oxalate content, fresh juice or only mildly diluted postpickled juice may contain high quantities of oxalate.

Cranberry concentrate tablets also can lead to an increase in urinary excretion of oxalate. Ma huang ingestion also has been reported to lead to kidney stones, and the use of ephedrine and guaifenesin individually or in combination has been shown to cause greater than 35% of urinary stones that are related to pharmaceutical metabolites and 0.1% of all urinary stones.[37]

Hyperkalemia

Dietary potassium restriction is commonly recommended for people with renal impairment, especially because hyperkalemia is a side effect of medications used to slow down the progression of renal disease. Common foods high in potassium include oranges, bananas, tomatoes, and potatoes. However, some health drinks are also very high in potassium. Noni juice, often taken to increase energy, contains more potassium than any other fruit juice. The legume alfalfa *(Medicago sativa)* and the plants dandelion *(Taraxacum officinale),* stinging nettle *(Urtica dioica),* and horsetail *(Equisetum arvense)* all contain significant amounts of potassium[40] and may induce hyperkalemia in people with CKD.

Urinary Obstruction

Djenkol beans or Jering *(Pithecellobium jiringa)* are broad, round, reddish beans that grow during monsoon season in Myanmar, Indonesia, and Malaysia and are considered a delicacy. The Jering seeds are extolled for their supposed ability to prevent diabetes and high blood pressure. In addition, the seeds have bladder spasmodic properties and are used as a remedy to eliminate stones from the bladder. Jering poisoning or djenkolism is characterized by spasmodic pain, urinary obstruction, and AKI.[41] The underlying pathology is an obstructive uropathy. On a more chronic basis, djenkol bean consumption is associated with a fourfold higher risk of nonglomerular hematuria.[42]

Renal Toxicity from Contaminants Within Herbal Medicines

Herbal medicines may be contaminated with excessive or banned pesticides, microbial contaminants, heavy metals, or chemical toxins or adulterated with orthodox drugs. These contaminants are related to the source of these herbal materials, whether grown in a contaminated environment or contaminated during collection of these plant materials. The herbal materials may be contaminated with chemical toxins unintentionally or intentionally during storage. The presence of orthodox drugs is often a result of the intentional adulteration of the herbal remedy by the manufacturers.[43] A report found undeclared pharmaceuticals or heavy metals in 32% of Asian medicines sold in the state of California. These included ephedrine, chlorpheniramine, methyltestosterone, phenacetin, sildenafil, corticosteroids, and fenfluramine; 10% to 15% contained lead, mercury, or arsenic. Out of more than 500 Chinese drugs, approximately 10% contained undeclared drugs or heavy metals.[4]

There have been case reports concerning these adulterations leading to renal injury. The first was a report of a 73-year-old Malaysian woman who presented with renal failure and bilateral papillary necrosis after having consumed two tablets daily of a traditional herbal preparation, freely available from Chinese medical halls, for 10 years for osteoarthritis. She denied the consumption of any other analgesics, but the analysis of the herbal preparation showed 120 mg of phenylbutazone in each tablet. The second report was of a 34-year-old housewife taking a mixture of Chinese herbs who presented with Fanconi syndrome and nephrogenic diabetes insipidus. She was found to have urinary excretion of cadmium 50 times greater than normal. In another report, a patient presented with AKI, with marked albuminuria, microscopic pyuria, and hematuria after a 4-week treatment with Tung Shueh pills for arthralgias. The cause was acute interstitial nephritis, and the Tung Shueh pills were found to contain both diazepam and mefenamic acid. In Morocco, the traditional *el badia,* a powder made of the seeds of *Tamarix orientalis*, is used by women for hair dye; however, in times when the *T. orientalis* seeds are scarce, they are replaced with Takaout roumia, which contains paraphenylenediamine. This substitution is responsible in Morocco for about 10% of all cases of AKI, 50% of all cases of rhabdomyolysis, 25% of intensive care unit (ICU) admissions for poisonings, and two thirds of poisoning-related deaths.[4,6]

In Thailand and other parts of Southeast Asia and India, herbal remedies have been shown to be contaminated with lead, cadmium, and/or mercury. In South Africa, about 15% of herbal remedies are contaminated with uranium. In the United States, ginseng dietary supplements have been shown to contain the pesticides quintozene and hexachlorobenzene, or to have exceeded the standard for lead content.

Herb-Drug Interactions Resulting in Adverse Renal Effects

Herbs are often administered in combination with therapeutic drugs, with potential for pharmacokinetic and/or pharmacodynamic herb-drug interactions. Pharmacokinetic herb-drug interactions are caused by altered absorption, metabolism, distribution, and excretion of drugs. A frequent underlying mechanism of altered drug concentrations by concomitant herbal medicines is the induction or inhibition of hepatic and intestinal cytochrome P-450 enzymes (CYPs). There are reports of 32 drugs interacting with herbal medicines in humans. These drugs include anticoagulants (warfarin, aspirin, and phenprocoumon), sedatives and antidepressants (midazolam, alprazolam, and amitriptyline), oral contraceptives, anti–human immunodeficiency virus (HIV) agents (indinavir, ritonavir, and saquinavir), cardiovascular drug (digoxin), immunosuppressants (cyclosporine and tacrolimus), and anticancer drugs (imatinib and irinotecan). Most of them are substrates for CYPs and/or P-glycoprotein (P-gp), and many have narrow therapeutic indices. Toxicity arising from drug-herb interactions may be minor, moderate, or even fatal, depending on a number of factors associated with the patients, herbs, and drugs.[1]

St John's wort, derived from the plant *Hypericum perforatum,* has been used since ancient times for depression and anxiety. It is the most common antidepressant used in Germany. St John's wort induces a hepatic enzyme through activation of the CYP system, leading to decreased plasma levels of a wide range of prescribed drugs, with possible clinically serious consequences. For example, St John's wort ingested for 10 days by a group of healthy volunteers reduced the bioavailability of digoxin by an average of 25%. St John's wort ingested for 2 weeks reduced total absorption of indinavir by 50%, which is large enough to cause treatment failure. Other reports indicated significant increases in the metabolism of warfarin, theophylline, oral contraceptives, or cyclosporine. In transplant recipients, toxicity and underdosage of calcineurin inhibitor–based immunosuppression have been linked to phytochemically triggered activity changes of cytochrome P-450 isoenzyme CYP3A4 metabolism and drug transport proteins. Concomitant use of St John's wort in renal transplant recipients treated with cyclosporine or tacrolimus could favor graft rejection.[44,45]

Gingko biloba is one of the most popular plant extracts in Europe and recently received approval in Germany for treatment of

Websites Providing Data on Herbal Therapy Hazards	
Web Address	**Website**
www.fda.gov	On the Food and Drug Administration website under the title Medwatch, some herb warnings can be found ("special adverse event monitoring system" link)
www.nnlm.nlm.nih.gov/pnr/uwmhg/	University of Washington Medicinal Herb Garden
www.nim.nih.gov/medlineplus/herbalmedicine.html	Provides an update on ongoing clinical studies involving herbal products, news, and many links
www.update-software.com/abstracts/mainindex.html	The Cochrane Collaboration maintains an updated international database of clinical trials involving complementary and alternative medicine
www.amfoundation.org	An organization that provides consumers and professionals with responsible evidence-based information on the integration of alternative and conventional medicine
www.herbmed.org	An interactive electronic herbal database that provides hyperlinked access to scientific data underlying the use of herbs for health; an evidence-based information resource for professionals, researchers, and the general public
http://nccam.nih.gov	The National Center for Complementary and Alternative Medicine is 1 of 27 institutes and centers that make up the U.S. National Institutes of Health; their mission is to support rigorous research on complementary and alternative medicine, train researchers, and disseminate information to the public and professionals
http://toxnet.nlm.nih.gov	A cluster of databases on toxicology, hazardous chemicals, and related areas

Table 78-3 Some websites providing data on herbal therapy hazards. *(From reference 6.)*

dementia. *G. biloba* is composed of several flavonoids, terpenoids (e.g., ginkgolides), and organic acids believed to act synergistically as free radical scavengers. It has been suggested that *G. biloba* should not be administered with concomitant anticoagulation or in patients with bleeding disorders. Concomitant use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), as well as anticoagulants such as warfarin and heparin, is ill advised. Spontaneous hyphema and spontaneous bilateral subdural hematomas have been observed in patients taking *G. biloba* and attributed to ginkgolide B, a potent inhibitor of platelet-activating factor needed to induce arachidonate-independent platelet aggregation. Hemorrhagic complications were observed often in patients administered concomitant antiaggregant or anticoagulant therapy. The exact mechanism of the interaction of *G. biloba* with aspirin, warfarin, and NSAIDs remains unclear. Experimental data from rats suggest that a *G. biloba* diet markedly increased the content of CYP and activity of glutathione-*S*-transferase and markedly induced the level of CYP2B1/2, CYP3A1, and CYP3A2 messenger RNA in the liver.[46]

In summary, herbal medicines may exert renal toxicity through their inherent properties, occasionally dose-related or idiosyncratic toxicity, herb-drug interactions, and misidentification and adulteration of the preparation. Herbal medicines also may be hazardous for renal patients because of interactions with drugs such as cyclosporine or because of their potassium content. However, most information about the toxicity of herbal medicines is found only in case reports. Precise identities of the culprit substances and the toxicologic characteristics and pathogenic mechanisms of herbal medicines remain largely unknown. Whereas many herbs have been used for centuries without incidence of acute renal damage, insidious damage caused by long-term use is a concern because many herbs have not been rigorously tested for toxicity. There are websites that provide data on herbal therapy hazards (Table 78-3).

OVER-THE-COUNTER MEDICINES AND THE KIDNEY

In addition to the increasing popularity of OTC health foods, nutritional supplements, and medicinal products from plants or other natural sources, there is increasing consumption in many countries of pharmaceutical products bought OTC. These particularly include analgesics and agents for treatment of dyspepsia.

Analgesics

Over-the-counter analgesics constitute one of the most widely used classes of drugs in the developed world. The primary indications for use of OTC analgesics include fever and minor musculoskeletal symptoms; population studies and World Health Organization (WHO) statistics indicate that 10% to 50% of individuals have a history of musculoskeletal disorders. NSAIDs, such as aspirin, ibuprofen, and naproxen, are also used to treat inflammatory conditions; and aspirin is used prophylactically as an anticoagulant in thrombosis-related disorders. Acetaminophen (paracetamol), aspirin, ibuprofen, and naproxen are available OTC in many countries, sometimes in combinations. Easy access to OTC analgesics runs the risk of unwarranted and unsupervised chronic intake. Although studies on the association between the long-term use of aspirin, NSAIDs, and other analgesics and ESRD have given conflicting results, many studies have suggested an association between chronic ingestion of analgesics and kidney disease.

Because analgesic use is very widespread, even a small percentage of increased risk of kidney disease may have major public health implications. NSAIDs inhibit cyclooxygenase and may inhibit lipoxygenase, decreasing the production of prostaglandins and leukotrienes, which accounts for many NSAID-induced renal effects. In patients with volume depletion, renal perfusion depends on circulating prostaglandins to vasodilate the afferent arterioles, allowing more blood flow through the glomerulus. So the contribution of prostaglandins to renal homeostasis is most critical in elderly patients and those with circulatory disturbances, such as renal or liver dysfunction, congestive heart failure, or volume depletion.[47]

Patients who warrant chronic therapy with analgesics and NSAIDs should be closely monitored by regular screening with dipstick urinalysis and serum creatinine for early evidence of kidney injury. Early detection and removal of the offending agent could halt or even reverse analgesic-induced kidney injury. There is a pressing need for multicenter prospective trials to assess the true incidence of this

problem and to study the effects of various analgesic agents (alone and in combination) in at-risk populations.

Analgesic Nephropathy

Analgesic nephropathy is defined as a disease resulting from the habitual consumption over several years of compound analgesics, which is characterized by renal papillary necrosis and chronic interstitial nephritis. It is an increasingly rare condition because phenacetin (the analgesic most implicated as a causative agent) has been banned in many countries. A retrospective cohort study using data from the Australia and New Zealand Dialysis and Transplant registry showed that among 31,654 patients receiving renal replacement therapy over the previous 35 years, 10.2% had analgesic nephropathy, but there was a marked decrease in the incidence more recently to less than 3.5% in 2005.[48] Analgesic nephropathy is discussed further in Chapter 64.

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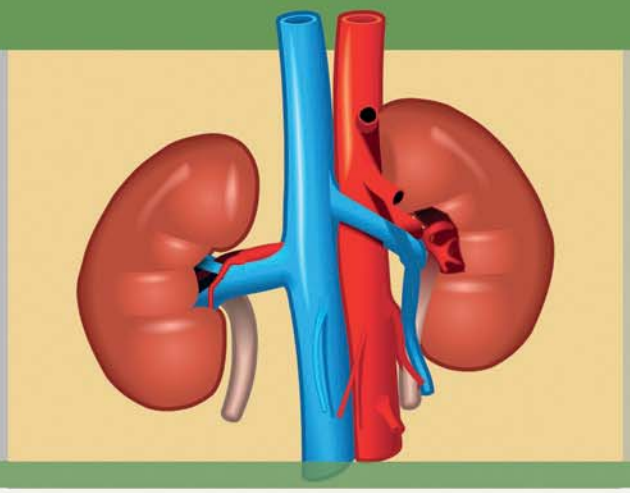
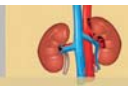


SECTION XVI

Chronic Kidney Disease and the Uremic Syndrome

CHAPTER 79



Epidemiology, Natural History, and Pathophysiology of Chronic Kidney Disease

Meguid El Nahas and Arif Khwaja

DEFINITION AND CLASSIFICATION OF CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is defined as kidney damage or an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m^2 persisting for 3 months or more irrespective of the cause. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines have classified CKD into five stages.[1] The Kidney Disease: Improving Global Outcomes (KDIGO) group suggested clarifications including the addition of the suffix *T* for patients with renal allografts and *D* to identify CKD stage 5 patients on dialysis.

The latest 2012 KDIGO CKD classification recommends detailing the cause of CKD and classifying into six categories related to glomerular filtration rate (G1 to G5, with G3 split into 3a and 3b) but also based on three levels of albuminuria (A1, A2, and A3), each assessed according to the urinary albumin-creatinine ratio (in mg/g or mg/mmol in an early morning "spot" urine sample). The term *microalbuminuria* is no longer incorporated into this classification; the term *moderate level of albuminuria* is used (30 to 300 mg/g or 2.5 to 30 mg/mmol) (Fig. 79-1).[2]

The improved classification of CKD has been of benefit to identify prognostic indications related to decreased kidney function as well as increased albuminuria. This has led to increased awareness of CKD as well as appreciation of the significant impact of CKD on health care worldwide. However, a downside of the use of the classification systems is the possible overdiagnosis of CKD, at least among certain categories of eGFR and albuminuria, especially among the elderly.

Limitations of Chronic Kidney Disease Classification

Estimating Glomerular Filtration Rate

The current CKD classification is based on eGFR (see Chapter 3). The Modification of Diet in Renal Disease (MDRD) study equation and the more recently developed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation are both commonly used equations to calculate eGFR; however, both are relatively inaccurate in reflecting measured glomerular filtration rate (mGFR) above 60 ml/min/1.73 m^2. This underestimation by eGFR of true mGFR can lead to misclassification of a large number of individuals as having CKD stage 3a, whereas in reality their true GFR is above 60 ml/min. Also, the inaccuracy of eGFR to reflect mGFR above 60 ml/min/1.73 m^2 makes the distinction between CKD stages 1 and 2 difficult and artificial. The limitations of using creatinine-based estimations have spurred the search for alternative filtration biomarkers, such as β-trace protein (βTP), cystatin C, and β_2-microglobulin (β_2M). (See Chapter 3 for alternative estimations of GFR.)

Microalbuminuria (Moderately Increased Albuminuria) as a Definition for Chronic Kidney Disease

Isolated microalbuminuria (i.e., moderate level albuminuria; A2 category) is a common feature of aging and can be associated with a large number of acute and chronic inflammatory as well as vascular pathologies.[3] It is also associated with obesity, cigarette smoking, and unhealthy diets. Furthermore, microalbuminuria is often transient and reversible, thus not justifying its specific defining role in CKD (stages 1 and 2). Whereas microalbuminuria may highlight those at increased relative risk of CKD progression or cardiovascular risk, the absolute risk to the individual remains low. Therefore the retention of microalbuminuria as a sole definition of CKD in spite of its obvious lack of specificity to kidney disease remains controversial and potentially misleading.

Age-Related Decline in Kidney Function

The great majority of individuals classified as having CKD in the community are over the age of 60 years—in part a reflection of physiologic age-related decrease in kidney function.[3] The current CKD definition and classification are age neutral; therefore the difference in outcomes among different age groups is not recognized. Thus, under the current classification, an 80-year-old man with G4A1 is deemed to be at higher risk of progression to end-stage renal disease (ESRD) than a 20-year-old with G3A2, yet the outcomes in CKD are markedly age sensitive. This was elegantly demonstrated by the calculation of a threshold eGFR. ESRD exceeded the risk of death in a cohort of more than 200,000 U.S. veterans with CKD stages 3 to 5; the level of eGFR below which the risk of ESRD exceeded the risk of death varied by age, being 45 ml/min/1.73 m^2 for 18- to 44-year-olds to 15 ml/min/1.73 m^2 for those 65 to 85 years old.[4] Thus in the absence of associated albuminuria, CKD is seldom progressive to ESRD in the elderly, as it may to a large extent reflect age-related decline in kidney function.

Further Considerations

The current classification takes no notice of the single most important risk factor associated with CKD, namely, systemic hypertension. The current classification also does not determine whether CKD is progressive or not—that is, it does not incorporate values for the trajectory of renal function (eGFR) over time. KDIGO suggests defining progressive kidney disease as a sustained decline in eGFR of more than 5 ml/min/1.73 m^2/yr or a decline in GFR category accompanied by a greater than 25% drop in eGFR from baseline. Defining progression is problematic because the eGFR equations perform relatively poorly when the GFR is greater than 60 ml/min/1.73 m^2 and because serum creatinine often fluctuates in patients with nonprogressive CKD. Also, declining true or measured GFR concomitant with loss of muscle mass (sarcopenia) may not be

KDIGO Classification and Prognosis of Chronic Kidney Disease 2012

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min/1.73 m²) description and range				Persistent albuminuria categories description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red: very high risk.

Figure 79-1 Classification and prognosis of chronic kidney disease from 2012 KDIGO guidelines. *CKD,* Chronic kidney disease; *GFR,* glomerular filtration rate; *KDIGO,* Kidney Disease: Improving Global Outcomes. *(From reference 2.)*

appropriately detected by creatinine-based eGFR assessment. Thus the current classification system has no mechanism to alert the clinician to the patients in whom the disease is actually progressing and who therefore may require intervention.

Altogether, although classification of CKD based on eGFR and albuminuria has undoubted advantages and has achieved greater awareness of CKD and its impact on global health, there remain a number of limitations that may give rise to misinterpretation and miscategorization of individuals, particularly in the growing elderly population.

EPIDEMIOLOGY OF CHRONIC KIDNEY DISEASE

The true incidence and prevalence of CKD within a community are difficult to ascertain because early to moderate CKD is usually asymptomatic. However, various epidemiologic studies suggest a prevalence of CKD of approximately 10% to 14% in the general population, albuminuria (mostly microalbuminuria or A2) of approximately 7%, and GFR below 60 ml/min/1.73 m^2 of approximately 3% to 5% (Fig. 79-2 and Table 79-1).[5]

Most of these studies are limited by the fact that individuals were tested only once; thus the studies merely reflect a snapshot with no clear evidence of chronicity.[6] KDOQI stipulates that tests should be undertaken on three occasions over a 3-month period, with two of three results being consistently positive to justify the labeling of chronicity and CKD.[1]

Of note, the high reported prevalence of CKD is confounded by a number of facts:

- Low-level albuminuria (previously designated *microalbuminuria*) is included, despite its obvious lack of specificity to kidney disease (discussed earlier)
- The majority of those screened in the community and found to have reduced eGFR are elderly individuals, most probably with age-related decline in kidney function.
- Formulas such as those of MDRD and CKD-EPI are used to estimate GFR in spite of their known limitations (see Chapter 3). It is interesting to note that the prevalence of CKD in communities varies up to threefold based on the type of equation applied.[7]

All these limitations of current CKD screening strategies are at risk of overinflating the true prevalence of significant CKD.

CHRONIC KIDNEY DISEASE DETECTION RECOMMENDATIONS

The rationale for screening at-risk individuals for CKD is to permit earlier detection of CKD, allowing interventions aimed at slowing its progression. In addition, detection of CKD may identify individuals within communities at risk for complications, including cardiovascular disease (CVD) and associated morbidity and mortality.

Several guidelines for screening, mostly targeted at high-risk individuals, have been issued and implemented worldwide. Those include the KDOQI guidelines in the United States, the CKD National Institute for Health and Care Excellence (NICE) guidelines, and the Australian Caring for Australasians with Renal Impairment (CARI) guidelines. There are few differences regarding the recommended targeted high-risk populations, but they invariably include individuals with hypertension and diabetes mellitus (Table 79-2). The KDOQI guidelines additionally recommend screening those older than 65 years. Screening should consist of urinalysis, a urine albumin or protein estimation (such as urine albumin-creatinine ratio [uACR]), and measurement of serum creatinine and estimation of GFR (see Chapter 3), preferably by the CKD-EPI equation (KDIGO 2012). Targeted screening is the most cost-effective

CKD Prevalence by CKD Stages in the United States

Percentage of US population by eGFR and albuminuria category: KDIGO 2012 and NHANES 1999–2006				Persistent albuminuria categories description and range			
				A1	A2	A3	
				Normal to mildly increased	Moderately increased	Severely increased	
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol	
GFR categories (ml/min/1.73 m^2) description and range	G1	Normal or high	≥90	55.6	1.9	0.4	57.9
	G2	Mildly decreased	60–89	32.9	2.2	0.3	35.4
	G3a	Mildly to moderately decreased	45–59	3.6	0.8	0.2	4.6
	G3b	Moderately to severely decreased	30–44	1.0	0.4	0.2	1.6
	G4	Severely decreased	15–29	0.2	0.1	0.1	0.4
	G5	Kidney failure	<15	0.0	0.0	0.1	0.1
				93.2	5.4	1.3	100.0

Figure 79-2 Chronic kidney disease (CKD) prevalence by CKD stages in the United States. *eGFR,* Estimated glomerular filtration rate; *KDIGO,* Kidney Disease: Improving Global Outcomes; *NHANES,* National Health and Nutrition Examination Survey. *(From reference 2.)*

Representative Population-Based Studies on Chronic Kidney Disease (CKD) Epidemiology

				Outcome (%)	
Study	**Country**	**Design**	**N**	**MA**	**CKD**
NHANES III	United States	CS, L	15,626	12	11
PREVEND	Netherlands	CS, L	Approximately 40,000	7	
NEOERICA	United Kingdom	CS, service based	130,226		11 F, 6 M
HUNT II	Norway	CS	65,181	6	10
EPIC-Norfolk	United Kingdom	CS	23,964	12	
MONICA Augsburg	Germany	CS	2136	8	
AusDiab	Australia	CS	11,247	6	10
Taiwan	Taiwan	CS, L	462,293		12
Beijing	China	CS	13,925		13
Takahata	Japan	CS	2,3217	14	
CNSCKD	China	CS	47,204	9.4	1.7
India	India	CS	5000	2.25	4.2/13.3
Japan	Japan	CS	527,594		20

Table 79-1 Representative population-based studies on CKD epidemiology. Outcome = patients with CKD or microalbuminuria (MA). *AusDiab,* Australian Diabetes, Obesity and Lifestyle study; *CNSCKD,* China National Survey of Chronic Kidney Disease; *CS,* cross-sectional; *EPIC,* European Prospective Investigation into Cancer and Nutrition; *F,* female; *HUNT II,* second Nord-Trøndelag health study; *L,* longitudinal; *M,* male; *MONICA,* Monitoring Trends and Determinants in Cardiovascular Diseases; *N,* number of participants; *NEOERICA,* New Opportunities for Early Renal Intervention by Computerised Assessment; *NHANES III,* Third National Health and Nutrition Evaluation Survey; *PREVEND,* Prevention of Renal and Vascular End-Stage Disease; *service based,* patients' data were collected from general practitioner computer records.

International Recommendations for Targeted Screening for Chronic Kidney Disease (CKD)

	Guidelines			
Targeted Group	**KDOQI**	**NICE**	**CARI**	**CSN**
Elderly	•			
Hypertension	•	•	•	•
Diabetes mellitus	•	•	•	•
Atherosclerotic		•	•	•
Cardiovascular disease, heart failure		•		•
Urologic disease, stone disease, recurrent urinary infections	•	•		
Systemic autoimmune conditions	•	•		•
Nephrotoxic drugs	•	•		•
High-risk ethnic groups	•		•	•
Family history of CKD	•	•		
Other high-risk groups may include smokers and patients with metabolic syndrome, obesity, low birth weight, systemic infections, reduced renal mass, and previous acute kidney injury.				

Table 79-2 International recommendations for targeted screening for CKD. *KDOQI,* Kidney Disease Outcomes Quality Initiative; *NICE,* U.K. National Institute for Health and Care Excellence; *CARI,* Caring for Australasians with Renal Impairment; *CSN,* Canadian Society of Nephrology.

approach, and there is no evidence to justify screening asymptomatic individuals in the general population for CKD (see Table 79-2).[8]

Chronic kidney disease screening would best be associated with broader national strategies and programs to minimize obesity, diabetes, hypertension, and primarily CVD. This is the essence of the U.K. National Vascular Campaign strategy launched in 2009 and of the campaigns implemented by the Centers for Disease Control and Prevention (CDC) in the United States and in Australia.

EPIDEMIOLOGY OF END-STAGE RENAL DISEASE

Incidence rates of ESRD refer to the number of patients per million population per year (pmp/yr) beginning renal replacement therapy (RRT). Incidence rates of ESRD in most national registries do not take into account patients not treated with RRT and therefore underestimate the true incidence of ESRD (CKD stage G5). This is true not only in countries where provision of RRT is limited or absent, but also in countries where there is an active conservative management program for patients who opt not to have RRT (Table 79-3).

The prevalence rate of ESRD is the number of patients per million population (pmp) who have undergone treatment for ESRD. Prevalence rate is a function of the incidence rate (newly treated cases) and outcomes (i.e., mortality and return of ESRD after a failed renal transplant) in a given population. It is important to note that the eGFR at initiation of dialysis will have a marked impact on the prevalence of ESRD—indeed, most of the growth in the ESRD population in the United States in the last 15 years may be accounted for by earlier initiation of dialysis rather than by a true increased incidence of ESRD.[9,10]

Disparities in the incidence and prevalence of ESRD relate to cultural, socioeconomic, and demographic factors. Racial and ethnic diversity within societies affects not only the prevalence of diabetes and hypertension but also progression rates and ESRD prevalence.

Incidence and Prevalence of End-Stage Renal Disease (ESRD) in Different Countries (2010)

Country and Ethnicity	**Incidence**	**Prevalence**
United States	348	1752
Caucasians	295	1218
African Americans	924	5242
Asians	320	2000
Hispanics	480	2606
Australia	101	849
Aboriginal/Torres Strait	353	2151
Japan	288	2260
Taiwan	361	2584
Mexico	425	1402
Bangladesh	20	158
United Kingdom	107	832
France	149	1060
Russia	40	186

Table 79-3 Incidence and prevalence of ESRD in different countries.

Differing referral patterns and quality of pre-ESRD care have all been linked to the heterogeneity of ESRD rates in different parts of the world. Developed countries with liberal access policies toward ESRD treatment will logically have the highest prevalence rates of treated ESRD,[11] although economically emerging countries with historically low ESRD treatment rates can experience rapid growth rates when access to treatment improves. Presently, 90% of the global RRT population is from high-income economies, and more than 100 countries have no provision for RRT.

During the forthcoming decades, even industrialized nations will struggle to meet the demands of expanding ESRD programs; in the United States, the annual expenditure on ESRD will likely reach more than $52 billion by 2030.[12] The improving survival rate while patients are undergoing treatment (dialysis or transplantation) aggravates the spiraling cost of care. In the United Kingdom, expenditure on ESRD currently consumes about 2% of the National Health Service budget, even though the number of patients undergoing ESRD treatment is about 0.05% of the population. Globally, the number of individuals receiving RRT has risen from 426,000 in 1990 to 2.5 million in 2010, and the cumulative global cost for RRT is estimated to exceed $1 trillion during the current decade.[12]

The limited provision of RRT in some low and middle economies may also reflect the fact that CKD and ESRD are not health care priorities in these countries. This is a direct consequence of the fact that CKD and its associated mortality ranked as low as the 18th cause of death in 2010, well after coronary heart disease, chronic respiratory diseases, diabetes, hypertension, cancer, and major communicable diseases.[13] Increased awareness of the detrimental and multiplicative effect of CKD on other major causes of global morbidity and mortality may in the future increase the awareness of the global health care impact of CKD.

Impact of Chronic Kidney Disease on Morbidity and Mortality

A decrease in eGFR below 60 ml/min/1.73 m^2 and increased albuminuria are associated with increased cardiovascular as well as overall morbidity and mortality, and the effects of combined

decreased GFR and increased albuminuria on mortality are synergistic (see Chapter 82).[14] However, decreased GFR and increased albuminuria are markers of ill health, thus generally reflecting poor outcomes. Also, albuminuria is increasingly defined by a raised uACR. Interpretation of the predictive value of albuminuria as albumin-creatinine ratio (ACR) is confounded by the inclusion of urine creatinine because a fall in urinary creatinine excretion that causes a rise in ACR, may also reflect ill health and the associated sarcopenia. Sarcopenia may also be associated with a low serum creatinine and an elevation of eGFR (>120 ml/min) that has been associated with poor outcomes.[14]

The fall in GFR with age has been linked to underlying comorbidities such as lifelong hypertension and diabetes. The term *cardio-kidney-damage* has been coined to highlight the close links between cardiovascular and kidney damage.[15] It is therefore not surprising that CKD in the elderly predicts cardiovascular morbidity and mortality.

Nevertheless, when the predictive values of albuminuria and/or eGFR on morbidity and mortality have been compared with or when these values have been added to well-established cardiovascular prognostic markers and scores, such as the Framingham Risk Score (FRS), they were found to add very little to the accuracy of risk prediction.[16]

NATURAL HISTORY OF CHRONIC KIDNEY DISEASE

Describing the natural history of CKD calls for a distinction between CKD detected in the general population (community CKD) and in those who are referred to nephrology centers (referred CKD).

Community CKD is to a large extent a disease of elderly individuals with comorbidities, associated with a reduced and very slow age-related decline in GFR, with the majority dying before reaching ESRD. In contrast, referred CKD patients often have significant acquired or inherited nephropathies causing early renal functional impairment and progression with time to ESRD. The cause and natural history of these two populations is likely to be considerably different.

Causes and Natural History of Community Chronic Kidney Disease

In the developed world, the majority of community CKD is identified in older people. The average rate of decline of GFR in this population is approximately 0.75 to 1 ml/min/yr after the age of 40 to 50 years.[3] CKD affects those who have had a lifelong exposure to cardiovascular risk factors—hypertension and diabetes—that can also affect the kidneys. U.S. Medicare data demonstrate that 48% of patients with CKD have diabetes, 91% are hypertensive, and 46% have atherosclerotic heart disease. Given that more than one third of aging adults have systolic hypertension and about 20% have type 2 diabetes mellitus (T2DM), it is not surprising that up to 40% of such individuals have evidence of CKD. They also have a higher incidence of cardiovascular and atherosclerotic diseases. This has led to the formulation of prediction scores of incident community-based CKD, based on the presence of vascular risk factors such as hypertension and diabetes as well as peripheral vascular disease and heart failure—the SCORED model (Screening for Occult Renal Disease).[17]

In a large analysis of community-based CKD over 5 years, only 1% and 20% of patients with CKD G3 and G4 required RRT, whereas 24% and 45%, respectively, died, predominantly from CVD.[18] Thus death rather than progression to ESRD is the predominant outcome in elderly community-based CKD.[18]

Community CKD in emerging countries is often multifactorial because of communicable and noncommunicable disease affecting the kidneys. In these countries, in addition to the poverty that has an impact on CKD, individuals often develop infections that can cause CKD (see Chapters 53 to 58). They are also subject to increased globalization and westernization of lifestyle that predispose them to obesity, diabetes, hypertension, and CVD, which can lead to CKD. The renal risk is increased further by unfavorable environmental factors, including maternal deprivation and malnutrition, which relate to CKD in later life[19]; air and water pollution; exposure to heavy metals and agricultural pollution; and aristolochic acid (see Chapter 64) and other herbal toxins, in particular in China and Taiwan (see Chapter 78). Reports of epidemics of CKD have emanated from a number of regions of the world, including Central American countries such as Salvador, among agricultural workers in sugar cane and cotton plantations who are exposed to excessive heat resulting in chronic dehydration, hypokalemia, and premature death.[20] These effects may be compounded by exposure to pesticides and consumption of nonsteroidal anti-inflammatory drugs (NSAIDs).

Causes and Natural History of Referred Chronic Kidney Disease

In contrast to community CKD, the causes and natural history of referred CKD vary considerably. Patients with referred CKD often present at an earlier age because of an underlying hereditary nephropathy (such as autosomal dominant polycystic kidney disease [ADPKD]) or acquired nephropathy (such as glomerulonephritis [GN], diabetic nephropathy, or tubulointerstitial disease) causing progressive damage and loss of function. Some present early with signs of kidney damage such as moderate albuminuria or hematuria in the absence of impaired kidney function (CKD stages G1 and G2, A1 and A2). The prognosis of such patients in the absence of hypertension, overt proteinuria, and/or impaired renal function is generally good because they can remain within these stages for years without progressing to CKD stage G3 or higher. However, some go on to progress with time, thus justifying vigilance and regular follow-up.

The rate of progression of referred CKD varies according to the underlying nephropathy and between individual patients. Historically, the rate of decline in GFR of patients with diabetic nephropathy has been among the fastest, averaging around 10 ml/min/yr. Control of systemic hypertension, hyperglycemia, and other factors slows the rate of GFR decline (see Chapter 80). In nondiabetic nephropathies, the rate of progression of CKD is usually faster in patients with chronic proteinuric GN than in those with chronic interstitial nephritis and low-level proteinuria. It is slowest in those with hypertensive nephrosclerosis with good blood pressure (BP) control and minimal proteinuria. Patients with ADPKD and impaired renal function, CKD stage G3b and beyond, may also have a fast rate of progression compared with patients with other nephropathies.

It is generally assumed that the majority of patients with underlying nephropathies reaching CKD stages G3 to G5 progress relentlessly to ESRD, yet even in the referred population progression is variable, with a sizable percentage of patients either having stable kidney function or dying prematurely of CVD. A Canadian study showed the natural history of referred CKD stages G3 and G4 to be variable, reflecting the patient's risk factor profile.[21,22] Even some patients with CKD stage G5 remain stable for a number of years.

A straight-line relationship is often found between the reciprocal of serum creatinine (1/SCr) values or the eGFR and time (for methodologic aspects, refer to Chapter 80). However, this is not the rule because many patients have a nonlinear decline in renal function. Many patients have breakpoints in their progression slopes, suggesting acceleration or slowing down of the rate of progression of CKD, in particular because of intercurrent or superimposed acute kidney injury (AKI). However, the true significance of the association between AKI and CKD remains to be elucidated because there is co-localization of risk factors for both AKI and CKD.[23]

PREDICTORS OF PROGRESSIVE CHRONIC KIDNEY DISEASE

Prediction of CKD progression is essential in targeting therapeutic intervention and planning care. In older community-based CKD patients, a history or manifestations of CVD or even subclinical signs such as an increased carotid-intima thickness or cerebral microinfarcts have all been associated with incident as well as progressive CKD.[24]

In younger patients with referred CKD, progression is predictable by the degree of impaired kidney function at presentation, hypertension and its control, and the severity of proteinuria and albuminuria. One such model includes age, gender, eGFR, albuminuria, serum calcium, serum phosphate, serum bicarbonate, and serum albumin.[21] Models of CKD progression and its cardiovascular complications as well as those predicting all-cause mortality linked to CKD have been systematically reviewed and found to lack strong validation and usefulness justifying additional research.[25]

Whether novel biomarkers of CKD (circulatory or genetic) can improve prediction remains unclear, and impact studies of CKD prediction models have not been conducted.[25] Given the diverse complexity of the pathophysiologic processes underpinning progression, it is unlikely that a single biomarker will identify those at risk of progression with robust sensitivity and specificity.

CHRONIC KIDNEY DISEASE RISK FACTORS

Progression of age-related mostly community CKD tends to be slow and most likely affected by the severity of the underlying atherosclerotic vascular pathology (Box 79-1). In fact, some research has shown that the baseline severity of atherosclerosis, as estimated by the carotid intima-media thickness, correlates well with the severity of age-related decline in kidney function.

In referred CKD, once kidney function reaches stages G3 and above (eGFR <60 ml/min), progression is common and is influenced by a number of modifiable and nonmodifiable risk factors.

Nonmodifiable Chronic Kidney Disease Progression Risk Factors

Age (older age), gender (generally worse in males), and ethnicity (generally worse in non-Caucasian and ethnic minorities in the West: African Americans, Afro-Caribbean individuals, Hispanics, and Asians [South Asians and Pacific Asians]) all affect CKD progression.

Genetics

Genetic factors play an important role in CKD and its progression (discussed in Chapter 19). Genome-wide association studies (GWASs) have identified certain major histocompatibility complex (MHC) loci that affect the rate of CKD progression. Patients with monogenic conditions, such as ADPKD carrying the genotype PKD1, are thought to have a worse prognosis than others. Progression of CKD may also be influenced by polymorphisms of genes coding for putative mediators of renal scarring, including those coding for the renin-angiotensin-aldosterone system (RAAS).[26] Increasing interest has focused on the role of the myosin heavy chain MYH9 locus and the adjacent *APOL1* gene coding for apolipoprotein L1, on chromosome 22, in the development and progression of kidney disease in individuals of African descent (discussed in Chapter 19). Also, mutations affecting the structure and composition of podocytes (podocytopathies) have been identified in individuals affected by a range of conditions causing nephrotic syndrome in children and adults, with some linked to resistance to available therapies and progressive focal segmental glomerulosclerosis (FSGS). GWAS analysis also showed that single-nucleotide polymorphisms (SNPs) in the genes *TCF7L2* and *MTHFS* are associated with diabetic kidney disease and CKD progression in population-based cohorts.[26] Also, increasing attention is being paid to mutations of the uromodulin (Tamm-Horsfall protein) gene *(UMOD)* and its link to hypertension, hyperuricemia, tubulointerstitial fibrosis, and the progression of CKD.[27,28] Finally, epigenetic modifications may also be involved in the expression and progression of CKD.

Risk Factors Associated with Chronic Kidney Disease

- Age (older)
- Race or ethnicity (non-Caucasian)
- Genetics
- Birth weight (low)
- Systemic hypertension
- Diabetes mellitus
- Cardiovascular disease
- Albuminuria
- Obesity or metabolic syndrome
- Dyslipidemia
- Hyperuricemia
- Smoking
- Low socioeconomic status
- Nephrotoxin exposure: nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, traditional herbal use, heavy metals (such as lead)

Box 79-1 Risk factors associated with chronic kidney disease (CKD).

Modifiable Chronic Kidney Disease Progression Risk Factors

Modifiable risk factors for CKD progression include systemic hypertension, proteinuria, and metabolic factors.[29] In addition, interest has focused on the contribution of cigarette smoking, alcohol consumption, herbal agents, and recreational drug use to the risk for development of ESRD (see also Chapters 78 and 80).

Hypertension

Systemic hypertension is an important cause, consequence, and presenting feature of CKD (see Chapter 80) (Fig. 79-3). It is one of the leading causes of ESRD worldwide, the second leading cause in the United States after diabetes. Some experimental and epidemiologic studies have shown that sustained hypertension is indeed a significant contributor to the progression of CKD. Strong evidence

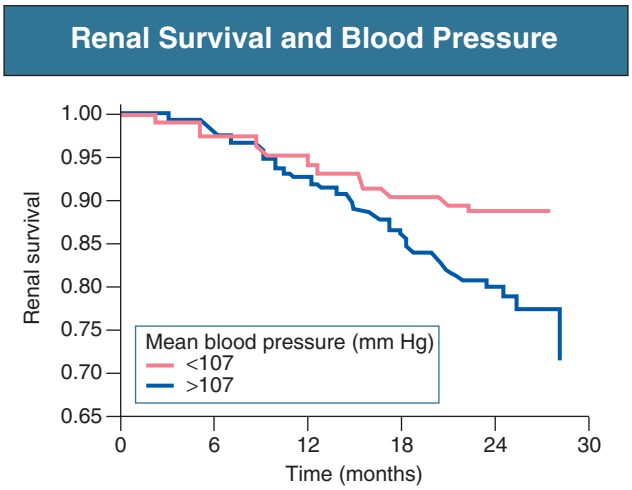


Figure 79-3 Actuarial renal survival in relation to blood pressure. *(Modified from reference 65.)*

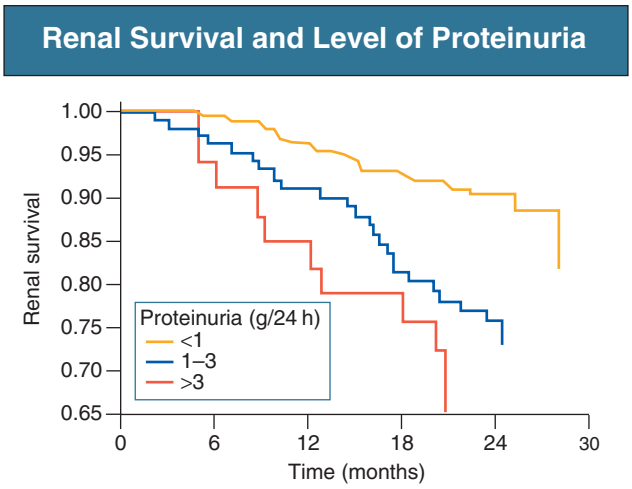


Figure 79-4 Actuarial renal survival in relation to proteinuria. *(Modified from reference 65.)*

links the progression of CKD to systemic hypertension in diabetic and nondiabetic kidney disease.[1] It is believed that the transmission of systemic hypertension into the glomerular capillary beds and the resulting glomerular hypertension contribute to the progression of glomerulosclerosis.[30]

Blood pressure parameters that correlate with the rate of progression of CKD include casual or office BP measurements, daytime versus nighttime BP, and 24-hour ambulatory BP measurement (ABPM). Nighttime and 24-hour ABPM seem to correlate best with CKD progression. Systolic BP (SBP) is also more predictive of CKD progression than diastolic BP and has also been linked to CKD complications. However, a U-shaped curve of SBP has also been reported with SBP values below 110 mm Hg, associated with faster rates of decline in eGFR.[31,32]

Target BPs in CKD patients are discussed in Chapter 80. It is most likely that target BP levels have to be individualized, with age, level of proteinuria, and comorbidities taken into consideration when patients with CKD are being treated, as suggested by the KDIGO CKD and management of blood pressure guidelines of 2012.[32]

Proteinuria

Numerous studies in patients with diabetic and nondiabetic renal diseases confirm that marked proteinuria (or albuminuria A3) is associated with a faster rate of CKD progression (Fig. 79-4).[33] Furthermore, reduction of marked proteinuria by diet or RAS blockade is often associated with a better renal outcome (see also Chapter 80); the extent of reduction in proteinuria is often, but not always, proportional to the benefit accrued by such intervention on CKD progression. A threshold of 1 g/day predicts progression in most kidney diseases but may be higher in certain glomerular diseases (such as membranous nephropathy).

Albuminuria or proteinuria is more likely to be a marker than a cause of progressive CKD because it reflects the severity of the underlying kidney damage. Interventions aimed at modifying the level of proteinuria, although mostly beneficial with regard to CKD progression, have been dissociated from the rate of decline in kidney function in some large interventional studies (e.g., Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension [ACCOMPLISH],[34] Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial [ONTARGET],[35] Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints [ALTITUDE][36]), in which significant declines in GFR were noted in spite of marked reduction in albuminuria. Consequently, moderate-level albuminuria (A2) is not a reliable surrogate marker for CKD progression in intervention clinical trials because reduction of albuminuria can be linked to both improving and worsening of CKD progression.

Renin-Angiotensin-Aldosterone System

The links between systemic hypertension, proteinuria and albuminuria, and CVD may be mediated by changes in the RAS in CKD. Experimental and clinical studies have implicated the RAS in the pathogenesis of hypertension, proteinuria, and renal fibrosis throughout the course of CKD. Consequently, interventions aimed at inhibition of the RAAS have proved effective in slowing the progression of CKD (see also Chapter 80). This has led to the almost universal treatment of patients with proteinuric and/or diabetic CKD with inhibitors of the RAAS.

Some uncertainty remains regarding whether the nephroprotective effect of renin-angiotensin system (RAS) inhibitors is completely dissociated from their antihypertensive effect.[37] Blood pressure has seldom been accurately measured, beyond casual office readings, in trials of RAS inhibition and CKD progression to dispel this assumption. In addition, GFR has once been measured accurately in randomized controlled trials (RCTs) of RAS inhibition and CKD progression; the sole exception is a small subgroup analysis of the Ramipril Efficacy in Nephropathy (REIN) study.[38]

Of interest, an analysis of progression of diabetic kidney disease in T1DM over the last 20 years, since the introduction of RAS inhibition, failed to show a significant impact of interventions on the rising trend of ESRD caused by diabetic nephropathy in the United States.[39] In older patients with T2DM, some studies have shown a detrimental impact of RAS blockade on the progression of CKD.[40,41] Finally, some preliminary observations suggest that the discontinuation of RAS inhibitors in advanced CKD may reverse functional decline to ESRD and lead to some functional recovery and delay in the initiation of RRT in selected patients.[42]

Regarding dual RAS blockade, the ONTARGET study proved such combination to be detrimental to renal function despite a reduction in proteinuria.[35] Dual blockade with renin antagonists failed in the ALTITUDE study, combining an ACE inhibitor and aliskiren (a renin antagonist) to slow progression of diabetic nephropathy, had to be stopped due to increased mortality; this in spite of a reduction in proteinuria.[36] There is consensus that RAS

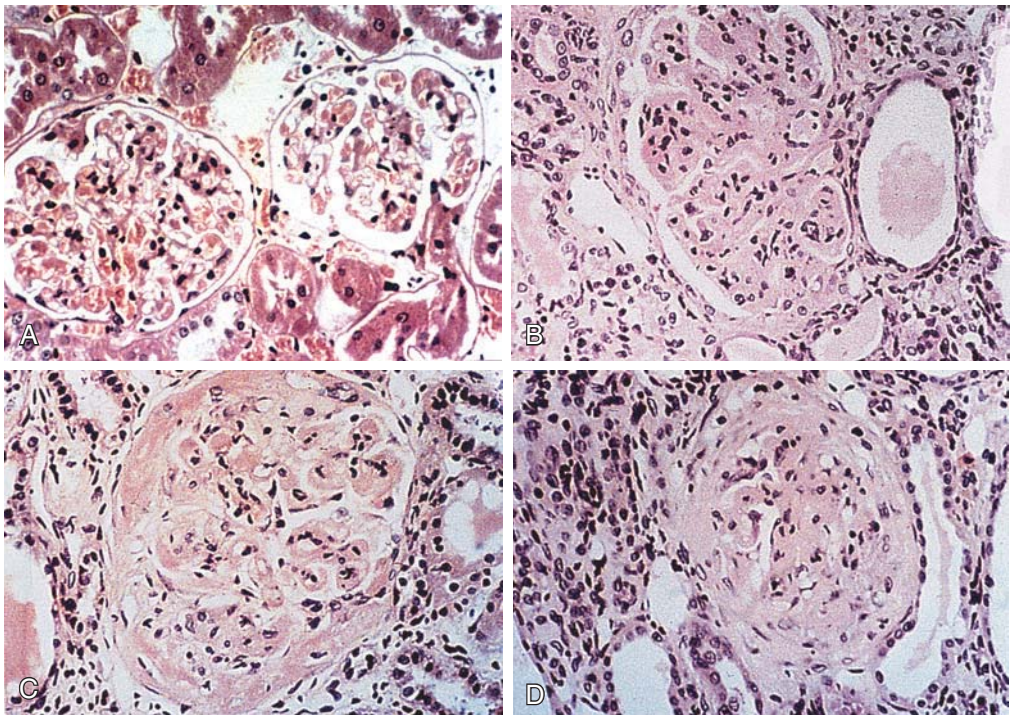


Figure 79-5 Histologic development of glomerulosclerosis. A, Normal glomerulus. **B,** Mesangial hypercellularity. **C** and **D,** Glomerulosclerosis of increasing severity. Note the tubular atrophy and dilation in **B** to **D,** indicating the parallel development of tubulointerstitial scarring.

inhibition is beneficial in hypertensive and proteinuric nephropathies,[32] but its use should be carefully monitored and caution exerted when prescribed in the elderly and those with underlying atherosclerotic disease. Combination therapy should be avoided in diabetic and high-risk individuals.

Additional Factors Implicated in Chronic Kidney Disease Progression

Obesity and smoking have been linked to the development and progression of CKD. Metabolic factors, including the metabolic syndrome and some of its components, such as insulin resistance, dyslipidemia,[43] and hyperuricemia,[44] have been implicated in the development and progression of CKD. In addition, high alcohol intake; use of recreational drugs, herbal agents and remedies, analgesics (paracetamol, phenacetin, and combinations of phenacetin, aspirin, and caffeine), and NSAIDs; and chronic exposure to lead and other heavy metals have all been linked to the development of CKD. The impact of glycemia control on the progression of diabetic nephropathy is discussed in Chapter 31.

MECHANISMS OF PROGRESSION OF CHRONIC KIDNEY DISEASE

Management of CKD is aimed at slowing progression, minimizing complications, and controlling modifiable progression factors such as hypertension, proteinuria, and RAS stimulation. In addition, a better understanding of the pathophysiology of CKD may open the way to treatments based on correction of key mediators of renal scarring and fibrosis.[45,46]

Unlike transient AKI, which often heals and after which the kidney functionally recovers, chronic and sustained insults to the kidney, such as those characterizing chronic and progressive nephropathies, evolve to progressive kidney fibrosis with destruction of the normal microarchitecture of the kidney and its replacement by fibrous tissue made of collagenous extracellular matrix, leading to loss of function and CKD and ESRD. This affects all three functional compartments of the kidney, namely the glomeruli, the tubules, and the interstitium, as well as the vessels and manifests histologically as glomerulosclerosis, tubulointerstitial fibrosis, and vascular sclerosis (Figs. 79-5 through 79-8).

Kidney scarring or fibrosis is a complex, overlapping, multistage phenomenon that could be characterized by a number of processes:

- An inflammatory response with infiltration of damaged kidneys by extrinsic inflammatory cells (blood borne and bone marrow derived)
- Activation, proliferation, and loss of intrinsic renal cells (through apoptosis or necrosis and including mesangiolysis and podocytopenia)
- Activation and proliferation of extracellular matrix (ECM)–producing cells, including myofibroblasts and fibroblasts
- Deposition of ECM replacing the normal renal architecture

Inflammatory Response to Tissue Injury

Inflammatory cells play an important role in both the renal healing and the scarring processes.[47,48] The outcome of initial renal damage depends on the balance between healing and scarring, thus determining whether kidney function recovers or declines.

The severity of the renal inflammatory cellular infiltrate correlates closely with the severity of renal dysfunction and predicts progressive CKD. Nonresolving tissue injury invariably initiates an inflammatory response with further recruitment of neutrophils, lymphocytes, monocytes and macrophages, dendritic cells, and masts cells to injured tissue, perpetuating a cycle of ongoing inflammation, tissue damage, and fibrosis.[47,48]

Neutrophils, platelets, eosinophils, and mast cells have, through their release of products, also been implicated in the pathogenesis of acute and chronic renal inflammation and fibrosis. But for the most part, a marked lymphomonocytic renal interstitial infiltrate is often the hallmark of progressive CKD.

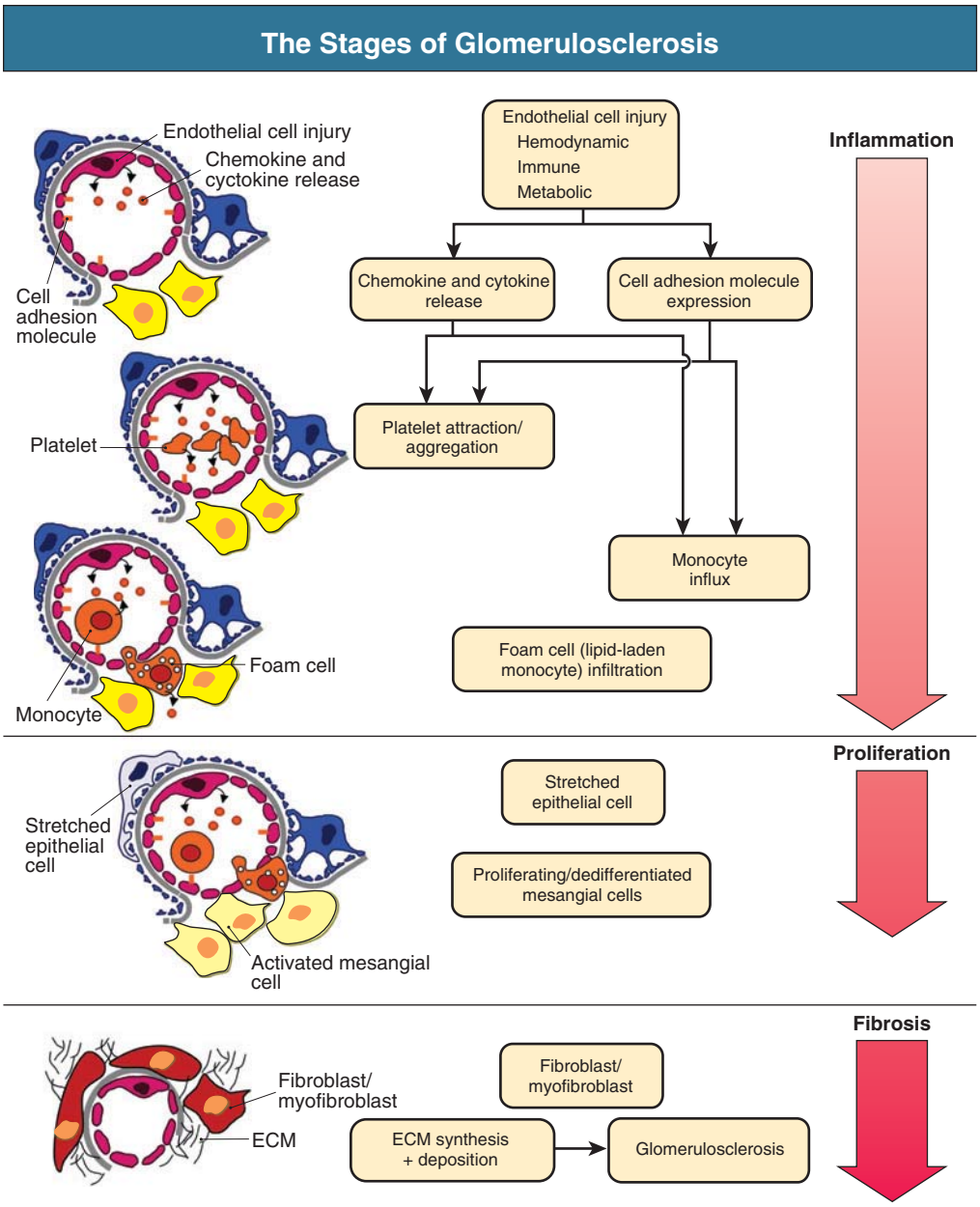


Figure 79-6 The stages of glomerulosclerosis. *ECM,* Extracellular matrix.

Lymphocytes

Lymphocytes, including helper and cytotoxic T cells, are often identified within damaged kidneys. It has been postulated that the balance between the proinflammatory T helper 1 (Th1) and the anti-inflammatory T helper 2 (Th2) lymphocytes may be a key factor in the progression or resolution of renal scarring.[49] This may also depend on the profile of the cytokines released by the T cells, with some—such as interleukin (IL)-1 and IL-2 and tumor necrosis factor α (TNF-α)—having proinflammatory and proliferative properties, and others—IL-4, IL-10, IL-13, and IL-25—having anti-inflammatory and antifibrotic properties. T lymphocytes may be directly cytotoxic but may also activate or attenuate the effector response of other inflammatory cells including monocytes.[49] Evidence also implicates $CD4^+$ T cells in fibrogenesis, either directly through stimulation of myofibroblast and fibroblast proliferation and ECM production or indirectly through activation of macrophages. Another subset of T cells (T regulatory cells [Tregs]) may exert beneficial effects on renal inflammation and fibrosis by switching off the proinflammatory effect of activated macrophages.

Monocytes

Monocytes play an important role in renal healing as well as scarring processes because they evolve into tissue macrophages on infiltration of the damaged kidney.[49,50] It is now clear that when circulating monocytes are recruited to damaged kidneys, they differentiate into two broad macrophage phenotypes. Classically activated (M1) macrophages have a proinflammatory, cytotoxic phenotype, whereas alternatively activated (M2; a to c) macrophages display a wound-healing phenotype that is likely to be the dominant form in response to chronic injury.[50] Macrophages appear to switch phenotype in response to their microenvironment. The release by these cells of cytokines, growth factors, reactive oxygen species (ROSs), and procoagulant factors is likely to contribute to the pathogenesis of glomerulosclerosis and tubulointerstitial fibrosis.

A protective role for macrophages in renal healing is now recognized; these cells also contribute to the termination and resolution of the renal inflammatory response, thus preventing fibrosis. Research based on the depletion of M1 macrophages in a range of experimental models of renal inflammation and fibrosis showed a

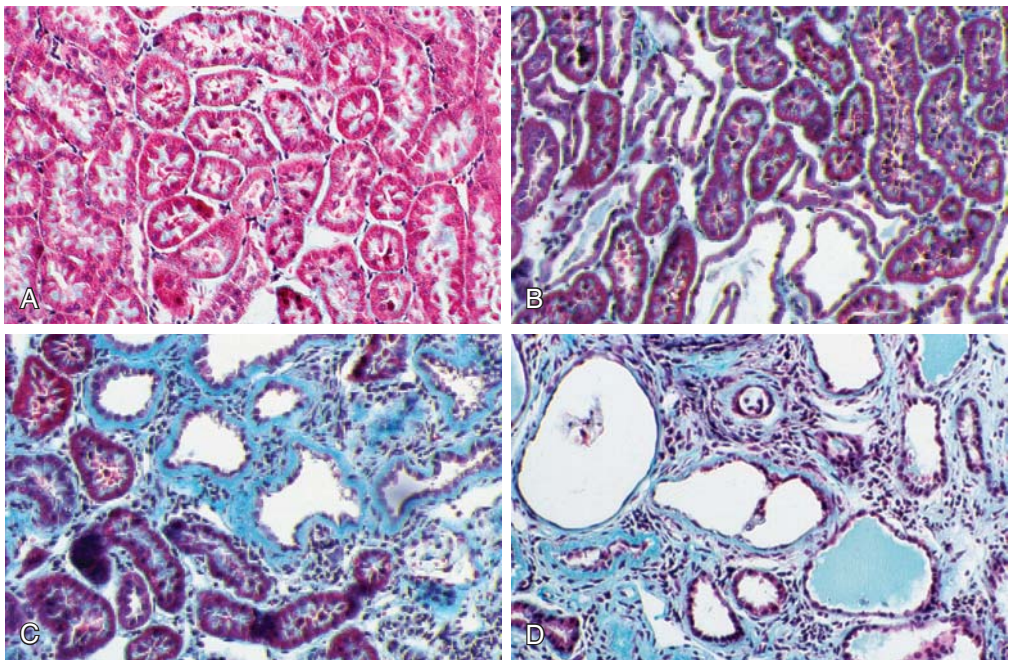


Figure 79-7 Histologic development of tubulointerstitial fibrosis. A, Normal tubulointerstitium. **B,** Mild tubulointerstitial scarring with tubular atrophy and interstitial edema. **C,** Segmental interstitial fibrosis. **D,** Diffuse interstitial fibrosis with tubular atrophy and dilation.

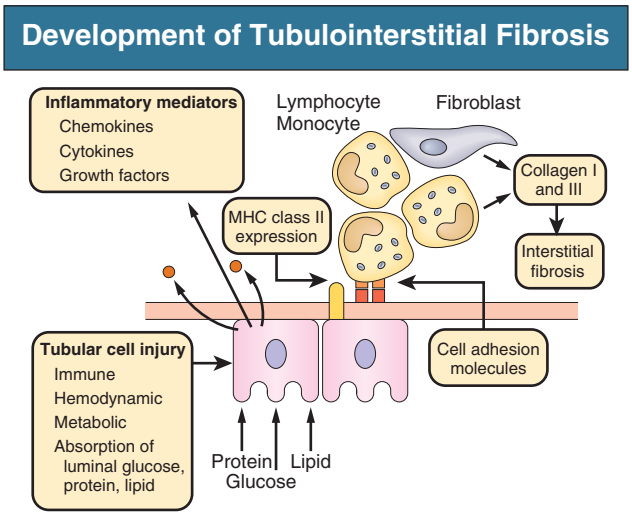


Figure 79-8 Development of tubulointerstitial fibrosis. *MHC,* Major histocompatibility complex.

protective effect. Similarly, the stimulation of M2 macrophages and/or their administration attenuates renal inflammation and subsequent fibrosis.[49,50] Thus, organ-specific and disease phase–specific microenvironments as well as the balance of phenotypic and functional macrophage changes may determine whether there is resolution of inflammation or progression to fibrosis. Macrophages are also capable of stimulating fibrogenesis either directly through their conversion to fibrocytes or the activation of myofibroblasts or indirectly through the stimulation of the transformation of pericytes to myofibroblasts.[51]

Dendritic Cells

Dendritic cells (DCs), a subset of cells that play an essential role in immunopathology of the kidney and the crosstalk with other proinflammatory cells, including T lymphocytes, also have a central role in the pathogenesis of kidney inflammation in different disease processes.[52,53] Immature DCs (iDCs) receive activation signals from injured kidney cells and acquire a mature phenotype that allows their migration into lymph nodes. These mature DCs (mDCs) are highly stimulatory (sDCs) and induce a range of effector responses through interactions with other tissue inflammatory cells.

As with lymphocytes and macrophages, dendritic cells play a role in the resolution of injury through assumption of protective phenotypes, such as tolerogenic dendritic cells (tDCs) and exhausted dendritic cells (exDCs). In fact, injection of activated plasmacytoid dendritic cells in an experimental model of renal fibrosis led to a switching off of the inflammatory response and reduction of fibrosis.

Bone Marrow–Derived Cells

Glomerular remodeling (repair-healing or scarring) may depend on the influx of hematopoietic and mesenchymal stem cells (MSCs) with the potential for repair or scarring.[54] The detection of cells displaying embryonic mesenchymal characteristics in glomeruli has led to the hypothesis that hematopoietic stem cells may be involved in normal glomerular cell turnover as well as in the response of glomeruli to injury. Experiments based on bone marrow transplantation have demonstrated the potential involvement of bone marrow–derived cells in normal mesangium turnover and in glomerular repair-repopulation after experimental mesangial injury. Also, interstitial and medullary renal progenitor cells may be called on after an acute injury to accelerate renal homeostasis and repair.

It has also been postulated that bone marrow–derived MSCs may be involved in fibrogenesis by migrating into scarred kidneys and contributing to the pool of fibroblasts. However, caution must be exerted before assumption of the therapeutic potential of these cells because some experiments have demonstrated their maldifferentiation, for example, into adipocytes within glomeruli. In humans, so far the safety of MSC therapy seems promising, but its efficacy remains to be established.

INTRINSIC RENAL CELL ACTIVATION, PROLIFERATION, AND LOSS

The secretion of profibrotic cytokines in an inflamed kidney leads to the activation of matrix-producing cells in the glomeruli and the tubulointerstitial space. These mediators are released by both infiltrating as well as resident cells. They include autacoids such as angiotensin II, endothelin, nitric oxide, and prostanoids, as well as growth factors such as transforming growth factor β1 (TGF-β1),[55] connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF).[47,48] These factors promote fibrosis by activating a variety of intracellular signaling cascades with consequent multiple effects on cellular activation, transformation, proliferation, migration, and ECM synthesis. Many of these mediators are potential targets for antifibrotic therapy. Of note, the progression of renal scaring and the associated fibrosis depend on the balance between these potentially harmful mediators and some protective ones such as lipoxins, resolvin, and relaxin,[56] as well as growth factors such as hepatocyte growth factor (HGF), and bone morphogenic protein 7 (BMP-7).

Glomerular Cells

Endothelial Cells

Glomerular endothelial damage can be triggered by an acute inflammatory process but also by a metabolic insult, as in diabetes, or hemodynamic shear stress, as in hypertension. The endothelial capillary lining normally displays protective anticoagulant, anti-inflammatory, and antiproliferative functions. Damage to the glomerular endothelium transforms this protective cellular layer to a proaggregatory, proinflammatory, and mitogenic surface, leading to the accumulation of the inflammatory cells discussed earlier as well as platelets within the glomerular capillaries.[57] This leads to the stimulation and proliferation of the mesangial cells. This process bears strong similarities to atherosclerosis with microthrombus formation, infiltration of the glomerular tufts by macrophages and foam cells, and proliferation of the smooth muscle cell equivalent, the mesangial cell.

Mesangial Cells

The mesangial cell is the glomerular capillary equivalent of the smooth muscle cell and provides structural support for the glomerulus, tightly regulates ECM turnover, and interacts closely with endothelial cells and podocytes. Glomerular myofibroblasts arise from mesangial cells and promote ECM accumulation in glomerulosclerosis. Dedifferentiation of mesangial cells into an embryonic mesenchymal (i.e., myofibroblastic) phenotype with the acquisition of stress fibers and α-smooth muscle actin (αSMA) allows these cells to proliferate, to migrate, and to restore the glomerular structural integrity with the laying down of collagenous ECM to seal the wound and to repair structural damage. Chronic injury will, however, lead to aberrant mesangial cell hypertrophy, proliferation, and subsequent ECM accumulation, with the development of glomerulosclerotic lesions.[58]

Podocytes

Visceral glomerular epithelial cells or podocyte are terminally differentiated, specialized epithelial cells of mesenchymal origin that have little capacity to proliferate in response to injury. The interdigitating foot processes of podocytes, maintained by microfilaments in the cytoplasm, are an integral part of the filtration barrier. Mutations in proteins within the foot process are commonly associated with nephrotic syndrome or the risk of developing FSGS (see Chapter 19). Experimental data indicate that podocyte loss of more than 40% leads to segmental sclerosis and progressive CKD. Thus there is now clear evidence that the podocyte is a target in a variety of progressive glomerular diseases, including diabetic nephropathy, most glomerulonephritides, and systemic diseases such as lupus nephritis.

In addition to disease-forming mutations, podocytes can be targeted by other insults such as circulating factors, which leads to reorganization of the actin cytoskeleton and foot process effacement. If the injury is severe or chronic, the podocyte detaches from the GBM because it has little capacity to replicate and as a result exposes areas of denuded GBM. This leads to sclerosis of glomerular capillaries and further interactions between the exposed GBM and parietal epithelial cells, leading to the formation of capsular adhesions and subsequent FSGS.[59] Capsular adhesions formed by contact between the GBM and the parietal epithelial lining of the Bowman capsule may lead to misdirected filtration with the accumulation of amorphous material in the paraglomerular space and the subsequent disruption of the glomerulotubular junction, resulting in atubular glomeruli. Misdirected filtration may also contribute to tubular atrophy and interstitial fibrosis. Tuft-capsule adhesions may allow the influx of periglomerular fibroblasts into the glomerular tuft, thus contributing to glomerulosclerosis.

Tubular Cells and the Renal Interstitium

As with glomerular cells, injury to tubular cells is followed by an attempt at regeneration and repair. After an acute insult, some tubular cells die through necrosis or apoptosis. Apoptosis has been well documented during the course of experimental and clinical models of CKD. Surviving cells attempt to restore tubular integrity by dedifferentiation into an embryonic phenotype that allows them, through the acquisition of cytoplasmic αSMA and stress fibers, to proliferate, to migrate, and to repopulate acellular tubules. Healing and recovery of renal function ensue. On the other hand, repeated or sustained insult will lead to peritubular infiltration of inflammatory cells, activation of ECM-producing myofibroblasts, and possibly epithelial mesenchymal transformation (EMT) of tubular epithelial cells into myofibroblasts (see later). Loss of tubular epithelial cells as a result of both apoptosis and EMT leads to tubular atrophy and further decline in kidney function.

Myofibroblasts are the major driver of interstitial fibrosis and, in addition to expressing αSMA, also express other fibroblastic markers including vimentin and fibroblast-specific protein 1 (FSP1). They derive from a number of cellular sources (Fig. 79-9).[51] Most of the myofibroblast pool probably arises as a result of activation and proliferation of interstitial fibroblasts by growth factors and cytokines such as PDGF, TGF-β1, CTGF, basic FGF, and tissue-type plasminogen activator. However, there are several other important sources of interstitial myofibroblasts.

It was originally thought that EMT of tubular epithelial cells with subsequent migration across the tubular basement membrane makes a significant contribution to myofibroblast number. More recent evidence suggests that some myofibroblasts may arise as a result of endothelial-to-mesenchymal transition (EndMT) which has been elegantly demonstrated by coexpression of endothelial and fibroblast markers in murine models of kidney fibrosis. Another source of myofibroblasts may be bone marrow–derived, blood-borne cells known as *fibrocytes* (bone marrow–derived MSCs) that can migrate from the circulation into the scarred tubulointerstitium. The detection these cells in glomeruli has led to the hypothesis that hematopoietic stem cells may be involved in normal glomerular cell

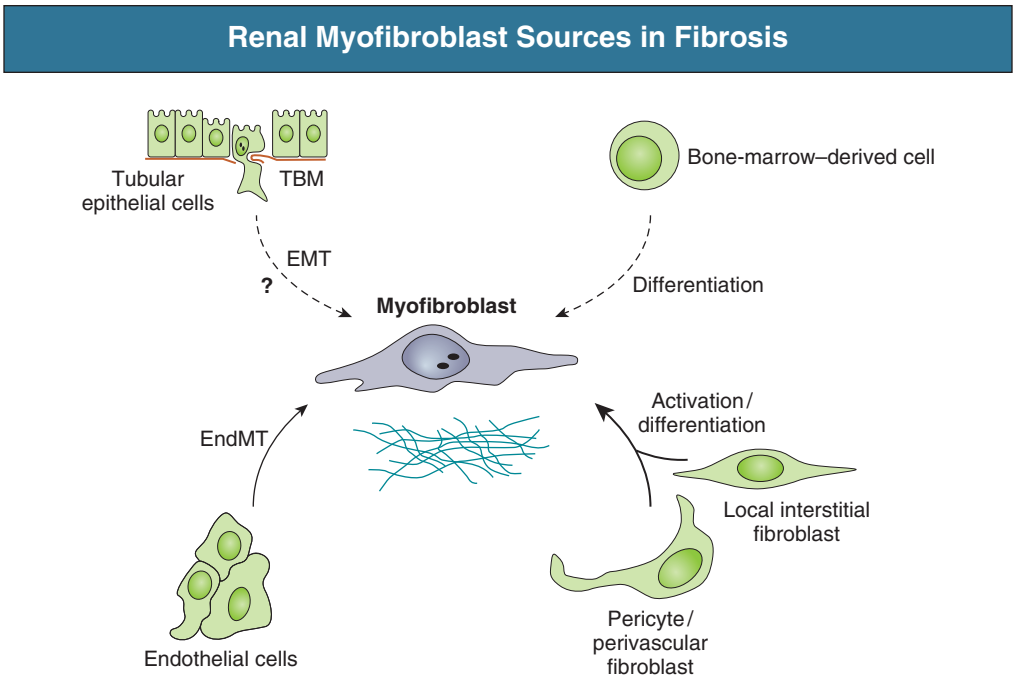


Figure 79-9 Renal myofibroblast sources in fibrosis. *EMT,* Epithelial mesenchymal transformation; *EndMT,* endothelial mesenchymal transformation; *TBM,* tubular basement membrane. *(Modified from reference 50.)*

turnover as well as in glomerular remodeling in response to injury. Finally, there is growing interest in the perivascular pericyte, which is an αSMA-negative, PDGF receptor–positive stromal cell that interacts closely with peritubular capillaries and thereby helps maintain endothelial integrity. Genetic fate mapping studies have suggested that pericytes are a source of the interstitial myofibroblast pool and not EMT,[51] but even the role of pericytes has become controversial very recently.

Vascular Cells

Vascular sclerosis is an integral feature of the renal scarring process. Renal arteriolar hyalinosis is present in CKD at an early stage, even in the absence of severe hypertension. Furthermore, these vascular changes are often out of proportion to the severity of systemic hypertension. Vascular sclerosis is associated with progressive CKD in GN. Hyalinosis of afferent arterioles has been implicated in the pathogenesis of diabetic glomerulosclerosis. Changes in postglomerular arterioles and damage to peritubular capillaries may further exacerbate interstitial ischemia and fibrosis.[50] Ischemia and the ensuing hypoxia are fibrogenic influences that stimulate tubular cells and kidney fibroblasts to produce ECM components and to reduce their collagenolytic activity.[61]

Loss of peritubular capillaries with the associated impaired angiogenesis has been linked in experimental models of renal scarring to a fall in the renal expression of the proangiogenic vascular endothelial growth factor (VEGF). Together with an overexpression by scarred kidneys of thrombospondin, an antiangiogenic factor, this would perpetuate microvascular deletion and ischemia.

Recent evidence also points to lymphatic neoangiogenesis in association with interstitial inflammation and progressive renal fibrosis.[62] Such a process appears to be driven by macrophages that express the lymphangiotropic growth factor VEGF-C. It may play a role in interstitial remodeling because it provides an exit route for inflammatory cells involved in interstitial inflammation.

EXTRACELLULAR MATRIX ACCUMULATION

Accumulation of abnormal ECM laid down by activated myofibroblasts is the final step in renal fibrogenesis. The ECM is composed of a number of proteins, including various collagens, elastin, laminin, fibronectin, and glycoproteins. The ECM is not inert but in a constant state of flux, modulating cell migration, proliferation, and survival. Therefore ECM accumulation not only results in replacement of normal kidney tissue with matrix but also promotes loss of resident renal cells as a result of downregulation of integrin-mediated survival signals from normal matrix.

Fibrogenic cytokines, discussed earlier, stimulate a host of intracellular signaling cascades that ultimately upregulate the transcription of matrix proteins such as collagen and fibronectin. Thus there is both a qualitative and a quantitative change in the nature of deposited ECM, with tubulointerstitial fibrosis being associated with excessive deposition of collagens I, III, and IV, whereas type III collagen predominates in glomerulosclerosis.

Ultimately, ECM accumulation reflects the balance between synthesis from myofibroblasts and degradation by collagenolytic enzymes such as matrix metalloproteinases (MMPs) and plasmin. MMPs are further regulated by tissue inhibitors of matrix metalloproteinases (TIMPs), and plasmin can both directly degrade matrix proteins and indirectly activate MMPs. Plasmin itself is generated as a result of the cleavage of plasminogen by urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA), both of which are inhibited by protease plasminogen activator inhibitor 1 (PAI-1). Cytokines such as TGF-β1 can further drive ECM accumulation by (1) decreasing matrix degradation by inhibiting proteases as well as activating protease inhibitors (e.g., PAI-1), and (2) promoting cell matrix interactions by upregulating integrin expression.[63]

Recent evidence points to another putative pathway to excessive deposition of ECM, namely, resistance to breakdown through structural modification and cross-linking of deposited ECM by an enzyme

called tissue transglutaminase.[64] This enzyme is upregulated during the course of experimental and clinical nephropathies. Mice lacking this enzyme have a reduced propensity for renal scarring. Synthetic inhibitors of this enzyme have been shown to considerably attenuate experimental renal fibrosis.

The process by which renal scarring and fibrosis cause progressive CKD is intricate, involving interactions between invading and resident renal cells with transformation, proliferation, and ECM production culminating in renal fibrosis, loss of function, and ESRD. A better understanding of CKD natural history and the underlying mechanisms of renal scarring has suggested a number of current therapies and will undoubtedly open the way to new strategies and therapies aimed at prevention and slowing of the progression of CKD (Table 79-4).

Mediators of Chronic Kidney Disease and Interventions

Target	Intervention	Mechanism of Action	Evidence Level
Transforming growth factor β1 (TGF-β1)	Administration of bone morphogenetic protein 7 (BMP-7)	Inhibitor of the TGF-β1–Smad signaling pathway	Experimental models of kidney disease Clinical development limited by bone formation at injection site Orally active mimetics in development
	Administration of hepatocyte growth factor (HGF)	Inhibits nuclear translocation of receptor-regulated Smads and upregulates the expression of Smad co-repressors	Experimental models of kidney disease and trials in promoting angiogenesis
	Inhibition of connective tissue growth factor (CTGF)	Mediator of TGF-β1–induced fibrosis	Experimental kidney disease and early clinical studies in diabetic nephropathy
	TGF-β antibodies	Inhibits TGF-β1 signaling pathway	Fresolimumab in Phase I study in FSGS Other TGF-β antibodies have resulted in adverse events in systemic sclerosis
	Serine-threonine kinase receptor and small molecule inhibitors	Inhibits TGF-β1 Smad signaling pathway by targeting activin receptor–like kinase 5	Experimental models of fibrosis
	Tranilast	Inhibits TGF-β1–induced ECM synthesis	Experimental models of kidney disease Early clinical data in diabetic nephropathy and used in the treatment of hypertrophic scars and scleroderma
	Decorin	Sequesters TGF-β1 in the extracellular matrix	Experimental models of kidney disease
Proliferative mitogens	Anti–platelet derived growth factor (PDGF)—for example, PDGF aptamers, imatinib mesylate, CR002, trapidil	Imatinib mesylate, kinase inhibitor of PDGF transduction CR002, monoclonal antibody targeting PDGF-D	Experimental data indicates potential of CR002 in mesangioproliferative disease—Phase I trial completed Cardiotoxicity limits use of imatinib mesylate in clinical use in oncology and beneficial effects in experimental models of kidney disease
	Anti-epidermal growth factor (EGF)	Inhibition of renal fibroblast proliferation and collagen expression	Experimental models of kidney disease
Intracellular transduction cascade	Ras-Raf-Mek-Erk pathway inhibition by Ras: prenyltransferase inhibitors, farnesylthiosalicylic acid (FTS), Raf and Mek kinase inhibitors	Inhibition of cellular proliferation, differentiation, and apoptosis	Experimental model and Phase II clinical trial in cancer treatment
	Rho kinase inhibition: fasudil	Interference with cell proliferation, tubulointerstitial fibrosis, and glomerular hemodynamics	Experimental models of kidney disease and in coronary heart disease Fasudil in clinical use in Japan for cerebral vasospasm
	p38 Mitogen-activated protein kinase inhibitors	Inhibition of proinflammatory and profibrotic mediators	Experimental models and clinical trials in rheumatoid arthritis and type 1 diabetes mellitus
	Protein kinase C inhibitors such as ruboxistaurin	Inhibition of cell growth most evident in diabetic nephropathy	Experimental models Early clinical data with ruboxistaurin in patients with early diabetic nephropathy In development in diabetic retinopathy
	Vasopressin 2 receptor antagonist	Inhibition of cAMP-mediated tubulogenesis and cell proliferation	TEMPO study revealed promising effects of tolvaptan on kidney function and cyst size in polycystic kidney disease (PKD)
Cell cycle inhibitors	Cyclin-dependent kinase inhibitors such as roscovitine	Inhibition of cell cycle progression	Experimental models including polycystic kidney disease and Phase II trials in cancer

Table 79-4 Mediators of CKD and interventions. *cAMP,* cyclic adenosine monophosphate; *ECM,* extracellular matrix, as in chapter body; *EMT,* epithelial mesenchymal transformation; *EPO,* erythropoietin; *Erk,* extracellular–signal-regulated kinase; *FSGS,* focal segmental glomerulosclerosis; *HIF,* hypoxia-inducible factor; *mTOR,* mammalian target of rapamycin; *Nrf2,* nuclear 1 factor (erythroid-derived 2)-related factor 2; *Raf,* rapidly accelerated fibrosarcoma; *Ras;* renin-angiotensin system; *TEMPO,* Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; *VEGF,* vascular endothelial growth factor.

Mediators of Chronic Kidney Disease and Interventions			
Target	**Intervention**	**Mechanism of Action**	**Evidence Level**
Immunosuppressants	mTOR inhibitors	Interference with cell proliferation by regulation of ribosomal biogenesis and protein translation	Experimental models variable but can induce proteinuria Everolimus shown to reduce cyst size in PKD but no effect on kidney function Licensed for treatment of angiomyolipomas
Other agents	Pentoxifylline	Phosphodiesterase inhibitor interfering with cell proliferation and EMT	Experimental models of CKD Ongoing clinical trials assessing role in proteinuric CKD with some reduction of proteinuria in Phase II studies
	Endothelin antagonists	Reduce cellular proliferation and intraglomerular hypertension, inflammation, and podocyte dysfunction	Experimental models Ongoing clinical trials in diabetic nephropathy Reduction in blood pressure and proteinuria but risk of fluid retention
	Pirfenidone	Inhibits ECM accumulation	Experimental models of CKD Phase II data in diabetic nephropathy and FSGS Licensed in pulmonary fibrosis
	Peroxisome proliferator-activated receptor gamma agonists	Reduce cell growth, inflammation Antiproteinuric effect	Experimental and clinical data Reduce proteinuria in diabetic nephropathy Ongoing clinical trials in diabetic and nondiabetic CKD
	Prolyl hydroxylase domain (PHD) inhibitors	Upregulation of HIF-regulated genes such as VEGF and EPO	Experimental models Phase II and III clinical trials under way for the treatment of anemia
	Bardoxolone	Antioxidant and anti-inflammatory effects through induction of Nrf2 antioxidant response pathway	Phase III trial terminated because of drug toxicity—improvements in creatinine and estimated glomerular filtration rate (eGFR) caused by weight loss rather than intrinsic effect on kidney function Highlights the importance of measuring GFR when evaluating new therapies
	N-acetylcysteine	Anti-inflammatory	Phase II studies under way in diabetic nephropathy
	Vitamin D	Multifunctional	Phase II studies showing reduction of albuminuria
	Allopurinol	Lowers uric acid	Pilot studies show slowing of eGFR in CKD with asymptomatic hyperuricemia

Table 79-4 Mediators of CKD and interventions—cont'd

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CHAPTER 80

Retarding Progression of Kidney Disease

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Progression to end-stage renal disease (ESRD) usually occurs because of activity of the primary kidney disease and the mechanisms of natural progression (see Chapter 79). In those older than 40 years of age, the nephropathy of aging can also contribute to progression. Its pathogenesis is unclear; however, the nephropathy of aging appears to be categorically different from that of natural progression because, unlike natural progression, the nephropathy of aging proceeds without important increases in proteinuria (see Chapter 67). Whether therapy can slow the nephropathy of aging is unclear. However, natural progression is treatable. This chapter focuses on its treatments.

Natural progression creates a vicious cycle that is approached when nephron loss leads to hyperperfusion of the surviving glomeruli and to the metabolic dysfunctions of decreased glomerular filtration rate (GFR). The vicious cycle is entered when the hyperperfusion and metabolic dysfunctions are sufficient to inflict kidney injury. At this point, nephron loss begets more nephron loss. Described herein are evidence-based therapies to prevent entry into the vicious cycle or to slow the cycle once it has been entered.

LEVEL OF GLOMERULAR FILTRATION RATE AND THE RISK OF NATURAL PROGRESSION

Typically, natural progression does not proceed until nephron loss exceeds 50%.[1,2] For example, unilateral nephrectomy as occurs in living kidney donors does not usually lead to natural progression.[1,2] However, a normal solitary kidney is vulnerable to natural progression if the condition is congenital or acquired early in life[3] or if it is associated with obesity, hypertension, hyperlipidemia, or hyperglycemia. Low birth weight, particularly in males, may lead to ESRD in adulthood, by natural progression, presumably because of defective nephron development.[2]

PROTEINURIA MAGNITUDE AND THE RISK OF NATURAL PROGRESSION

Proteinuria-induced glomerular and renal tubular injury is a key mechanism of natural progression (see Chapter 79). The threshold for natural progression attributable to proteinuria appears to be crossed when proteinuria exceeds 500 mg/day.[2] Proteinuria magnitude is the strongest single risk factor in chronic kidney disease (CKD) progression (Fig. 80-1).[1] An exception is highly selective proteinuria (the urine protein is almost entirely albumin), which can persist in the nephrotic range for more than 10 years without causing renal structural damage.[2]

DIAGNOSIS OF NATURAL PROGRESSION

Natural progression is a diagnosis of exclusion. Therefore, in the CKD patient showing signs of progression, it must first be determined whether the primary renal disease is active. If that can be reasonably excluded, it must then be determined whether another kidney disorder has been superimposed (see Chapter 71). The nephropathy of aging must also be excluded. This is relatively easy because it starts after 40 years of age, the decline in GFR is slow (about 1 ml/yr), and it generally does not involve important increases in proteinuria (see Chapter 67).[1] Findings that help confirm the diagnosis of natural progression are as follows:

- The serum creatinine (S_{Cr}) generally is above the expected level for the patient's age, sex, and race (Box 80-1). Natural progression is unlikely if the S_{Cr} is normal.
- Natural progression is usually indolent—for example, the increased S_{Cr} has been stable for at least several years before signs of progression occur.[4] An exception can occur when there are extraordinarily strong forces promoting natural progression, such as a very high salt intake, poorly controlled hypertension, or both.[4]
- Increase in proteinuria is usually the first sign of natural progression. Only after a year or more of rising proteinuria does the S_{Cr} begin to increase.[4]
- The urine sediment is unremarkable, although broad hyaline and granular casts may be present.

In summary, natural progression is seen mainly in those with increased S_{Cr}. Increasing proteinuria is the first sign of natural progression. Only after a prolonged period of increasing proteinuria does the S_{Cr} begin to increase. This pattern is also commonly seen in CKD patients whose condition is progressing because of activity of the glomerular disease. In contrast, certain forms of CKD can show substantial progression even though proteinuria is minimal (Box 80-2).

MONITORING KIDNEY DISEASE PROGRESSION

Progression can be monitored by structural changes—for example, with renal biopsy or renal ultrasound—or by functional changes—for example, change in GFR or proteinuria. Here we discuss the latter, which are the most practical and commonly used methods to monitor progression.

Monitoring Proteinuria Trends

Proteinuria is the strongest single predictor of GFR decline. Therapies that decrease proteinuria generally slow GFR decline (see Chapter 79).[1,5] The most widely used methods to assess proteinuria are measurement of urine albumin and urine total protein (see Chapter 4). The latter is the sum of urine albumin plus nonalbumin proteins. In the typical CKD patient the nonalbumin urine proteins consist mainly of low-molecular-weight proteins such as β_2-microglobulin. They escape reabsorption because of tubular damage (see Chapter 15). In this chapter, total proteinuria is referred to simply as *proteinuria*.

Relationship Between Baseline Proteinuria and Subsequent Glomerular Filtration Rate Decline

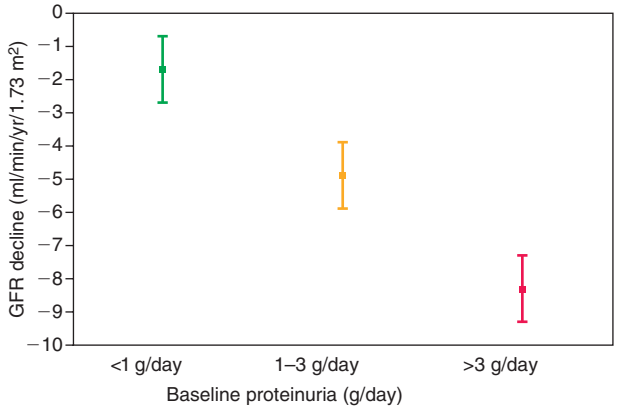

Figure 80-1 Relationship between baseline proteinuria and subsequent glomerular filtration rate (GFR) decline. *(Data from Study A of the Modification of Diet in Renal Disease study. Modified from reference 41.)*

Suggested Thresholds for Abnormal Serum Creatinine (S_{Cr})

- Large (e.g., >90 kg) nonobese men: S_{Cr} ≥1.30 mg/dl (1.40 mg/dl if African ancestry)
- Small (e.g., <60 kg) nonwasted men: S_{Cr} ≥1.10 mg/dl (1.20 mg/dl if African ancestry)
- Large (e.g., >70 kg) nonobese women: S_{Cr} ≥1.00 mg/dl (1.10 mg/dl if African ancestry)
- Small (e.g., <50 kg) nonobese women: S_{Cr} ≥0.80 mg/dl (0.90 mg/dl if African ancestry)

Box 80-1 Suggested thresholds for S_{Cr} according to body size, sex, and race. The estimates are based on experience with a clinical laboratory that reports a normal S_{Cr} range for men of 0.8 to 1.30 mg/dl, and for women of 0.60 to 1.10 mg/dl. The Modification of Diet in Renal Disease (MDRD) study estimated glomerular filtration rate (eGFR) that corresponds to each of the listed categories of S_{Cr} according to sex and race were calculated for persons aged 40 years. Each S_{Cr} value yielded an abnormal eGFR value (<90 ml/min/1.73 m²). For men the eGFR values ranged from 65 to 86 ml/min/1.73 m²; for women the eGFR values ranged from 65 to 79 ml/min/1.73 m². For persons older than 40 years, the corresponding eGFR values would be even lower.

Common Forms of Chronic Kidney Disease (CKD) in Which Important Progression Can Occur with Any Minimal Proteinuria

1. Early phase of diabetic nephropathy, type 1 or type 2 diabetes mellitus
2. Hypertensive nephrosclerosis in persons of African ancestry
3. Autosomal dominant polycystic kidney disease
4. Chronic NSAID (nonsteroidal anti-inflammatory drug) nephropathy
5. Obstructive uropathy
6. Nephropathy of aging

Box 80-2 Common forms of CKD in which important progression can occur with any minimal proteinuria. For example, S_{Cr} increases to above 2.0 mg/dl, but 24-hour protein urine is low—for example, albumin-creatinine ratio (ACR) below 0.2, protein-creatinine ratio (PCR) below 0.3. For conditions 1 through 6, see Chapters 29, 33, 44, 56, 62, and 65, respectively.

Recently, albuminuria measurement has gained favor over proteinuria measurement in CKD management. However, of the two studies that compared urine albumin-creatinine ratio (ACR) and urine protein-creatinine ratio (PCR) as predictors of GFR decline, one found ACR better than PCR,[6] and the other found PCR not inferior to ACR.[7] Kidney Disease: Improving Global Outcomes (KDIGO) recommends ACR. However, albumin assays are expensive compared with protein assays. Furthermore, above a proteinuria of 500 mg/day, ACR and PCR generally change in parallel.[7,8] If 24-hour proteinuria is below 500 mg/day, this parallelism is lost and ACR is more sensitive. On this basis, we recommend ACR for detection of early CKD progression. Thereafter, PCR is recommended. The recommended methods for monitoring proteinuria trends in individual patients are shown in Table 80-1. The key points are as follows:

- The gold standard for monitoring proteinuria is the protein content of an accurately collected 24-hour urine specimen. Unfortunately, in practice, nominal 24-hour urine collections often are largely undercollections or overcollections. For this reason we prefer the term "intended" 24-hour urine collection when such collections are made.[9,10]
- Creatinine should be measured in all intended 24-hour urine collection specimens. The PCR of the *intended* collection is a reliable estimate of the PCR of the complete 24-hour collection, if the intended 24-hour urine collection is at least 50% complete based on its total creatinine content.[9,10]
- In individual patients, the PCR of spot (single void) urine collections is an unreliable estimate of proteinuria magnitude given the large and inherent variability of the PCR (Fig. 80-2).
- Urine collections of intermediate duration (e.g., overnight collections) have merit. However, such collections may not be representative of the ACR or PCR of the entire 24-hour collection. For example, variations in diet, timing of antihypertensive medications, exercise on the day of the overnight collection, or contamination with semen may substantially alter the ACR or PCR, rendering the overnight collection nonrepresentative.
- Cost of ACR and PCR from spot collections is essentially the same as that of ACR and PCR from 24-hour urine collections. Given the high degree of unreliability of spot ACR and PCR, spot collections can be regarded as having an unfavorable cost-benefit ratio.
- The inconvenience of 24-hour urine collections can be lessened by the following:
  - It is acceptable if an occasional void is missed, but the gap should not be large (e.g., the entire work day).
  - A wide mouth "sports bottle" that is carried in a duffle bag can be used to collect urine when not at home. It is not necessary to refrigerate the collected urine unless it will be several days before the urine specimen is submitted to the clinical laboratory.

Dipstick testing for proteinuria is convenient but unreliable (see Chapter 4). It is not recommended for assessing proteinuria trends in individual CKD patients.[9]

Proteinuria testing in CKD is recommended every 6 to 12 months if proteinuria is low level (e.g., <500 mg/day, ACR <0.2, PCR <0.3 when expressed as mg/mg creatinine, in an average-sized person) and every 2 to 4 months for those with heavier proteinuria. If PCR increases from below 0.5 to 1.0 or higher, or from below 1.0 to 2.0 or higher, likely these are real changes.[11] Most of the measures that slow natural progression also reduce proteinuria.

Recommended and Nonrecommended Methods for Monitoring Proteinuria or Albuminuria	
Methods	**Comments**
Recommended	
PCR or ACR* of intended 24-h urine collections that are at least 50% complete based on creatinine content†	Most accurate method (see text). Can also be used to assess nutrient intake relevant to CKD management (e.g., Na, K, urea nitrogen, water). Inconvenient, but this can be lessened. See text.
PCR or ACR ratio from overnight collections (first morning void)	More convenient than 24-h collections but provides a lower estimate of proteinuria than 24-h collections and is more vulnerable to artifacts (see text).
Not Recommended	
Intended 24-h urine collection in which protein or albumin is measured but creatinine is not measured	Large overcollections and undercollections are common in intended 24-h urine collections. If creatinine content is not measured, the degree of overcollection or undercollection cannot be reliably assessed.
Spot PCR or ACR	Convenient but highly inaccurate estimate. Cost-benefit ratio is low because cost is about the same as 24-h urine testing, but often the results of spot testing are misleading.
Dipstick test for proteinuria (albuminuria)	Convenient and low-cost point-of-care measure but not reliable for monitoring CKD patients.

Table 80-1 Recommended and nonrecommended methods for monitoring proteinuria or albuminuria. E = (140 − Age) × Weight (nonobese) in kg × 0.2 × 0.85 if female. An M/E ratio exceeding 0.5 is evidence that the collection is more than 50% complete. *ACR,* Albumin-creatinine ratio; *CKD,* chronic kidney disease; *PCR,* protein-creatinine ratio. *ACR is recommended if 24-hour proteinuria is below 500 mg (PCR if below 0.3 for average-sized person). PCR is recommended if 24-hour proteinuria is above 500 mg. †Degree of completeness of an intended 24-hour urine collection = measured creatinine content *(M)*/expected creatinine content *(E).*

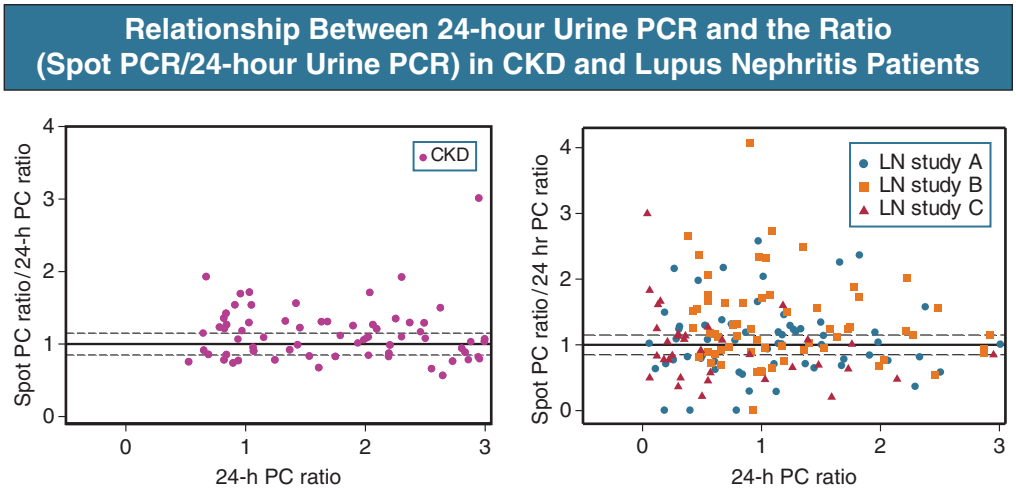

Figure 80-2 Relationship between 24-hour urine protein-creatinine ratio (PCR) and the ratio of spot PCR to 24-hour urine PCR in chronic kidney disease (CKD) and lupus nephritis (LN) patients. The *dashed line* indicates the expected limits of agreement if morning spot PCR provides the same results as testing an aliquot of the intended 24-hour collection. This figure shows that spot PCR is an unreliable estimate of 24-hour PCR, especially in lupus nephritis. *(From reference 8.)*

Monitoring Glomerular Filtration Rate Trends

In individual patients, it is usually sufficient to monitor GFR trends by serial S_{Cr} measurements. In interpreting S_{Cr} change, one must keep in mind the circumstances that can change S_{Cr} by mechanisms that do not involve a change in GFR, as follows: increased creatinine production (eating cooked meat, creatine ingestion, increased exercise, increasing muscle mass, fenofibrate therapy), or decreased creatinine production (vegetarian diet, muscle wasting, decreased exercise). Also, S_{Cr} can be increased spuriously by certain drugs and by increased serum ketones (from fasting or poor diabetes control) or actually increased by drugs that decrease tubular secretion of creatinine (cimetidine, trimethoprim). If a chronic progressive change in creatinine production is occurring (e.g., muscle wasting), GFR trends can be monitored by measuring serial 24-hour urine creatinine clearance. Creatinine clearance is not importantly affected by change in creatinine production. If creatinine clearance is used, an accurate 24-hour collection is essential.[1]

Glomerular filtration rate can also be monitored by the creatinine-based estimated glomerular filtration rate (eGFR) estimating equations—in particular, the Modification of Diet in Renal Disease (MDRD4) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations (see Chapter 3). These approaches to standardizing GFR assessment have greatly advanced the study of CKD epidemiology. In addition, they account for the influence of age on GFR. This is important in monitoring GFR trends over 10 years or more.[1] However, the eGFR equations have important limitations when applied to individuals, as follows:

- The MDRD4 and CKD-EPI equations assume that all patients of the same age, sex, and race have the same rate of creatinine production and the same body surface area. As a result, these equations substantially underestimate actual GFR in those with high creatinine production and substantially overestimate actual GFR in those with low creatinine production.[12]
- Because of inaccuracy, clinical laboratories generally do not report eGFR by MDRD4 or CKD-EPI equation if the eGFR is greater

than 60 ml/min/1.73 m^2. In this circumstance the clinician must determine whether the S_{Cr} is likely to be normal or abnormal. The following can be helpful:

- Large normal persons have higher S_{Cr} values than small normal persons.
- Men have higher S_{Cr} values than women.
- In North America, those of African ancestry have higher S_{Cr} values than those of non-African ancestry.

Box 80-1 provides specific numerical recommendations for interpretation of S_{Cr} when the eGFR is greater than 60 ml/min/1.73 m^2.

Glomerular Filtration Rate Trajectories in Chronic Kidney Disease

The chronic kidney disease GFR trajectory generally is well described as a linear decline; thus GFR loss per unit of time is approximately constant.[1,2] However, those of African ancestry deemed to have hypertensive nephrosclerosis can experience large unexplained changes in eGFR trends, especially decreases followed by stability. A concern is that increased variability of GFR decline over time is associated with increased mortality.[13]

Indexing Proteinuria and Albuminuria by Estimated Glomerular Filtration Rate to Predict Risk of Chronic Kidney Disease Progression

Recent work has emphasized that at any given level of albuminuria, the lower the eGFR, the greater the risk of CKD progression. This is referred to as *indexing* the risk of progression according to both proteinuria and eGFR.[14] Indexed GFR and albuminuria levels also are associated with increased cardiovascular mortality.

THERAPY FOR NATURAL PROGRESSION

Because of the benefit of even small decreases in CKD progression rate in delaying the onset of ESRD, an aggressive, multiple–risk factor intervention to slow GFR decline is warranted. This, however, does not apply to patients with low ESRD risk. Low-risk patients include those with corticosteroid-responsive minimal change disease (MCD); those with a solitary kidney that is normal, is acquired in adulthood, and is not accompanied by other CKD risk factors; normotensive adults with hereditary nephritis or thin basement membrane in whom the only renal manifestation is microscopic hematuria; and the elderly with idiopathic and moderately elevated S_{Cr} (1.30 to 2.00 mg/dl), a 24-hour urine PCR below 1.0, and whose renal parameters have been stable for at least 1 year. Patients in the last group are much more likely to die of cardiovascular disease (CVD) than to progress to ESRD.[2]

Therapies recommended in this chapter are listed in Box 80-3. A Level 1 (highest) recommendation is based on one or more large, high-quality randomized clinical trials (RCTs) that showed documented effects on GFR decline. A Level 2 recommendation is based on secondary analysis of the Level 1 RCT, RCTs that showed documented effects on proteinuria but not GFR decline, RCTs that appear to have been of adequate quality but may not have been definitive because of study size, and nonrandomized studies that were rigorous and confirmed by other rigorous studies.

The goals of progression therapy are to reduce proteinuria as much as possible, ideally to less than 500 mg/day, and to slow GFR decline as much as possible, ideally to about 1 ml/min/yr, which is the rate of GFR decline attributable to the nephropathy of aging (see Chapter 67).

Recommended Kidney Protective Therapies According to Level of Recommendation

Level 1 Recommendations

1. Control blood pressure (BP).
2. Administer angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), or renin inhibitor.
3. Avoid dihydropyridine calcium channel blockers (DHCCBs) unless needed for BP control.
4. Control protein intake.

Level 2 Recommendations

1. Restrict NaCl intake and diuretic therapy.
2. Administer NDHP-CCB therapy.
3. Control each component of the metabolic syndrome.
4. Administer aldosterone antagonist therapy.
5. Administer allopurinol therapy.
6. Control serum phosphorous.
7. Instigate smoking cessation.
8. Perform alkali therapy.
9. Administer β-blocker therapy.
10. Avoid overanticoagulation with warfarin.

Box 80-3 Recommended kidney protective therapies according to level of recommendation. The goal for the chronic kidney disease (CKD) patient is to implement all Level 1 recommendations and as many Level 2 recommendations as is feasible. *NDHP-CCB,* Nondihydroyridine calcium channel blocker.

Level 1 Recommendations to Slow Natural Progression

Control Blood Pressure

The low blood pressure (BP) goal (sitting systolic BP in the 120s or less, if tolerated) is recommended. However, the evidence supporting the low goal is not robust.[15] It is based largely on the subset of patients in the MDRD study whose baseline proteinuria was greater than 1.0 g/day; the African American Study of Kidney Disease and Hypertension (AASK), but only in the long-term cohort study; and the Effect of Strict Blood Pressure Control and ACE Inhibition on Progression of Chronic Renal Failure in Pediatric Patients (ESCAPE) trial in children.

Another reason to favor the low BP goal is that in both the MDRD study and AASK, those assigned to the low BP goal had a significantly lower risk of ESRD during long-term (post-trial) follow-up than those assigned to the usual (higher) BP goal. This is remarkable because during the post-trial follow-up the low BP goal was recommended to all patients.[15] In addition, in a meta-analysis of placebo-controlled randomized trials of antihypertensive drug therapy in which there was post-trial follow-up of at least 7 years, it was found that the mortality rate during post-trial follow-up was significantly lower in the group that had been randomized to the study drug than in the group that had been randomized to placebo—even though during the post-trial follow-up both groups were advised to receive the study drug. This benefit of having received the antihypertensive study drug during the randomized trial was independent of the class of the antihypertensive study drug.[16]

When these findings are taken together, it seems that the low BP goal is more beneficial than the usual BP goal, even though it may take several years for the benefit to be shown. These results also suggest that achieving the low goal BP sooner rather than later is important.

In CKD patients, in general, the greater the proteinuria, the greater the benefit of the low BP goal in slowing CKD progression.[1,17,18] The low BP goal was also better than the usual BP goal at slowing the progression of proteinuria during the trials.[1,2] This may be evidence of kidney protection.

Systolic BP is the recommended target because, in general, it correlates better with CKD progression than diastolic BP.[1,19,20] Also, specifying both a systolic and a diastolic BP goal can be confusing if one goal is met but the other is not, and could lead to overtreatment or undertreatment of BP.[1]

However, the low BP goal is not recommended for all CKD patients. The traditional (usual) BP goal, a sitting systolic BP in the 130- to 140-mm Hg range, is recommended for the CKD patient who is elderly (frail), has evidence of significant CVD, or is intolerant of the low BP goal. Intolerance can be manifested by lightheadedness, orthostatic symptoms, chest pain, fatigue, or progressively increasing S_{Cr} after achievement of the low BP goal.

Administration of antihypertensive medications at night may increase their efficacy in preventing cardiovascular events.

Whenever possible, BP control should be assessed with home BP monitoring (HBPM) rather than in the office or clinic. The latter is a poor predictor of risk compared with HBPM or ambulatory BP monitoring (ABPM). Among hypertensive CKD patients, masked hypertension (BP is normal in the office or clinic but hypertensive by HBPM or ABPM) and white coat hypertension are common and may be present in more than 50% of CKD patients.[20,21] The technique of HBPM is discussed in Chapter 33.

The optimum frequency of HBPM measurement has not been rigorously studied. We recommend that initially HBPM be measured twice daily—morning and evening—until the BP is at goal. The frequency of HBPM can then be decreased. The recommended minimum frequency of HBPM is every 1 or 2 weeks, including both morning and evening testing. The HBPM measures need to be recorded and averaged. The average BP should be used to determine the degree of BP control.

The classes of antihypertensive drugs used to achieve BP control importantly influence CKD progression.[1] Evidence-based and experience-based algorithms for BP control in CKD are shown in Figures 80-3 and 80-4. Although the algorithms recommend beginning with a single drug, if the systolic BP is more than 20 mm Hg above goal, two or more antihypertensive agents will usually be needed.[1]

Renin-Angiotensin System Blockers

Renin-angiotensin system (RAS) blockade with ACE inhibitors or angiotensin receptor blockers (ARBs) is recommended first-line therapy to reduce proteinuria, CKD progression, and cardiovascular risk (see Fig. 80-3). These benefits appear to be comparable between ACE inhibitors and ARBs. ARBs do not increase the risk of cancer. RAS blockade is recommended in CKD even if hypertension is not present, because the kidney and cardiovascular protection of RAS blockade is, at least in part, independent of BP control.[1] In general, the greater the ACE inhibitor or ARB dose, the greater the effect on control of hypertension and proteinuria.[1,22]

Renin-angiotensin system blockers are antiproteinuric even in inflammatory glomerulonephritis (GN), and should be continued even if GFR declines to stage 4 CKD (15 to 29 ml/min/1.73 m^2).[1] For prevention of hyperkalemia, dietary potassium restriction and the concomitant use of furosemide and sodium bicarbonate may be needed.[1]

Adipose tissue expresses all RAS components. Thus angiotensin II may play a greater role in obese CKD patients. Indeed, in the Ramipril in Non-diabetic Renal Failure (REIN) trial, ACE inhibitor therapy was significantly more effective in slowing GFR decline in the obese than in the nonobese.[23]

Combination Angiotensin-Converting Enzyme Inhibitor and Angiotensin Receptor Blocker Therapy

In general, combination ACE inhibitor and ARB therapy is more antihypertensive and more antiproteinuric than use of an ACE inhibitor or ARB alone. Therefore it is surprising that the randomized trials comparing ACE inhibitors, ARBs, and ACE inhibitors plus ARBs did not find benefit of the combination. However, in mice, severe blockade of the RAS can induce renal injury, so combination therapy might block the RAS too severely. Currently, combination therapy is not recommended in CKD management, particularly in the elderly.[24] However, there may be a role for combination therapy in the nonelderly with heavy proteinuria. Whether patients with very heavy proteinuria (e.g., 10 g/day, serum albumin 2.5 g/dl) are benefitted if the dose of combination therapy is pushed above the recommended levels has not been well studied. However, in our experience such high-dose therapy has not been helpful, even when combined with aldosterone antagonists, salt restriction, protein restriction, diuretic therapy, and statin therapy. Also, this aggressive antiproteinuria therapy often had to be abandoned because of overcontrolled BP.

Renin Inhibitor Therapy

Aliskiren, a direct renin inhibitor, is an effective antihypertensive agent and has been shown to reduce albuminuria in diabetic nephropathy and IgA nephropathy. However, when aliskiren was added to ACE inhibitor or ARB therapy in patients with type 2 diabetes and nephropathy, there was increased risk of renal impairment, hypotension, and hyperkalemia, without perceived benefit. Aliskiren may be a suitable alternative RAS blocker for those intolerant to either ACE inhibitors or ARBs.

Avoid Dihydropyridine Calcium Channel Blockers

There have been three randomized trials in CKD showing that those assigned to dihydropyridine calcium channel blocker (DHP-CCB) therapy experienced less kidney protection than those not assigned to DHP-CCB.[1,25] The mechanism may involve DHP-CCB–induced arteriolar vasodilation resulting in glomerular hypertension and thus promotion of proteinuria.[1] However, in the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, ACE inhibitor plus amlodipine therapy protected kidney function better than ACE inhibitor plus diuretic therapy, especially in non-Blacks.[26] Possibly, the benefit of amlodipine in ACCOMPLISH was seen because the CKD patients had low-level proteinuria.[26] In addition, there is evidence that chronic thiazide therapy is nephrotoxic.[27] Thus, if a CCB is needed for BP control, the first choice should be a nondihydropyridine CCB (NDHP-CCB) (discussed later).

Control Protein Intake

Reducing dietary protein intake from the usual level (in developed countries about 1 to 1.5 g/kg ideal body weight per day) to about 0.7 g/kg ideal body weight per day (low-protein diet) slows GFR decline in those with proteinuria of more than 1 g/day.[1] Another benefit of the lower protein intake in CKD is that it slows proteinuria progression, even in those who at baseline have only low-level proteinuria.[1] Diets incorporating soy proteins may be more antiproteinuric than those composed of animal proteins only.[1] Dietary protein intake should be monitored periodically, for example, every 4 to 6 months, by measuring urine urea nitrogen (UUN) excretion in

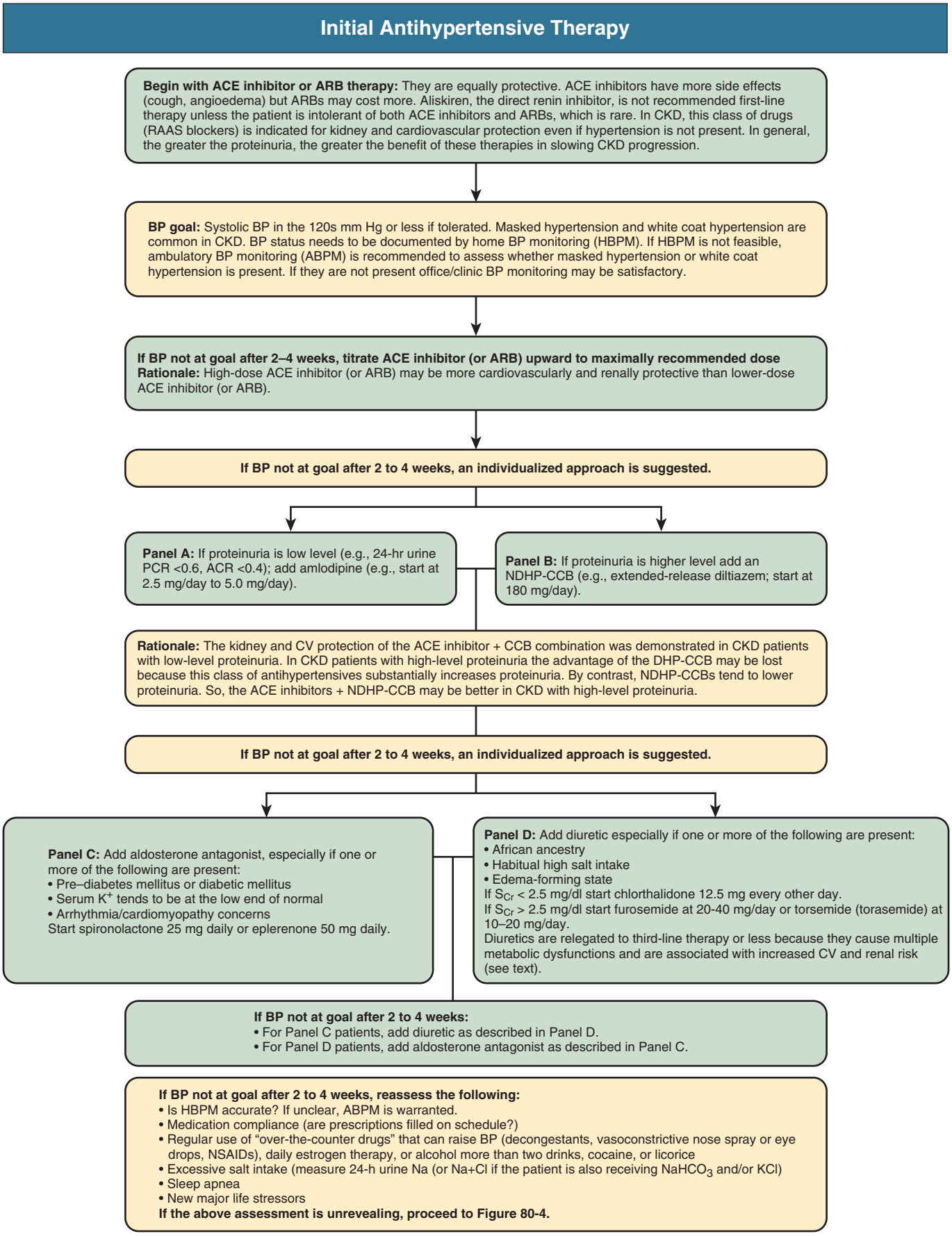

Figure 80-3 Initial antihypertensive therapy. The algorithm shown here assumes that nonpharmacologic therapy to control BP is in place (see text) and that the patient is not known to have renovascular hypertension, congestive heart failure, or ischemic or heart disease, and does not have hypertensive urgency. This approach focuses on BP control in proteinuric nephropathies, but is also appropriate for nephrosclerosis, polycystic kidney disease, and interstitial nephropathies. More details on each of the recommended drugs are provided in the text. *ACE,* Angiotensin-converting enzyme; *ACR,* albumin-creatinine ratio; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *CKD,* chronic kidney disease; *CV,* cardiovascular; *NDHP-CCB,* nondihydropyridine calcium channel blocker; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *PCR*, protein-creatinine ratio; *RAAS,* renin-angiotensin-aldosterone system.

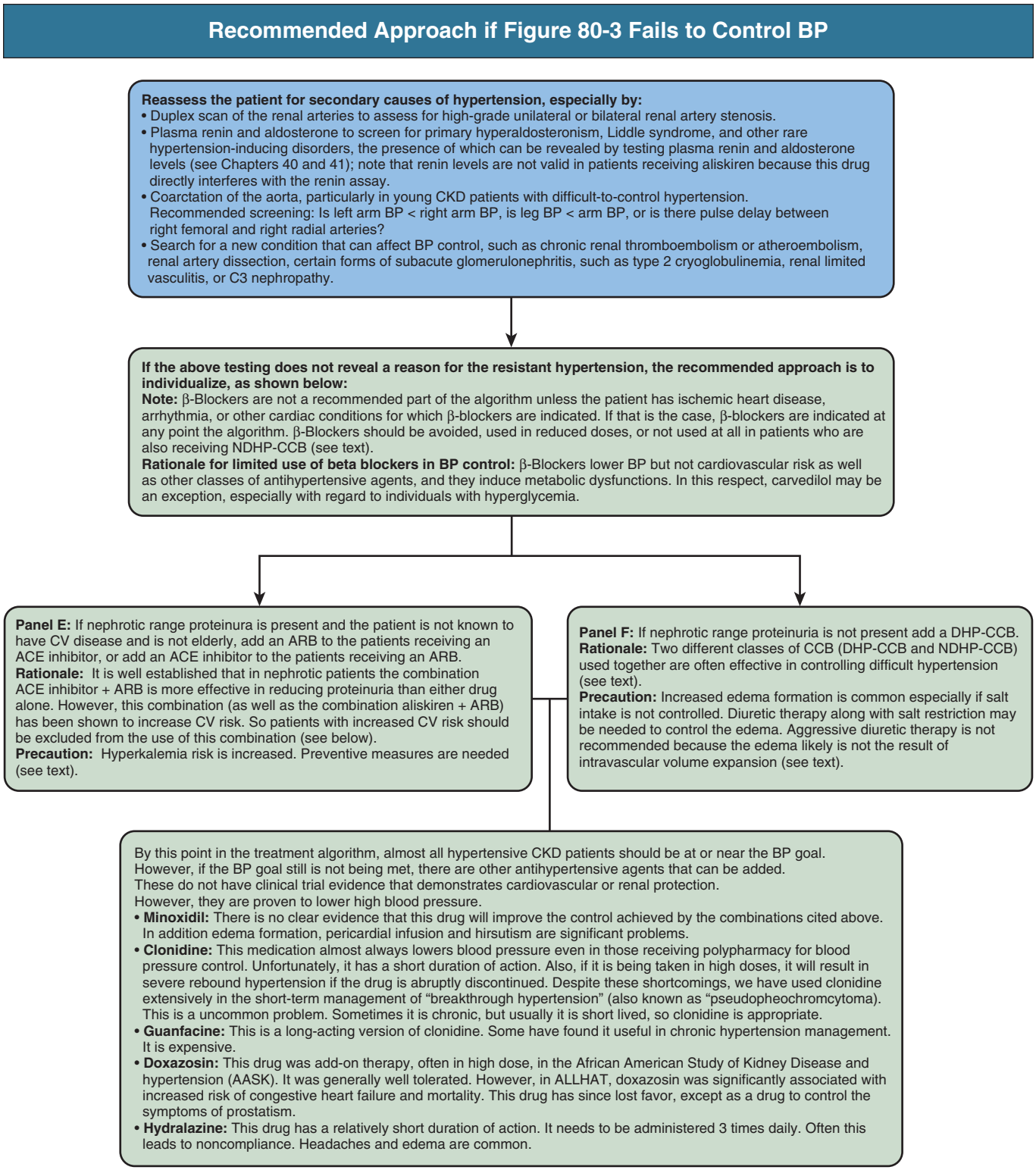

Figure 80-4 Recommended approach if Figure 80-3 fails to control BP. If patients are intolerant or allergic to the drugs recommended in the algorithms, suggested alternatives include ethacrynic acid for thiazide diuretics, aliskiren for ACE inhibitors or ARBs, and minoxidil for CCBs. Carvedilol or doxazosin may be appropriate at any point in patients in whom stress may play an important role in their hypertension, or in whom BP is particularly labile, in the absence of correctable factors to account for the lability. *ACE,* Antiotensin-converting enzyme; *ALLHAT,* Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trial; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *CCB,* calcium channel blocker; *CKD,* chronic kidney disease; *CV,* cardiovascular; *DHP-CCB,* dihydropyridine calcium channel blocker; *NDHP-CCB,* nondihydropyridine calcium channel blocker.

24-hour urine collections. For a 70-kg person, a 50-g protein diet would achieve the dietary goal of 0.7 g/kg ideal body weight per day. In such a patient, the 24-hour urine collection would contain about 8 g UUN. Monitoring protein intake is particularly important in those who are not achieving their proteinuria goal. Men and those with glomerular disease may particularly benefit from the low-protein diet.[2]

In the MDRD study, long-term follow-up of those on the very-low-protein intake (<0.6 g/kg/day) showed no further reduction in GFR decline, but these patients appeared to have an increased risk of death.[1] A risk of excessive protein restriction is protein-energy wasting. This occurs when protein catabolism does not appropriately compensate for decreased protein intake. Its consequences include muscle wasting and low serum albumin. The risk of protein-energy wasting increases with coexisting inflammatory disorders such as diabetes, severe atherosclerosis, or autoimmune diseases. Stage 4 and 5 CKD patients are particularly vulnerable to protein-energy wasting. Alkali therapy can mitigate protein-energy wasting (see the discussion of alkali therapy). Given the recent strong evidence that red meat and processed red meat are associated with increased risk of mortality, cancer, and CVD, it is reasonable that most of the reduction in protein intake should involve these protein sources.

Level 2 Recommendations to Slow Natural Progression

Restrict Salt Intake and Diuretic Therapy

A high salt intake (e.g., 200 mmol NaCl/day = 11.6 g NaCl and 4.6 g Na) can completely override the antiproteinuric effects of ACE inhibitor, ARB, or NDHP-CCB therapy. Also, high salt intake measured at baseline is a significant predictor of more rapid GFR decline.[28] In addition, it is well established that high salt intake worsens hypertension. Despite wide acceptance that salt restriction is important in CKD management, there have been no rigorous randomized trials of salt restriction in CKD.

The recommended NaCl intake in CKD (assuming that renal salt wasting is not present) is about 2 to 3 g Na (5-7.5 g NaCl). The NaCl intake of the average North American adult is about 10 g NaCl (4 g Na). Achievement of the CKD goal for salt intake would be documented by a 24-hour urine collection containing 80 to 120 mmol of sodium and is particularly important if the BP or proteinuria goal is not being met. Urine sodium should be measured each time 24-hour urine protein is measured (see the discussion of monitoring of proteinuria). In patients receiving NaHCO therapy, urine chloride rather than sodium should be monitored, taking into account whether the patient is also receiving KCl.[1] The rationale is that urine Cl is almost entirely derived from ingestion of NaCl, unless the patient is also receiving KCl therapy. So, if the patient is not receiving KCl, 24-hour urine chloride in milliequivalents is equal to 24-hour urine NaCl in millimoles.

High fructose intake (in the form of table sugar or high-fructose corn syrup used in sugar-sweetened beverages) should be avoided in CKD because it increases renal sodium reabsorption and can worsen BP control (see the discussion of metabolic syndrome).

In patients receiving RAS blockers, diuretic therapy improves BP control and decreases proteinuria. Nevertheless, the ideal is to avoid diuretics because of the evidence of nephrotoxicity[27] and its multiple metabolic dysfunctions, which include hypokalemia, hyperglycemia, hyperlipidemia, and stimulation of the RAS, all of which are known to increase cardiovascular risk.[1] Loop diuretics are more effective than thiazides if GFR is below 30 ml/min. If the GFR is higher, the preferred diuretic is chlorthalidone because of the evidence of superior protection against cardiovascular events compared with hydrochlorothiazide. The mechanism of the superior effect of chlorthalidone may be related to its more effective suppression of carbonic anhydrase and its ability to help regulate nitric oxide better than hydrochlorothiazide.[29]

Nondihydropyridine Calcium Channel Blocker Therapy

The NDHP-CCB class of agents, which includes diltiazem and verapamil, is antiproteinuric and may be renoprotective. An NDHP-CCB together with a DHP-CCB can be a potent antihypertensive combination when used along with other antihypertensive therapies (see Fig. 80-4).[1,2]

Control Each Component of the Metabolic Syndrome

The metabolic syndrome and each of its components are risk factors for CKD progression and are associated with the development of eGFR less than 60 ml/min, microalbuminuria, and overt proteinuria.[2] Also, the prevalence of microalbuminuria and CKD increases proportionately with the number of components of the metabolic syndrome.[30]

Each component of the metabolic syndrome has not been rigorously studied in randomized trials. Nevertheless, it is appropriate to discuss each component of the metabolic syndrome because, in general, an intervention that benefits any aspect of the metabolic syndrome likely benefits all of its aspects.

Obesity increases the risk of CKD and is associated with glomerulopathy, focal and segmental glomerulosclerosis, and proteinuria, which can be progressive. Reducing even moderate obesity can reduce proteinuria in CKD.[1,2] Bariatric surgery in morbidly obese patients reduces risk factors for CKD, including systolic BP and insulin resistance.

In CKD, increased intake of sugar-sweetened beverages, especially those sweetened by fructose, is an important contributor to metabolic syndrome. In CKD patients, lowering fructose intake lowers BP and inflammation.[31]

With regard to lipid control in CKD, the current KDIGO guidelines (www.kdigo.org) recommend a statin or a statin plus ezetimibe for all non-ESRD CKD patients 50 years of age or older, regardless of the lipid levels. Disregard of the lipid levels is based on the Study of Heart and Renal Protection (SHARP), which showed that the benefits of lipid therapy are not related to baseline lipid level. For non-ESRD CKD patients younger than 50 years, KDIGO does not recommend statin therapy unless there is increased cardiovascular risk. The KDIGO-recommended statin doses are low (e.g., atorvastatin 20 mg daily).

We suggest a less-restrictive policy for statin use than that of KDIGO. For example, all adult non-ESRD CKD patients, regardless of age and stage, should receive at least moderate-dose statin therapy (e.g., atorvastatin 40 mg daily). The rationale is that CKD itself is a strong cardiovascular risk factor, and the risk starts early in CKD (see Chapter 82). CVD has a long incubation period, so starting lipid therapy early in CKD patients may be prudent. Also, statins are well tolerated in CKD, even at high doses (e.g., atorvastatin 80 mg daily).[32] With regard to statin choice in CKD, atorvastatin may be better than simvastatin,[32] and rosuvastatin may have nephrotoxicity.[33] Also to be considered is the recent meta-analysis of randomized trials of fibrate therapy compared with placebo in mild to moderate CKD. Fibrate therapy reduced cardiovascular risk and albuminuria; however, ESRD risk was unchanged. S_{Cr} increased in patients taking fenofibrate, probably because of increased creatinine production. When fibrate was stopped after the trial, S_{Cr} decreased to below baseline values, suggesting that kidney function was protected during fibrate

therapy.[34] Fibrates decrease triglycerides significantly. Perhaps there is a role for add-on fibrate therapy for CKD patients at high cardiovascular risk whose triglycerides are not controlled by statin therapy or a statin-ezetimibe combination.

Aldosterone Antagonist Therapy

Spironolactone and the more selective aldosterone antagonist eplerenone have substantial antihypertensive, cardioprotective, and antiproteinuric effects even at low doses (e.g., spironolactone 25 mg/day) and in the presence of combined ACE inhibitor and ARB therapy.[35] The mechanism may involve blockade of aldosterone effects on endothelium and on fibrosis. Although there are no rigorous clinical trial data with hard end points such as ESRD, the available evidence supports the use of aldosterone antagonists in high-risk CKD patients who have not reached their BP and proteinuria goals despite other therapy (see Fig. 80-3). However, the use of aldosterone antagonists should be restricted to those with an eGFR above 30 ml/min. If spironolactone or eplerenone is used in patients receiving RAS blockers, it is especially important to prevent hyperkalemia. These measures include sodium bicarbonate therapy (see the discussion of alkali therapy), the avoidance of potassium-rich foods, and awareness of the symptoms of severe hyperkalemia. These include the relatively sudden onset of symmetric proximal muscle weakness (difficulty climbing stairs or rising from a chair) or muscle stiffness. This should prompt an immediate visit to the nearest emergency department. On arrival the patient should immediately advise the medical personnel that severely elevated serum potassium may be the problem.

β-Blocker Therapy

The AASK study showed that β-blocker therapy is more antiproteinuric and slows GFR decline better than DHP-CCB. However, β-blockers increase the likelihood of diabetes and, as monotherapy or when combined with diuretics, increase mortality compared with ACE inhibitors plus diuretics.[1,2] β-Blockers should be used in CKD to manage coronary heart disease or arrhythmia. However, in general, they should be avoided in the management of hypertension.[1,2] Carvedilol, which possesses both β-blocker and α_1-blocker effects, may be less likely to increase insulin resistance than metoprolol when it is used in combination with an ACE inhibitor.[1,2]

Control Serum Phosphorous

Serum phosphorus generally does not become abnormally elevated until stage 3 or 4 CKD. In CKD, there is a significant association between increased serum phosphorous and either CKD progression or incident CKD and ESRD. There is strong experimental evidence that hyperphosphatemia is harmful. However, there have been no high-quality randomized trials to test that hypothesis. To achieve phosphorus control (see Chapter 85), the following are suggested:

Phosphorus control should begin before the serum phosphorus is consistently greater than 4.0 mg/dl (1.3 mmol/l).

The first approach is to reduce phosphorous intake with the precaution that severely reducing meat and dairy products could lead to protein malnutrition. Proteins in grain (e.g., a vegetarian-type diet) have a lower phosphorus content than the proteins in meat or milk. If grains are substituted for meat and dairy products, better control of serum phosphorous can be achieved.

If dietary measures are ineffective, use of phosphate binders is generally recommended. Which type of phosphate binder is best is a subject of controversy. The evidence favors the notion that calcium-containing phosphorous binders are more likely to result in vascular calcification and increase cardiovascular risk than noncalcium phosphate binders (see Chapter 85).

Smoking Cessation

There are many compelling reasons for the CKD patient not to smoke. Cigarette smoking promotes progression of all forms of kidney disease in a dose-dependent manner, perhaps more in those of African American ancestry.[1] Cigarette smoking is associated with an increased risk of glomerular hyperfiltration and proteinuria and may cause a glomerulopathy that resembles diabetic nephropathy.

Allopurinol and Febuxostat Therapy

Three randomized trials[1,36] and one case-control study found that allopurinol therapy slows CKD progression. There is abundant experimental evidence that uric acid is proinflammatory and vasculotoxic[1] and that allopurinol is anti-inflammatory and cardioprotective by multiple mechanisms.

A major concern in recommending allopurinol to slow CKD is that the trials, although randomized, were open label. In addition, there is a risk, albeit very small, of severe and even fatal hypersensitivity reactions to allopurinol (e.g., Stevens-Johnson syndrome). However, given the likelihood that allopurinol has both kidney and cardiovascular protective properties and the likelihood that the severe risks can be avoided (see later), a cogent argument can be made that allopurinol has a favorable risk-benefit ratio in CKD, particularly in relationship to the traditional uses of allopurinol, which are to treat gout and kidney stones.

Reducing the risk of severe hypersensitivity reaction to allopurinol in CKD patients may be accomplished by reducing the dose[37] (see summary, later) and by advising patients who are about to start allopurinol to stop the drug immediately and call their physician should they develop rash, fever, or other signs of illness. This is practical advice because the risk of severe allopurinol reactions appears to be restricted to the first 8 weeks of therapy, and prompt withdrawal of the offending drug is associated with decreased mortality risk.[38] Also, allopurinol should be avoided in patients with high-risk alleles for severe allopurinol hypersensitivity. This is particularly seen in those of Asian ancestry. Testing Asians for these risk alleles has been recommended.

Another xanthine oxidase inhibitor, febuxostat, is now available. It is safe in patients intolerant of allopurinol. It does not need dose adjustment if eGFR is greater than 30 ml/min/1.73 m^2. Stevens-Johnson syndrome has been reported in postmarketing surveillance of febuxostat.

In summary, there is level 2 evidence that allopurinol therapy, properly approached, is prudent in hyperuricemic CKD patients to reduce cardiovascular risk and risk of CKD progression. For prevention of severe allergic reactions, the starting dose should be 1.5 mg × eGFR in ml/min/1.73 m^2. If after 8 weeks that dose is well tolerated, it can then be increased until the uric acid level is at goal (less than 7 mg/dl). Also, the patient should be strongly cautioned, when he or she starts allopurinol or when the dose is increased, to stop the allopurinol if rash, fever, or other signs of illness develop. The patient should then promptly seek medical advice. If allopurinol is being considered in those of Asian ancestry, testing for high-risk human leukocyte antigen (HLA) alleles is recommended. If they are present, allopurinol should not be used. Whether febuxostat is the appropriate next choice is not clear because there is no evidence from clinical trials that febuxostat is renal protective in hyperuricemic CKD, although that is plausible. Also, data on the long-term safety of febuxostat are lacking. Given these concerns, perhaps the most appropriate use of febuxostat in CKD is to treat gout or kidney stones in those allergic to allopurinol. Febuxostat might also be appropriate in the allopurinol-intolerant CKD patient who has severe hyperuricemia (e.g., >9.0 mg/dl). The rationale is that observational studies

show that the greater the uric acid level, the greater the risk of renal and cardiovascular end points.

Avoid Overanticoagulation with Warfarin

Warfarin-related nephropathy (WRN) is a newly recognized clinical syndrome. In this condition, patients with warfarin coagulopathy (international normalized ratio [INR] greater than 3.0) may have acute kidney injury (AKI) manifested by severe glomerular hemorrhage, even though the glomeruli are normal or nearly normal. WRN is particularly common in CKD.[39] Although most CKD patients recover from the AKI, the rate of CKD progression is increased.[39] Whether other classes of systemic anticoagulants can cause AKI is under investigation.

Alkali Therapy

The evidence that alkali therapy slows CKD progression is based on three randomized trials and one nonrandomized trial.[1] Alkali therapy may be kidney protective by blocking endothelin production, suppressing the alternative complement pathway, or reducing oxidative damage. Three different forms of alkali have been studied: sodium bicarbonate ($NaHCO_3$), sodium citrate, and diets high in fruits and vegetables (i.e., potassium citrate). If $NaHCO_3$ therapy is used, the recommended dose is three or four 650-mg tablets daily. They can be given twice daily. Taken together, the evidence favoring alkali therapy in CKD progression is plausible and prudent. Also, alkali therapy improves protein nutrition by suppressing protein catabolism and protects against hyperkalemia. Whether metabolic acidosis needs to be present for benefit to be derived from alkali supplementation is not clear. However, it appears that the benefit in slowing CKD progression is seen even in those whose pretreatment plasma bicarbonate level is within the normal range.

Correct Vitamin D Deficiency

Severe deficiency of 25-OH vitamin D is common in CKD. There is strong evidence from cross-sectional studies that severe vitamin D deficiency (25-OH vitamin D levels less than 15 ng/ml) is strongly associated with increased risk of CVD, infection, thrombotic disease, autoimmune disease, diabetes mellitus, bone disease, and progression of CKD. Vitamin D_3 supplementation is recommended for those with 25-OH vitamin D levels less than 30 ng/ml.[40] Vitamin D_3 doses of 1000 or 2000 IU daily or 50,000 IU monthly will usually restore 25-OH vitamin D levels to normal.

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CHAPTER 81

Clinical Evaluation and Management of Chronic Kidney Disease

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Although many patients with chronic kidney disease (CKD) progress to end-stage renal disease (ESRD) and require renal replacement therapy (RRT), the majority die of nonrenal causes, particularly premature cardiovascular events.[1] Early diagnosis of CKD is therefore important because it provides opportunities to delay progression of CKD (see Chapter 80) and to prevent cardiovascular complications (see Chapter 82).

DEFINITIONS

Chronic kidney disease is defined as abnormalities of kidney structure or function, present for at least 3 months, with implications for health (Table 81-1). The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend classification of CKD based on cause, category of glomerular filtration rate (GFR), and albuminuria (see Fig. 79-1).[2] Because of the impracticalities of using radioisotopes and 24-hour urine collections, the KDIGO classification system recommends that kidney function be assessed by estimating the GFR (eGFR) from the serum creatinine level through use of an appropriate equation, except in circumstances in which eGFR estimations are known to be less accurate, such as when there is significant muscle wasting. The Modification of Diet in Renal Disease (MDRD) equation has been in common use in clinical laboratories until recently, but KDIGO has recommended that this be replaced by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which more accurately categorizes the risk of mortality and progression to ESRD (see Chapter 3).[3] Although staging systems for CKD based on eGFR have limitations, they have proven to be useful in many clinical settings and are now deeply embedded into guidelines developed for CKD management.

The evidence base for the management of CKD is constantly evolving, and guidelines are updated in light of this. Although every effort has been made to ensure that this chapter reflects current recommendations, the reader is advised to check for any relevant guideline updates.

CLINICAL PRESENTATION

Chronic kidney disease is usually asymptomatic until late stage 4 or stage 5 and is commonly detected by routine blood testing. There is some evidence that early diagnosis with appropriate management may slow the rate of decline of kidney function and reduce cardiovascular risk.[4] Screening of the general population for CKD is not recommended, but in the United Kingdom the National Institute for Health and Care Excellence (NICE) proposes offering testing to people with conditions associated with an increased prevalence—those with diabetes, hypertension, cardiovascular disease (CVD), structural renal tract disease, renal calculi, prostatic hypertrophy, multisystem diseases with potential kidney involvement (e.g., systemic lupus), a family history of category G5 CKD, or hereditary kidney disease—and after opportunistic detection of hematuria or proteinuria.[5]

Evaluation of Chronic Kidney Disease

Establishing Chronicity

When an eGFR of less than 60 ml/min/1.73 m^2 is detected in a patient, careful attention needs to be paid to previous blood and urine test results and the clinical history to determine if this is a result of acute kidney injury (AKI), an abrupt decrease in kidney function, or CKD that has been present but asymptomatic for some time.

A detailed medical history covering issues, including other medical conditions, family history of kidney disease, prescribed medication, and illicit drug use, may suggest an underlying cause. There may be hints of a past history of kidney problems (e.g., hypertension, proteinuria, microhematuria) or symptoms suggestive of prostatic disease. The physical examination findings are not usually helpful, although skin pigmentation, scratch marks, left ventricular hypertrophy, and hypertensive fundal changes favor a chronic presentation (Fig. 81-1). Details of the social and personal circumstances are also crucial, particularly for patients with progressive kidney disease in whom RRT is likely to be required.

Blood tests for other conditions can be helpful if the findings indicate evidence of an acute illness that may be the cause of kidney failure, such as systemic vasculitis or multiple myeloma. A normochromic normocytic anemia is usual in CKD but may also be a feature of acute systemic illnesses and therefore is not discriminatory. Low serum calcium and raised phosphate levels also have little discriminatory value, but normal levels of parathyroid hormone (PTH) are more in keeping with AKI. Patients with grossly abnormal biochemical values—for example, blood urea nitrogen higher than 140 mg/dl, serum creatinine above 13.5 mg/dl (>1200 µmol/l), or blood urea greater than 300 mg/dl (>50 mmol/l)—who appear relatively well and are still passing normal volumes of urine are much more likely to have chronic than acute kidney disease.

Assessment of Glomerular Filtration Rate

For patients in whom the distinction between AKI and CKD is unclear, repeat testing of kidney function should be performed within 2 weeks of the initial finding of an eGFR below 60 ml/min/1.73 m^2. However, if previous results confirm that this is a

Criteria for Definition of Chronic Kidney Disease (CKD)	
CKD is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health. These may include the following.	
Markers of kidney damage	Albuminuria (AER ≥ 30 mg/24 h; ACR ≥ 30 mg/g [≥ 3 mg/mmol]) Urine sediment abnormalities Electrolyte and other abnormalities caused by tubular disorders Abnormalities detected through histology Structural abnormalities detected through imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m^2

Table 81-1 Criteria for definition of chronic kidney disease. *ACR,* Albumin-creatinine ratio; *AER,* albumin excretion rate; *GFR,* glomerular filtration rate. *(From reference 2.)*

Figure 81-1 Uremic pigmentation. Diffuse brown pigmentation as seen here suggests chronic kidney disease rather than acute kidney injury.

chronic finding, or if repeated blood test results over a 3-month period are consistent, CKD is confirmed. Other tests (such as cystatin C or an isotope-clearance measurement) may be required for confirmation of CKD in circumstances when eGFR based on serum creatinine is known to be less accurate.

Assessment of Proteinuria

Dipstick testing of the urine and urine culture are important.[6] This may reveal microhematuria, which can be a useful pointer toward an underlying diagnosis. Workup of hematuria is discussed in Chapter 4. Whether or not proteinuria is detected by dipstick, further measurement of urinary protein excretion should be conducted. Proteinuria is an important diagnostic and prognostic marker, and its presence indicates a higher risk for both progression of kidney disease and cardiovascular complications.[7] KDIGO recommends that the preferred method of assessing proteinuria is by measurement of the urinary albumin-creatinine ratio (ACR) using an early morning urine sample.[2] The degree of albuminuria is graded by the A1 to A3 category system, replacing previous terms such as *microalbuminuria* (see Fig. 79-1). However, it is important to be aware that some patients will excrete proteins other than albumin, and a urine protein-creatinine ratio (PCR) may be more useful for certain conditions.[8] Serial PCR measurements may be particularly useful in glomerular disease because of the higher variability of ACR and the greater cost of determining albumin in urine. Where appropriate, urine tests for Bence-Jones protein (immunoglobulin light chains) may be required because this is not detected by standard proteinuria or albuminuria testing.

Kidney Imaging

Imaging of the kidneys with ultrasound is useful for a number of reasons. Small kidneys with reduced cortical thickness, showing increased echogenicity, scarring, or multiple cysts, suggest a chronic process. Structural abnormalities such as autosomal dominant polycystic kidney disease (ADPKD), hydronephrosis caused by obstruction, or coarse renal scarring may be detected. NICE states that kidney ultrasound scanning is important only in certain circumstances and suggests counseling patients if ADPKD is suspected before imaging.[5] In some situations, imaging with computed tomography, magnetic resonance, or angiography may be useful, taking into account the risks of administering contrast media (see Chapter 5).

Further Investigations

Establishing the cause of CKD is important when possible, and further specific testing, as indicated by the history and results of initial investigations, may be required. There may be an underlying treatable condition that requires appropriate management, or there may be a genetic cause such as ADPKD, for which counseling should be offered. Furthermore, some kidney diseases may recur after transplantation (see Chapter 108), and an accurate diagnosis may therefore influence later management. Despite thorough investigation, however, the cause of CKD is often unclear, with an unhelpful past medical history, minimal abnormalities on urinalysis, and small kidneys on ultrasound. In such patients, investigation should not be pursued relentlessly because the implications for treatment are often minimal. Attempting to obtain biopsy material from small kidneys is associated with risk, and even if a biopsy is performed, histologic assessment may simply show nonspecific chronic scarring rather than diagnostic features that explain the cause of kidney damage.

PREDICTING PROGNOSIS

With the cause of CKD established if possible, the GFR and the level of proteinuria measured, and other comorbidities categorized, it may be possible to estimate the risk of CKD progression and likely future need for RRT. KDIGO recommends consideration of the GFR and the albuminuria categories according to a "heat map" of risk (see Fig. 79-1).[2] Other factors associated with CKD progression will also help inform prognosis. These include cause of CKD, age, sex, ethnicity, dyslipidemia, smoking, obesity, history of CVD, ongoing exposure to nephrotoxic agents, and degree of control of hypertension and hyperglycemia. However, often the best guide to future change in kidney function is the previous pattern of decline, highlighting the importance of considering results of previous blood and urine testing during the initial assessment.

Monitoring and Defining Progression

Once a diagnosis of CKD has been established, arrangements need to be put in place to ensure regular monitoring of kidney function and proteinuria. In patients at low risk of decline, this could be done annually. However, assessment should be undertaken more regularly

if the trajectory of the disease is not clear, and in patients at higher risk of progression.

Determining a true change in kidney function may be difficult because small fluctuations in eGFR are common and not necessarily indicative of progression. They may be caused by reversible factors, such as intravascular depletion or high meat intake, so repeat testing may be required. NICE defines progression as a decline in eGFR of more than 5 ml/min/1.73 m^2 within 1 year or more than 10 ml/min/1.73 m^2 within 5 years.[5] KDIGO refers to a sustained decline in eGFR of more than 5 ml/min/1.73 m^2 within 1 year as rapid progression and also specifies a drop in GFR category accompanied by a 25% or greater drop in eGFR from baseline as defining progression.[2] In patients with CKD progression, current management should be reviewed to detect reversible causes, and specialist referral should be considered.

When to Refer to the Nephrologist

Although management of patients with early nonprogressive CKD is increasingly becoming the responsibility of primary care physicians, nephrologists need to assess those individuals likely to progress to ESRD and to require RRT. Substantially similar criteria for referral have been developed by NICE and KDIGO (Table 81-2). Such criteria are not absolute but should provide a guide to the primary care physician as to which patients are likely to benefit from specialist care. For example, many patients with stable category G4 CKD are successfully managed in the community, often after initial assessment by or with advice from secondary care colleagues.

Unfortunately, a substantial proportion of patients with advanced CKD are referred late, often when they need dialysis. Late referral is often avoidable, although in some cases, patients may have had a truly silent illness or an acute presentation of a disease with rapid decline in kidney function.[9] There is evidence that over recent years the introduction of routine reporting of eGFR, which has facilitated better communication between primary and secondary care providers, has led to a substantial fall in late referrals.[10]

Late presentation is disadvantageous to the patient because it limits the time to select the mode of dialysis or to be listed for "preemptive" kidney transplantation. There may be increased psychological stress, making it difficult for the patient to come to terms with the illness. Furthermore, because an arteriovenous fistula takes several weeks to mature, patients presenting late start hemodialysis with central venous catheters. Catheters are prone to infectious complications and inevitably damage central veins, leading to thromboses and stenoses, which may manifest at a later stage when venous return from one or the other arm is increased by the subsequent construction of an arteriovenous fistula (see Chapter 91).[11] Late presentation of CKD also precludes effective treatment of complications such as hypertension and anemia, which may contribute to cardiovascular damage and ultimately limit life span.[12] Most important, late referral is associated with greater subsequent costs of medical care and a worse prognosis.[13]

PREVENTION OF CHRONIC KIDNEY DISEASE PROGRESSION

Management of CKD should be aimed at slowing the rate of decline of kidney function and minimizing the effects of other complications of CKD. Except for specific management of the underlying kidney disease where possible, the most effective intervention is control of blood pressure, including, in patients with proteinuric CKD, use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Control of glycemia for patients with diabetes and CKD is covered in Chapter 32.

Hypertension

Hypertension is very common in patients with CKD, and the level of blood pressure is associated with the rate of loss of kidney function.[14] Control of blood pressure slows the rate of decline of kidney function (see Chapter 80), and until recently this led to a focus on "the lower, the better" targets for hypertension management. However, in light of growing evidence about the adverse effects of hypotension, the paradigm has moved toward less-intensive and individualized blood pressure control.[15] Recently, guidelines by both NICE and KDIGO have considered management of hypertension in patients with CKD in depth.[5,16] Both sets of guidelines emphasize the

Suggested Criteria for Referral of Patients with Chronic Kidney Disease (CKD) to a Nephrologist

	NICE 2008	KDIGO 2012
Advanced CKD	Stage 4 and 5 CKD	Category G4 and G5 CKD
Proteinuria	High proteinuria: ACR ≥ 70 mg/mmol unless known to be caused by diabetes and appropriately treated	Consistent proteinuria: ACR ≥ 300 mg/g (≥30 mg/mmol)
Hematuria	Proteinuria (ACR ≥ 30 mg/mmol) together with hematuria	Urinary red cell casts, RBCs > 20 per high-power field sustained; not readily explained
Progression of CKD	Rapidly declining eGFR: >5 ml/min/1.73 m^2 in 1 yr >10 ml/min/1.73 m^2 in 5 yr	Progression of CKD: Sustained decline in eGFR > 5 ml/min/1.73 m^2 in 1 yr Drop in GFR category with a ≥25% drop in eGFR from baseline
Uncontrolled hypertension	Hypertension that remains poorly controlled despite the use of at least four antihypertensive drugs at therapeutic doses	CKD and hypertension refractory to treatment with four or more antihypertensive agents
Hereditary kidney disease	Known or suspected rare or genetic causes of CKD	Hereditary kidney disease
Other conditions	Suspected renal artery stenosis	Recurrent or extensive nephrolithiasis Persistent abnormalities of serum potassium

Table 81-2 Suggested criteria for referral of patients with CKD to a nephrologist. *ACR,* Albumin-creatinine ratio; *eGFR,* estimated glomerular filtration rate; *KDIGO,* Kidney Disease: Improving Global Outcomes; *NICE,* National Institute for Health and Care Excellence; *PTH,* parathyroid hormone; *RBC,* red blood cell. *(Data from references 2 and 5.)*

importance of considering coexistent CVD, other comorbidities, and side effects when choosing medications and blood pressure targets, particularly for elderly patients. Lifestyle modifications, including maintenance of a healthy weight, reductions in salt and alcohol intake, and regular exercise, should be encouraged (see Chapter 35).

Although current recommendations are based on office blood pressure recordings, recent studies suggest that readings obtained from home and ambulatory monitoring correlate better with cardiovascular and kidney outcomes.[17] It is alarming to note that up to 30% of CKD patients who were thought to have hypertension have normal blood pressures at home, and 40% of patients who were thought to be normotensive (or to have adequately treated hypertension) were hypertensive at home.[18] Although ambulatory monitoring is not yet universally recommended, there should be a very low threshold for undertaking 24-hour monitoring or asking patients to undertake self-measurements at home if they prefer.

Target blood pressure levels and antihypertensive therapy in CKD patients are discussed in Chapter 80. ACE inhibitors or ARBs are recommended as first-line agents for patients with evidence of proteinuria, but usually multidrug regimens are required to obtain good control. During intercurrent illness, patients with CKD are vulnerable to drug side effects, particularly hyperkalemia and AKI.[19] The KDIGO guidelines recommend the temporary discontinuation of potentially nephrotoxic and renally excreted drugs (including ACE inhibitors, ARBs, aldosterone inhibitors, direct renin inhibitors, diuretics, nonsteroidal anti-inflammatory drugs [NSAIDs], metformin, lithium, and digoxin) in patients with a GFR below 60 ml/min/1.73 m^2 (CKD categories G3a to G5) who have serious intercurrent illness.

Dietary Advice

Detailed dietary advice and education, along with ongoing support from an appropriately trained professional, are important in the management of patients with CKD. Obesity is associated with a more rapid decline of kidney function, so in early CKD, weight loss may be appropriate. However, in advanced CKD, malnutrition is common (see Chapter 87). The causes are multifactorial but include anorexia, acidosis, insulin resistance, inflammation, oxidative stress, and urinary protein loss. Biochemical indicators may demonstrate a decrease in serum albumin, transferrin, and cholesterol. Weight should be monitored in patients who progress to CKD categories G4 and G5. Serum creatinine concentrations, which in part reflect muscle mass, may stop rising despite a progressive loss of kidney function, because of compromised nutritional status.

In light of this, recommendations to restrict protein intake have been controversial. Although there is evidence that reduced protein intake may slow progression of decline of kidney function, many patients develop protein-calorie malnutrition on a low-protein diet.[20] KDIGO has recommended that protein intake should be lowered to 0.8 g/kg/day in adults with CKD and GFR below 30 ml/min/1.73 m^2, whereas high protein intake (>1.3 g/kg/day) should be avoided in adults with CKD at risk of progression. When this recommendation is followed, detailed dietary assessment and supervision are needed to ensure that malnutrition is prevented.

One of the earliest effects of CKD is to limit the ability of the kidney to compensate for large changes in sodium and water intake (see Chapter 7). Salt and water retention are major factors contributing to hypertension in CKD patients and, in more advanced stages, to morbidity and mortality through systemic or pulmonary edema. Therefore sodium intake should ideally be restricted to less than 90 mmol/day (5 g/day of sodium chloride), except in salt-wasting conditions. Advice about optimal fluid intake at each stage of CKD is needed to prevent volume overload. Salt substitutes containing potassium should be avoided because of the risk for hyperkalemia. In categories G4 and G5 CKD, education and advice about restriction of potassium and phosphate may be required.

MANAGEMENT OF COMPLICATIONS OF CHRONIC KIDNEY DISEASE

A detailed discussion of the complications of CKD is provided in Chapters 82 to 89. With the exception of hypertension, there are usually few clinical manifestations associated with CKD categories G1 and G2 (GFR > 60 ml/min/1.73 m^2). Other complications (discussed in the following sections) tend to develop progressively as GFR declines below 60 and in particular below 30 ml/min/1.73 m^2 (i.e., during CKD categories G4 and G5).

Anemia

Anemia is common in CKD categories G3a to G5 and is caused by a relative deficiency of erythropoietin (EPO), although reduced availability of iron and chronic inflammation are frequent contributory factors (see also Chapter 83). Anemia may have multiple adverse effects, including worsening cardiac dysfunction by increasing cardiac output and exacerbating left ventricular hypertrophy, exacerbating the decline of kidney function, and reducing cognition and concentration. However, clear evidence that reversal of anemia using erythropoiesis-stimulating agents (ESAs) is associated with improved clinical outcomes is lacking, and randomized trials have suggested that in some circumstances these agents may cause harm. This has led to reconsideration of anemia management in CKD in recent years.

A recent KDIGO guideline recommends that all patients identified as having CKD categories G3a and below should have their hemoglobin (Hb) levels monitored annually, increasing to twice a year for categories G4 and G5.[2] Anemia in adults is diagnosed when the Hb concentration falls below 13.0 g/dl in men and below 12.0 g/dl in women. NICE recommends that management of anemia should be considered in patients with CKD when the Hb level is 11 g/dl or lower.[5] In anemic patients, investigations for other causes should be conducted, including measurement of iron stores and serum vitamin B_{12} and folate levels. ESAs should not be started until treatment of iron deficiency or other underlying causes has been addressed, and only then after considering the balance of benefits (from the reduced requirement for blood transfusions and abrogation of anemia-related symptoms) against the potential harms, which may include an increased risk of stroke and malignancy.

If anemia does not respond to correction of underlying causes, such as iron deficiency, KDIGO recommends that ESAs be commenced when Hb concentrations are below 10.0 g/dl, if indicated.[21] Hb target ranges are discussed in Chapter 83.

Bone and Mineral Metabolism

Hyperphosphatemia, together with a deficiency of 1,25-dihydroxyvitamin D_3, contribute to secondary hyperparathyroidism and ultimately to the development of renal bone disease. These biochemical and endocrine changes, in association with the closely related histologic abnormalities of bone and soft tissue calcification, are collectively termed the *CKD–mineral and bone disorder* (see Chapter 85).[22] Bone disease may already be manifested in CKD category G3b and is well established in ESRD, even though patients may

remain asymptomatic. In addition to the need to prevent bone complications, active management of CKD–mineral and bone disorder may help to prevent some of the cardiovascular complications of CKD.[23]

Kidney Disease: Improving Global Outcomes recommends measuring serum levels of calcium, phosphate, PTH, and alkaline phosphatase activity in adults with GFR below 45 ml/min/1.73 m^2 (GFR categories G3b through G5). Determining the optimal level of PTH in CKD has been controversial. For patients with levels of intact PTH above the upper normal limit of the assay, efforts should be made to correct hyperphosphatemia, hypocalcemia, and vitamin D deficiency if present. KDIGO recommends that serum phosphate concentrations be maintained in the normal range according to local laboratory reference values,[24] whereas NICE supports a level between 0.9 and 1.5 mmol/l for patients with category G4 and G5 CKD.[25] Early advice on dietary phosphate management by a specialist dietician or other professional is important in helping patients to achieve this. Phosphate-binding drugs may be required, and their choice is discussed in Chapter 85. Prescription of vitamin D supplements or analogues, in the absence of documented deficiency, to suppress elevated PTH concentrations in patients with CKD not on dialysis is not routinely recommended.

Metabolic Acidosis

The metabolic acidosis associated with CKD is caused by failure of hydrogen ion excretion and may be compounded by the accumulation of organic acids and bicarbonate loss, particularly in interstitial kidney diseases. Clinical symptoms resulting from acidosis are rare until patients reach CKD category G5, when dyspnea may occur as a result of respiratory compensation. Other causes of dyspnea in advanced CKD, such as anemia and pulmonary edema, should always be considered. Acidosis aggravates hyperkalemia, inhibits protein anabolism, and accelerates calcium loss from bone where the hydrogen ions are buffered.[26] Correction of metabolic acidosis may also slow progression of kidney disease.[27]

Kidney Disease: Improving Global Outcomes recommends that in patients with CKD and serum bicarbonate concentrations below 22 mmol/l, oral bicarbonate supplementation should be given to maintain serum bicarbonate within the normal range, unless contraindicated. However, the associated sodium loading may aggravate hypertension and fluid retention, and severe metabolic acidosis associated with symptoms in a patient with CKD category G5 may be an indication to start dialysis.[2]

Cardiovascular Risk

Patients with CKD have an increased prevalence of CVD and are far more likely to die from a CVD-related cause than to progress to ESRD (see Chapter 82). Therefore, appropriate management of existing CVD and minimization of future CV risk is vital for all patients with CKD.

Unfortunately, many trials of interventions for CVD have excluded patients with CKD,[28] and a recent KDIGO update highlights doubt about the relevance of existing standards of care of CVD to patients with CKD.[29] Nonetheless, KDIGO recommend that the level of care for coronary heart disease offered to patients with CKD should not be prejudiced by their CKD. NICE suggests that antiplatelet drugs should be offered to patients with CKD for the secondary prevention of CVD, and KDIGO extends this recommendation to primary prevention for those at risk of atherosclerotic events. However, there is an increased risk of minor bleeding, and a recent systematic review of antiplatelet agents for patients with CKD found that although the incidence of myocardial infarction is reduced, major bleeding is increased. Thus the risks may outweigh benefits among individuals with low risk for cardiovascular events, including those with early stages of CKD, who do not have clinically evident occlusive arterial disease.[30]

For management of dyslipidemia, KDIGO recommends that cholesterol-lowering treatment be routinely offered for the prevention of CVD in patients with CKD who are older than 50 years and to younger patients with additional risk factors, irrespective of baseline lipid values.[31]

Risk of Infections

Infection is the second most common cause of death after CVD in patients with ESRD. This is in part because of defects in both cellular and humoral immunity, which make CKD a state of chronic immunosuppression (see Chapter 84).[32] T-cell responses to *de novo* antigens are deficient, partly because of impaired antigen presentation by monocytes. Neutrophil activation is defective, and although serum immunoglobulin levels are normal, antibody responses to immunization may be poor. Patients with CKD have an increased susceptibility to bacterial infection (particularly staphylococcal), increased risk of reactivation of tuberculosis (typically with a negative tuberculin skin test response), and failure to eliminate hepatitis B and C viruses after infection.

In view of these increased risks, KDIGO recommends that all adults with CKD be offered annual vaccination with influenza vaccine unless contraindicated and that all adults with eGFR below 30 ml/min/1.73 m^2 (GFR categories G4 to G5) and those at high risk of pneumococcal infection (e.g., patients with nephrotic syndrome, with diabetes, or who are receiving immunosuppression) receive vaccination with polyvalent pneumococcal vaccine unless contraindicated.[2] Patients who have received pneumococcal vaccination are offered revaccination within 5 years. In addition, those at high risk of progression of CKD with eGFR below 30 ml/min/1.73 m^2 (GFR categories G4 and G5) should be immunized against hepatitis B and the response confirmed by appropriate serologic testing. This should happen as early as possible to maximize the chances of seroconversion.[33]

CARE OF THE PATIENT WITH PROGRESSIVE CHRONIC KIDNEY DISEASE

To optimize the care of patients with progressive CKD, optimal management is provided in a multidisciplinary setting where a range of professionals are able to provide education and information about diet, different RRT modalities, transplant options, vascular access surgery, and social care. Psychological comorbidity is common among patients with CKD. Health care professionals working with patients with CKD should take account of the psychological aspects of coping with the condition and offer access to support groups, counseling, or a specialist nurse. The aim is to create an environment in which patients can become informed and proactive in their care.

Chronic Kidney Disease and Risk of Acute Kidney Injury

All patients with CKD are at increased risk of AKI, and AKI may be associated with more rapid progression to ESRD.[34] Imaging studies that require iodinated radiocontrast media carry a risk of AKI, and the benefit of a diagnostic scan needs to be balanced against the risks.

If the investigation is needed, the lowest dose of radiocontrast should be used, the patient should be adequately hydrated, and potentially nephrotoxic agents should be withdrawn before and after the procedure; however, the fear of radiocontrast-induced AKI should not prevent or impair a necessary diagnostic workup. The potential risk of nephrogenic systemic fibrosis from gadolinium-based contrast media and measures to reduce it are discussed in Chapter 5.

Many commonly used medications increase the risk of AKI, and the level of GFR should be considered when any drug is prescribed or its dosage determined. As discussed earlier, the need for temporary cessation of all medications should be considered during periods of severe intercurrent illness. Other causes of reduction in kidney perfusion can also lead to AKI, including volume depletion from excessive diuretics, insufficient fluid intake in hot weather, diarrhea or vomiting, heart failure, myocardial infarction, and tachyarrhythmias. Severe hypercalcemia, resulting from either coadministration of high doses of vitamin D and calcium-containing phosphate binders or from underlying disease, can also cause AKI.

Clinicians should always consider whether acceleration of loss of kidney function is a result of relapse of the underlying disease or of a superimposed problem such as acute interstitial nephritis (see Chapter 62), obstructive uropathy (see Chapter 60), or renal vein thrombosis.

Timing the Initiation of Renal Replacement Therapy

Despite all attempts to optimize the management of CKD, many patients will progress to needing RRT. All patients with eGFR below 20 ml/min/1.73 m^2 and/or who are likely to progress to ESRD within 12 months should receive education and counseling to aid their selection of the most appropriate RRT modality. If hemodialysis is the preferred option, an arteriovenous fistula should be constructed, remembering that it may take 8 to 12 weeks for veins to become adequately arterialized before needling can be attempted (see Chapter 91). Similar plans need to be made for preemptive insertion of a peritoneal dialysis catheter to allow time for healing and training before any acute need for commencement of dialysis (see Chapter 96). Peritoneal dialysis catheters can be inserted and completely buried subcutaneously some time before patients require dialysis, then superficialized for use once clinical circumstances dictate.

Early kidney transplantation may be associated with improved long-term outcome,[35] so patients should be assessed for their suitability and, when feasible, activated on the waiting list before dialysis is commenced. This maximizes the chances of the potential recipient remaining in reasonable health. The availability of a living donor should be explored to increase the chances of preemptive transplantation before the patient begins dialysis. KDIGO recommends that living donor preemptive kidney transplantation in adults be considered when the GFR is below 20 ml/min/1.73 m^2 and there is evidence of progressive and irreversible CKD over the preceding 6 to 12 months.[2]

Planned early initiation of dialysis is not associated with improvement in outcomes compared with commencement when indicated by signs and symptoms of uremia.[36] KDIGO suggests that dialysis be initiated when one or more of the following are present: symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, pruritus); inability to control volume status or blood pressure; a progressive deterioration in nutritional status refractory to dietary intervention; or cognitive impairment.[2] These problems often but not invariably occur when the GFR is below 15 ml/min/1.73 m^2 (see Chapter 90).

Conservative Management

The potential burden of commencing RRT in terms of high short-term mortality rates, recurrent hospitalizations, time spent travelling, and limited improvement in quality of life for some elderly patients and those with multiple comorbid disease is increasingly recognized. This has led to the practice of offering patients approaching ESRD the additional option of choosing not to start dialysis, but to maintain ongoing follow-up and symptomatic support through conservative management. Although dialysis may offer longer survival, those choosing conservative management may have as many hospital free-days as those who choose hemodialysis.[37] The symptoms of advanced uremia can be distressing, and it is important to ensure that patients who choose this pathway have access to members of the multidisciplinary team with expertise in palliative care to facilitate a death free of suffering.

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CHAPTER 82

Cardiovascular Disease in Chronic Kidney Disease

Peter Stenvinkel and Charles A. Herzog

The life span of patients with chronic kidney disease (CKD), particularly those with end-stage renal disease (ESRD), is reduced. In the United States, the all-cause mortality rate of prevalent dialysis patients in 2010 was 193 deaths per 1000 patient-years, 38% attributable to cardiac causes.[1] Diminished estimated glomerular filtration rate (eGFR) is a powerful graded, independent predictor of cardiovascular morbidity and mortality[2] and all-cause mortality (Fig. 82-1).[3] Even subtle kidney dysfunction, as suggested by albuminuria, increases cardiovascular risk[4] because it may reflect microvasculature health, including endothelial function. There is a strong association between urinary albumin excretion and other cardiovascular risk factors.[5] ESRD patients face an extraordinary risk for premature death, largely as a result of cardiovascular complications. However, the numbers of patients with non–dialysis-dependent CKD are much larger, and those with eGFR below 60 ml/min/1.73 m^2 are much more likely to die than to develop ESRD,[6] reflecting the burden of cardiovascular disease (CVD) in this high-risk population. The most effective strategy for reducing cardiovascular morbidity and mortality would be to target patients with mild renal impairment for prevention and treatment before severe CKD develops.

Unfortunately, CKD patients were often excluded from randomized controlled trials targeting CVD, or renal function was poorly described,[7] possibly reducing acceptance of evidence-based therapies (validated in nonrenal patients) and fostering "therapeutic nihilism" in clinicians who treat CKD patients.

Like conventional atheromatous occlusive vascular disease, CKD is characterized by generalized vasculopathy with other characteristics, including left ventricular hypertrophy (LVH), vascular calcification, and vascular noncompliance. Numerous CVD risk factors are specific for CKD and operate in addition to conventional risk factors found in the general population.

EPIDEMIOLOGY

Prevalence of Cardiovascular Complications in Chronic Kidney Disease

Interpretation of epidemiologic studies of CVD in CKD is problematic because of the difficulty in defining cause of death, but this difficulty is not limited to renal disease patients. Unexpected sudden death is most likely a result of arrhythmia, but a subarachnoid hemorrhage, massive embolic stroke, or aortic dissection might be indistinguishable from a primary arrhythmic event without an autopsy. The real conundrum, however, is defining "coronary heart disease" (CHD). In the general population, sudden cardiac death is rightly considered a primary complication of CHD; evidence-based interventions (e.g., statins) aimed at quelling the progression of atherosclerotic disease reduce the incidence of sudden death. However, in dialysis patients, sudden cardiac death is likely not to be a surrogate for CHD. Even use of a history of angina to classify a patient as having CHD is problematic because angina (as a result of supply-demand mismatch) can occur in patients with LVH and angiographically pristine coronary arteries. This probably relates to the increased myocardial fibrosis, diminished relative capillary density, and increased thickening of the intramyocardial vessel walls in uremia.

Of incident ESRD patients, 75% have LVH. Hypertension prevalence increases progressively with falling GFR; 75% to 85% of dialysis patients have hypertension. With hypertension, anemia, vascular noncompliance, and volume overload contribute to LVH. Based on echocardiography, 85% to 90% of patients have a left ventricular (LV) ejection fraction (EF) of 50% or higher, despite frequent congestive heart failure (CHF).[8] Because CHF is diagnosed in about 40% of incident ESRD patients within the first year,[9] many volume overload episodes may be attributable to diastolic dysfunction or circulatory congestion. CHF hospitalizations are associated with high long-term mortality.[10] Although occlusive CHD is common in CKD patients, acute myocardial infarction (AMI) accounts for only 13% of cardiac deaths; 69% of deaths in the United States Renal Data System (USRDS) database are attributable to arrhythmias.[11] In incident elderly dialysis patients, new atrial fibrillation (AF) occurs at an annual rate of 15%, with 59% mortality in the first year after incident AF.[12] Figure 82-2 provides a snapshot of CVD event rates in prevalent ESRD patients.

Congestive heart failure results from pressure overload, volume overload, and nonhemodynamic factors altering the myocardium.[13] Figure 82-3 summarizes cardiorenal syndrome pathophysiology leading to cardiomyopathy and CHF.

Cardiovascular Disease Is Present Before the Start of Renal Replacement Therapy

In elderly CKD patients at stage 2 or 3, traditional risk factors seem to be the major contributors to cardiovascular mortality. Atherosclerosis Risk in Communities (ARIC) data suggest that both traditional and novel risk factors are relevant at CKD stage 4,[14] and studies of dialysis patients suggest that novel risk factors are far more prevalent than in the general population (Fig. 82-4).[15] The Framingham predictive instrument does not accurately predict coronary events in CKD.[16] Mild to moderate CKD is associated with increased risk of venous thromboembolism,[17] supporting the concept of hypercoagulability in CKD. A Kidney Disease: Improving Global Outcomes (KDIGO) collaborative meta-analysis provides estimates of cardiovascular and all-cause mortality risk stratified by eGFR and urinary albumin-creatinine ratio (Fig. 82-5).[18] Figure 82-6 shows the burden of CVD in elderly patients with and without non–dialysis-dependent CKD.

Racial and International Differences in Cardiovascular Disease Prevalence

In the United States, African American dialysis patients have better survival than Caucasian dialysis patients. However, overall

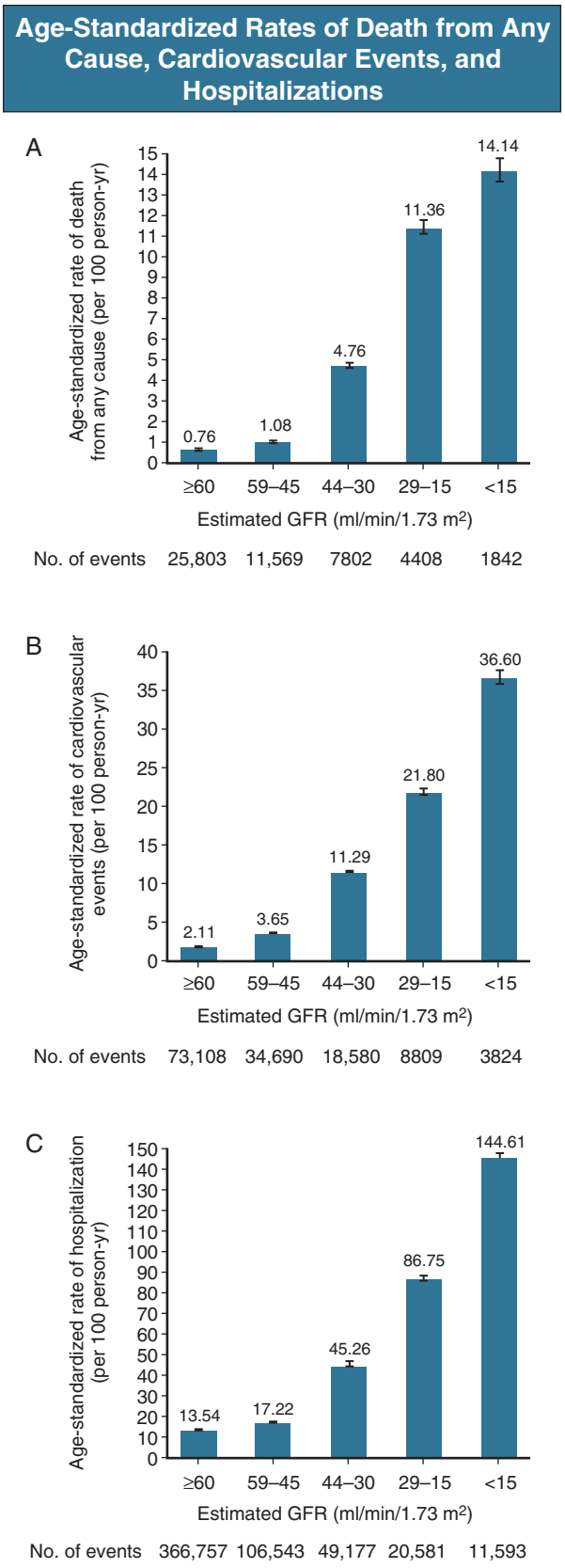

Figure 82-1 Age-standardized rates of death from any cause (A), cardiovascular events (B), and hospitalization (C) according to estimated glomerular filtration rate (GFR) among 1,120,295 ambulatory adults. A cardiovascular event was defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, or peripheral arterial disease. Error bars represent 95% confidence intervals. The rate of events is listed above each bar. *(From reference 2.)*

cardiovascular mortality among dialysis patients from the United States is significantly greater than is observed in Japan and Europe,[19] even after adjustment for standard risk factors and dialysis dose. Higher mortality rates in U.S. dialysis patients may be related to higher prevalence of sicker or diabetic patients or to differences in dialysis practice patterns; however, cultural habits, differences in diet, or genetic variations may also contribute.

Reverse Epidemiology

Reverse epidemiology refers to the paradoxical observation that the association among hypercholesterolemia, hypertension, obesity, and poor outcomes, including cardiovascular death, in the general population does not exist and may be reversed in the CKD population.[20] This concept is needlessly confusing and should be replaced by *confounded epidemiology.* Causality must not be confused with association. It is assumed (but open for debate) that patients with wasting and inflammation mostly account for poor survival and confounded epidemiology.

ETIOLOGY AND RISK FACTORS

Traditional Risk Factors

Age, Gender, and Smoking

The U.S. National Health and Nutrition Examination Surveys (NHANES) show the prevalence of cardiovascular risk factors and CVD prevalence in relation to age and CKD stage. In the United States, the average age at renal replacement therapy initiation is 63 years, when CVD is common. An individual-level meta-analysis including more than 2 million participants showed that low eGFR and high albuminuria were independently associated with mortality and ESRD regardless of age.[21] Female gender is associated with a 4% independent increased risk of mortality in incident dialysis patients,[5] and smoking with a 52% increased risk of death in dialysis patients.[22]

Diabetes Mellitus

Diabetes accounted for 44% of incident U.S. ESRD patients in 2010[1] and is the most common cause of ESRD in many countries. Diabetic patients starting renal replacement therapy have numerous cardiovascular risk factors, including dyslipidemia, hypertension, persistent inflammation, increased oxidative stress, and protein-energy wasting. Not surprisingly, diabetes at dialysis initiation is an independent risk factor for all-cause and CVD-related deaths, including after coronary revascularization or AMI; diabetic ESRD confers a 34% mortality risk after AMI compared with nondiabetic ESRD. Despite diabetes being a "CHD equivalent," the rate of incident AMI is even higher for patients with CKD stages 3b to 4 without diabetes than for patients with diabetes and eGFR of 60 ml/min/1.73 m^2 or higher.[23]

Hypertension

Hypertension is common but variably treated in CKD patients. Of NHANES[5] participants with CKD stages 3 and 4, 80% were hypertensive (defined as blood pressure ≥130/≥80 mm Hg for CKD patients), and only 20% were aware of it and treated, with the blood pressure adequately controlled. Of participants with CKD stages 1 and 2, 63% were hypertensive and only 11% of these were treated, with blood pressure adequately controlled. More recent data from NHANES 2001 to 2010 suggest modest improvement in hypertensive people with CKD stages 3 to 4.[24] Low blood pressure is correlated with mortality in some dialysis patients (see the discussion of reverse epidemiology). However, as in the general population,

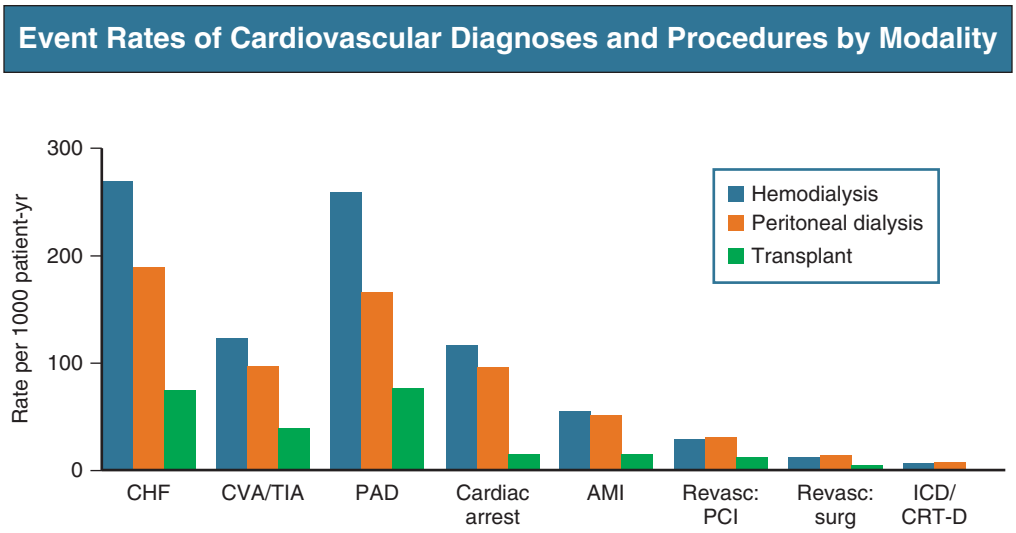

Figure 82-2 Event rates of cardiovascular diagnoses and procedures by modality. Point prevalent end-stage renal disease (ESRD) patients on January 1, 2005, age 20 and older, with Medicare as primary payer and survival for 90 days after ESRD diagnosis. *AMI,* Acute myocardial infarction; *CHF,* congestive heart failure; *CRT-D,* cardiac resynchronization therapy defibrillator; *CVA,* cerebrovascular accident; *ICD,* implantable cardioverter-defibrillator; *PAD,* peripheral arterial disease; *PCI,* percutaneous coronary intervention; *TIA,* transient ischemic attack. *(From reference 166.)*

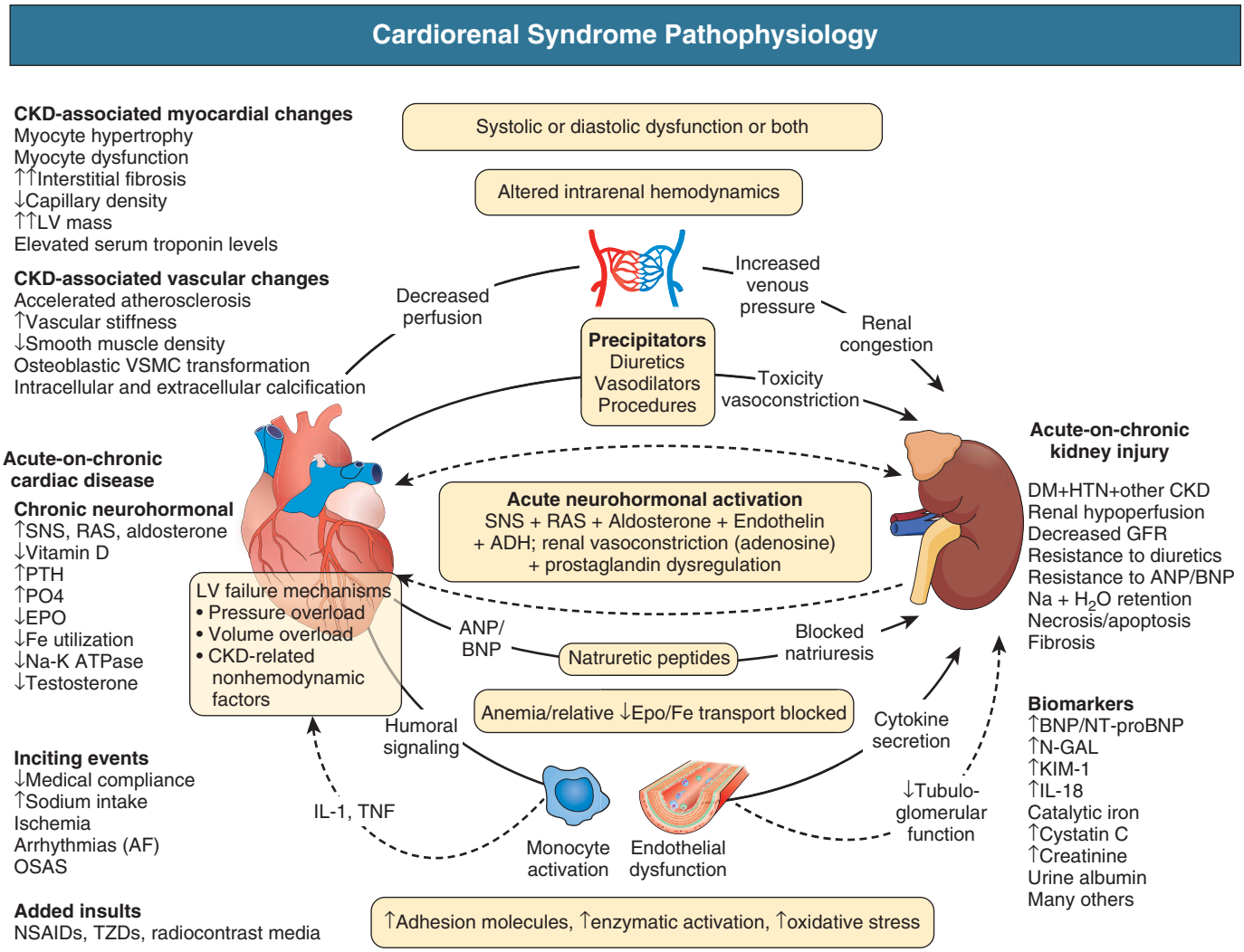

Figure 82-3 Cardiorenal syndrome pathophysiology. *ADH,* Antidiuretic hormone; *AF,* atrial fibrillation; *ANP,* atrial natriuretic peptide; *BNP,* brain natriuretic peptide; *CKD,* chronic kidney disease; *DM,* diabetes mellitus; *EPO,* erythropoietin; *GFR,* glomerular filtration rate; *HTN,* hypertension; *IL-1,* interleukin-1; *KIM-1,* kidney injury molecule 1; *LV,* left ventricular; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *N-GAL,* neutrophil gelatinase–associated lipocalin; *NT-proBNP,* N-terminal prohormone of brain natriuretic peptide; *OSAS,* obstructive sleep apnea syndrome; *PTH,* parathyroid hormone; *RAS,* renin-angiotensin system *SNS,* sympathetic nervous system; *TNF,* tumor necrosis factor; *TZDs,* thiazolidinediones; *VSMC,* vascular smooth muscle cell. *(From reference 13.)*

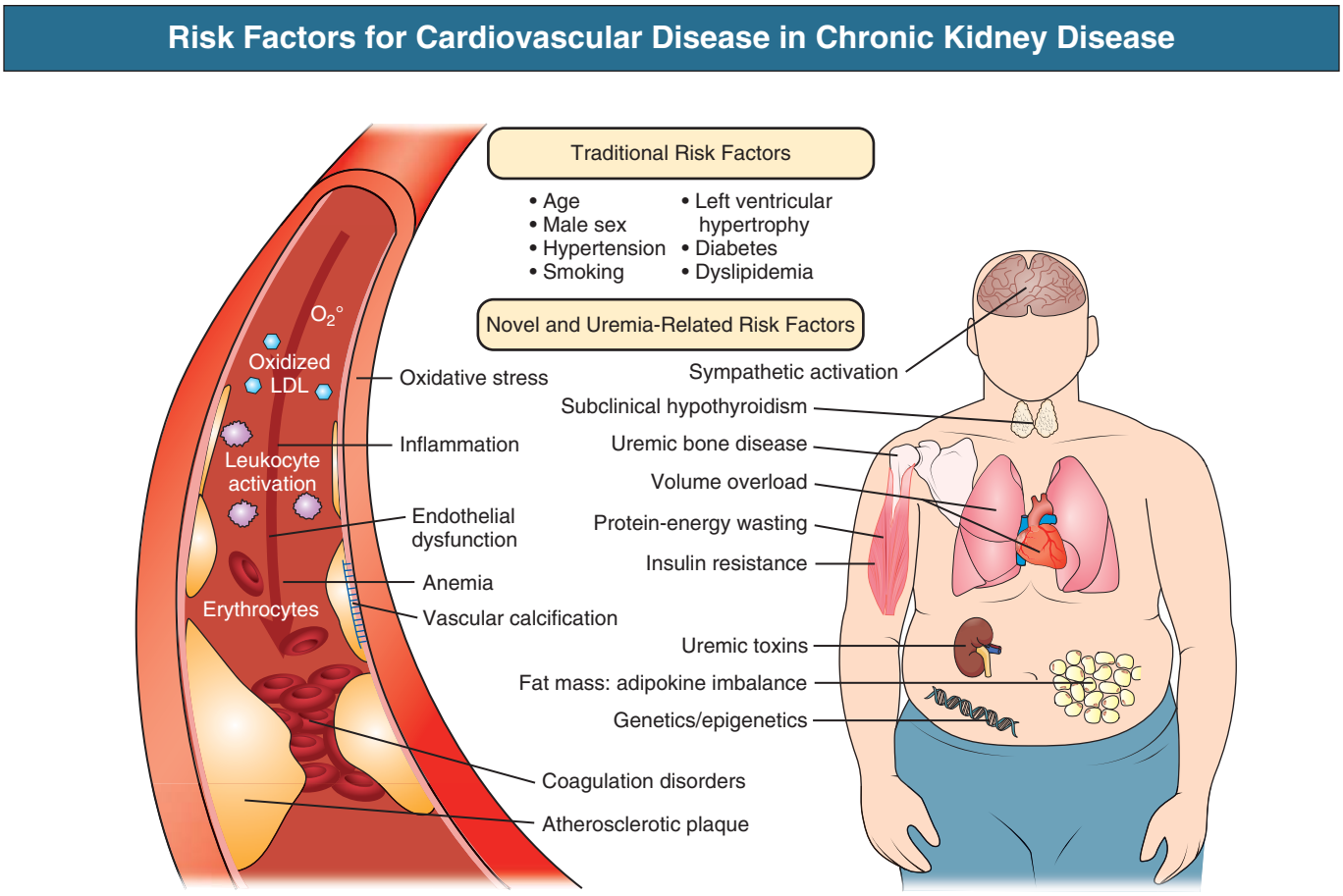

Figure 82-4 Risk factors for cardiovascular disease in chronic kidney disease. Overview of traditional (i.e., Framingham) risk factors and novel and uremia-related risk factors. *LDL,* Low-density lipoprotein. *(From reference 15.)*

Summary of Relative Risks for All Causes and Cardiovascular Death Based on eGFR and Albumin-Creatinine Ratio

All-cause mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ≥300
eGFR >105	1.1	1.5	2.2	5.0
eGFR 90–105	Ref	1.4	1.5	3.1
eGFR 75–90	1.0	1.3	1.7	2.3
eGFR 60–75	1.0	1.4	1.8	2.7
eGFR 45–60	1.3	1.7	2.2	3.6
eGFR 30–45	1.9	2.3	3.3	4.9
eGFR 15–30	5.3	3.6	4.7	6.6

Cardiovascular mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ≥300
eGFR >105	0.9	1.3	2.3	2.1
eGFR 90–105	Ref	1.5	1.7	3.7
eGFR 75–90	1.0	1.3	1.6	3.7
eGFR 60–75	1.1	1.4	2.0	4.1
eGFR 45–60	1.4	2.2	2.8	4.3
eGFR 30–45	2.2	2.7	3.4	5.2
eGFR 15–30	14	7.9	4.8	8.1

Figure 82-5 Summary of relative risks from categorical meta-analysis. *ACR,* Albumin-creatinine ratio; *eGFR,* estimated glomerular filtration rate. *(Adapted from reference 18.)*

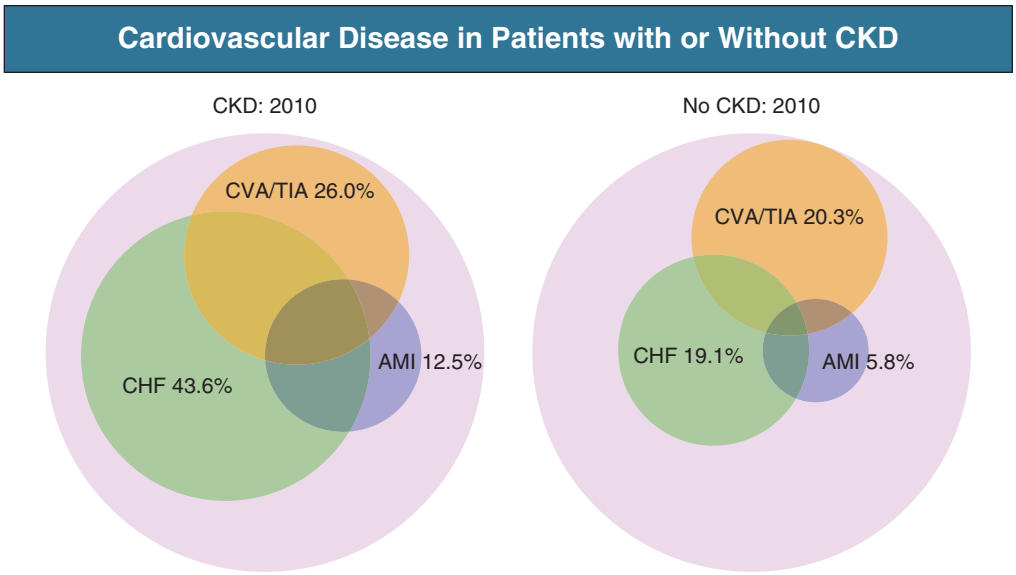

Figure 82-6 Cardiovascular disease in patients with or without chronic kidney disease, 2010. Relative frequency of cardiovascular disease in Medicare enrollees, age 66 and older, with or without CKD. *AMI,* Acute myocardial infarction; *CHF,* congestive heart failure; *CKD,* chronic kidney disease; *CVA,* cerebrovascular accident; *TIA,* transient ischemic attack. *(From reference 1.)*

Lipid Abnormalities in Renal Disease

	Cholesterol Levels			
Stage of Renal Disease	**Total**	**High-Density Lipoproteins**	**Low-Density Lipoproteins**	**Triglycerides**
Nephrotic syndrome	↑↑↑	↓	↑↑	↑
Chronic kidney disease	No change	↓	No change*	↑↑
Hemodialysis	No change	↓	No change*	↑↑
Peritoneal dialysis	↑	↓	↑	↑
Transplantation	↑↑	No change	↑	↑

Table 82-1 Lipid abnormalities in renal disease. Common patterns of hyperlipidemia in different stages of renal disease, compared with the healthy population. *Composition altered.

hypertension predicts mortality in CKD patients before or at dialysis initiation. Isolated systolic hypertension with increased pulse pressure is by far the most prevalent blood pressure anomaly in dialysis patients, resulting from arterial medial sclerosis with secondary stiffening. Stiff vessels cause increased pulse wave velocity, resulting in increased systolic peak pressure by a prematurely reflected pulse wave, progressive LV dysfunction, and finally CHF. This may subsequently result in decreased mean arterial and diastolic pressure and increased risk for cardiovascular death. The relationship between blood pressure and mortality is U shaped; isolated systolic hypertension and increased pulse pressure probably indicate high long-term risk in dialysis patients, whereas low mean and diastolic blood pressures predict early mortality. The invisible hypertension danger relates to numerous CKD patients being "nondippers" (see Chapter 33). CKD patients frequently also experience sleep apnea associated with nondipping, sympathetic nervous system activation, and cardiovascular risk.

Dyslipidemia

The relationship among hypercholesterolemia, CVD, and mortality in CKD patients is weak because some major cardiovascular abnormalities, such as cardiomyopathy and arteriosclerosis, may be less dependent on dyslipidemia than on other factors. Paradoxically, low rather than high serum cholesterol level is associated with poor survival in hemodialysis (HD) patients,[20] confounded epidemiology likely related to protein-energy wasting and inflammation. After adjustment for C-reactive protein (CRP) levels, high cholesterol level predicted risk in relatively healthy ESRD patients without inflammation.[25]

Progressive CKD leads to changes in blood lipids associated with vascular disease, including decreased levels of apolipoprotein A (apoA)–containing lipoproteins and increased levels of apoB-containing lipoproteins (Table 82-1). Plasma triglyceride levels are elevated in most ESRD patients, whereas total serum cholesterol levels may be elevated, normal, or low, depending on nutritional status and presence of inflammation. High-density lipoprotein (HDL) cholesterol is typically reduced, and low-density lipoprotein (LDL), intermediate-density lipoprotein, and very low-density lipoprotein cholesterol as well as lipoprotein(a) levels tend to be increased. Because of specific changes in its molecular composition, HDL anti-inflammatory activities are defective in the uremic milieu.[26] Compared with long-term HD patients, peritoneal dialysis (PD) patients more often have both hypercholesterolemia and hypertriglyceridemia. Both groups are characterized by low HDL and elevated oxidized LDL cholesterol levels; elevated lipoprotein(a) levels are associated with increased CVD mortality.

Insulin Resistance and Atherosclerosis

In the general population, impaired insulin-stimulated glucose disposal in muscle is often part of a metabolic syndrome that includes dyslipidemia, hypertension, endothelial dysfunction, and sympathetic overactivity. Many of these abnormalities are present in CKD.

Although insulin resistance was found to be an independent predictor of cardiovascular mortality in dialysis patients,[27] its contribution to CKD patient mortality is uncertain.

Nontraditional and Uremia-Specific Risk Factors

Several large prospective population studies have shown that even mild CKD is an independent risk factor for CVD, independent of hypertension, diabetes, and albuminuria, and similar in magnitude to diabetes and hypertension.[28,29] The uremic milieu may affect both quality and quantity of the atherosclerotic plaques. Coronary lesions in uremic patients, compared with nonrenal controls, are characterized by increased media thickness, infiltration, and activation of macrophages and marked calcification.[30] The mechanism by which a uremic milieu may accelerate atherosclerosis is not well established, but prevalence and magnitude of several nontraditional risk factors, such as oxidative stress, inflammation, vascular calcification, and advanced glycation end products (AGEs), increase as renal function deteriorates. Other uremic retention solutes, such as asymmetric dimethylarginine (ADMA), guanidine, indoxyl sulfate, and *p*-cresol, which accumulate in CKD, may have proatherogenic properties.[31] Finally, the kidneys produce substances that may inhibit CVD and atherogenesis—for example, renalase, a soluble monoamine oxidase that regulates cardiac function and blood pressure.[32]

Oxidative Stress

Oxidative stress may be implicated in the pathogenesis of atherosclerosis and the increased risk of atherosclerotic cardiovascular events and in other CKD complications, such as protein-energy wasting and anemia.[33] Increased production of reactive oxygen species in the vascular wall is a characteristic feature of atherosclerosis.[33] Early CKD (stage 3), and in particular uremia, is a pro-oxidant state resulting from reduced antioxidant systems (vitamin C and selenium deficiency, reduced intracellular vitamin E levels, reduced glutathione system activity) and increased pro-oxidant activity associated with advanced age, diabetes, chronic inflammation, retained uremic solutes, and dialysis membranes and solutions.[33] Four oxidative stress pathways can be hypothesized in CKD: carbonyl stress, nitrosative stress, chlorinated stress, and classical oxidative stress (Fig. 82-7).

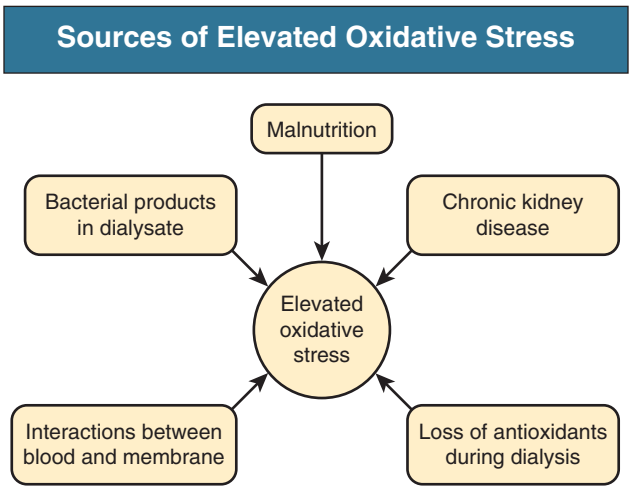

Figure 82-7 Sources of elevated oxidative stress.

Inflammation

Most dialysis patients are in a state of chronic inflammation; inflammatory biomarkers, such as CRP, interleukin (IL)-6, pentraxin 3 (PTX3), fibrinogen, and white blood cell count, are robust and independent predictors of mortality in CKD patients. Hypoalbuminemia, a biochemical factor strongly associated with systemic inflammation, is another strong outcome predictor in CKD. Whereas both dialysis-related factors and non–dialysis-related factors (infection, comorbidity, genetic factors, diet, renal function loss) may contribute to chronic inflammation, its primary causes are not always evident. As in the general population, it is unclear in CKD patients whether the acute-phase response reflects only established atherosclerotic disease or is involved in the initiation and progression of atherosclerosis. Some inflammatory biomarkers, such as IL-6, PTX3, and tumor necrosis factor, may have proatherogenic properties, such as promoting vascular calcification, oxidative stress, and endothelial dysfunction (Fig. 82-8). Evidence also suggests associations between inflammation and development of albuminuria. The link between septicemia and subsequent increased risk of death and cardiovascular events, including AMI, in observational studies further supports inflammation as a trigger for cardiovascular events.[34]

Endothelial Dysfunction

Endothelial dysfunction (as evaluated by impaired endothelium-dependent vasodilation) is a prominent feature of CKD. Reasons include inflammation, ADMA retention, oxidative stress, dyslipidemia, hyperglycemia, and hypertension. Plasma ADMA concentrations are associated with endothelial function in uremic resistance vasculature.[35] Surrogate markers of endothelial dysfunction, such as ADMA, PTX3, and adhesion molecules, independently predict death.[15] Detached circulating endothelial cells serve as potential markers of endothelial damage in renal and nonrenal patients and have prognostic value in HD patients.[15] Normally, in response to ischemic insult and cytokine stimulation, endothelial progenitor cells are mobilized from the bone marrow to act as repair cells for the endothelial injury. Because CKD patients seem to have reduced numbers or functional impairment of endothelial progenitor cells as a result of inflammation or uremic toxins, they seem predisposed to endothelial dysfunction. An independent association exists between circulating fibroblast growth factor 23 (FGF23) and endothelial dysfunction.[36]

Anemia

Anemia is a major cause of LVH and LV dilation in CKD. Although partial correction of anemia with erythropoiesis-stimulating agents (ESAs) results in LVH regression, current information suggests no cardiovascular outcome benefit of normalized hemoglobin (see Chapter 83).

Secondary Hyperparathyroidism and Mineral Metabolism

Disturbances of calcium and phosphate metabolism starting as early as CKD stages 3 and 4 might accelerate calcifying atherosclerosis and arteriosclerosis. Recent evidence suggests that chronically elevated FGF23 levels contribute directly to high rates of LVH and mortality in CKD.[37] In registry data, a strong independent mortality risk is predicted by hyperphosphatemia, an intermediate risk by elevated serum calcium levels, and a weak but significant risk by high or low serum intact parathyroid hormone levels. The overall mortality risk prediction attributable to mineral metabolism disorders is estimated to be about 17% in HD patients.[38]

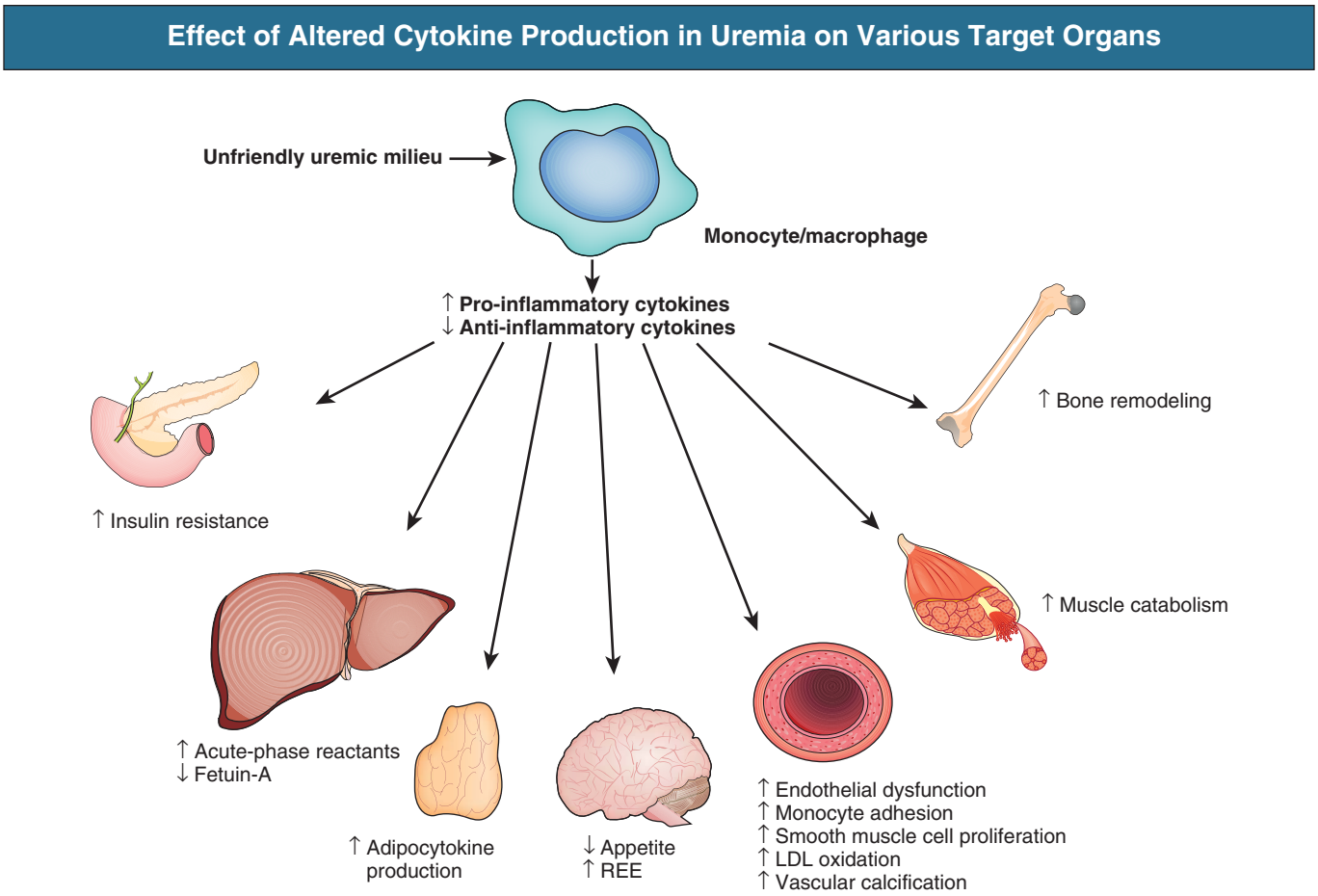

Figure 82-8 Potential mechanisms by which elevated circulating levels of proinflammatory and anti-inflammatory cytokines may promote accelerated atherosclerosis, other uremic complications, and wasting. *LDL,* Low-density lipoprotein; *REE,* resting energy expenditure. *(From reference 31).*

Cardiovascular Calcification

Cardiovascular calcification may affect the arterial media, atherosclerotic plaques, myocardium, and heart valves. Medial calcification causes arterial stiffness and, consequently, increased pulse pressure. The pathophysiologic role of plaque calcification is less clear because soft plaques are assumed to rupture and to cause AMI; atherosclerotic calcification is a potent risk marker of cardiovascular events, but its utility as a risk marker for clinical management of CKD patients remains controversial. Valvular calcification mostly affects the aortic and mitral (annulus) valves in dialysis patients and contributes to progressive stenosis and associated morbidity; mitral annular calcification is associated with increased mortality.[39] In dialysis patients, extensive vascular, especially coronary artery, calcification can occur at young ages. Calcium and phosphate metabolism disturbance is an important factor in cardiovascular calcification in ESRD. A serum phosphate level of 5.0 mg/dl or higher (≥1.62 mmol/l) is associated with increased risk of valvular heart surgery in HD patients.[40] Calciphylaxis (calcific uremic arteriolopathy), characterized by severe calcifications of cutaneous arterioles and tissue necrosis, is discussed in Chapter 88.

Vascular calcification is not derived only from passive calcium and phosphate precipitation. Rather, it is a highly regulated active process involving differentiation of vascular smooth muscle cells toward osteoblasts induced by phosphate, calcium, and other factors, such as calcitriol and proinflammatory cytokines. One way by which chronic inflammation promotes vascular calcification may involve downregulation of fetuin-A, the most potent circulating inhibitor of extraosseous calcification and formation of calciprotein particles.[41] In cross-sectional studies, dialysis patients with low serum fetuin-A levels showed significantly poorer survival than those with normal values.[42] Apart from fetuin-A, other inhibitors probably counteract unwanted calcification. Leptin, matrix GLA protein, FGF23, pyrophosphates, bone morphogenic proteins (e.g., BMP-2 and BMP-7), and osteoprotegerin may be related to accelerated vascular calcification in ESRD. Recent studies indicate that deficiency of vitamin K and/or treatment with vitamin K antagonists (warfarin) may accelerate the vascular calcification process in the uremic milieu.[43]

Advanced Glycation End Products

Advanced glycation end products accumulate in CKD patients as a result of nonenzymatic glycation, oxidative stress, and diminished clearance of AGE precursors. Stable AGE residues of long-lived proteins are biomarkers of cumulative metabolic, inflammatory, and oxidative stress; carbonyl stress is speculated to contribute to tissue aging and long-term CKD complications. Whether AGE inhibition may be a useful intervention to reduce cardiovascular events, progression, and mortality in CKD is unknown.

Dialysis Modality

Reports from dialysis registries are inconsistent with regard to whether HD or PD is associated with better outcomes.[44] Valid mortality comparisons between modalities would require stratification

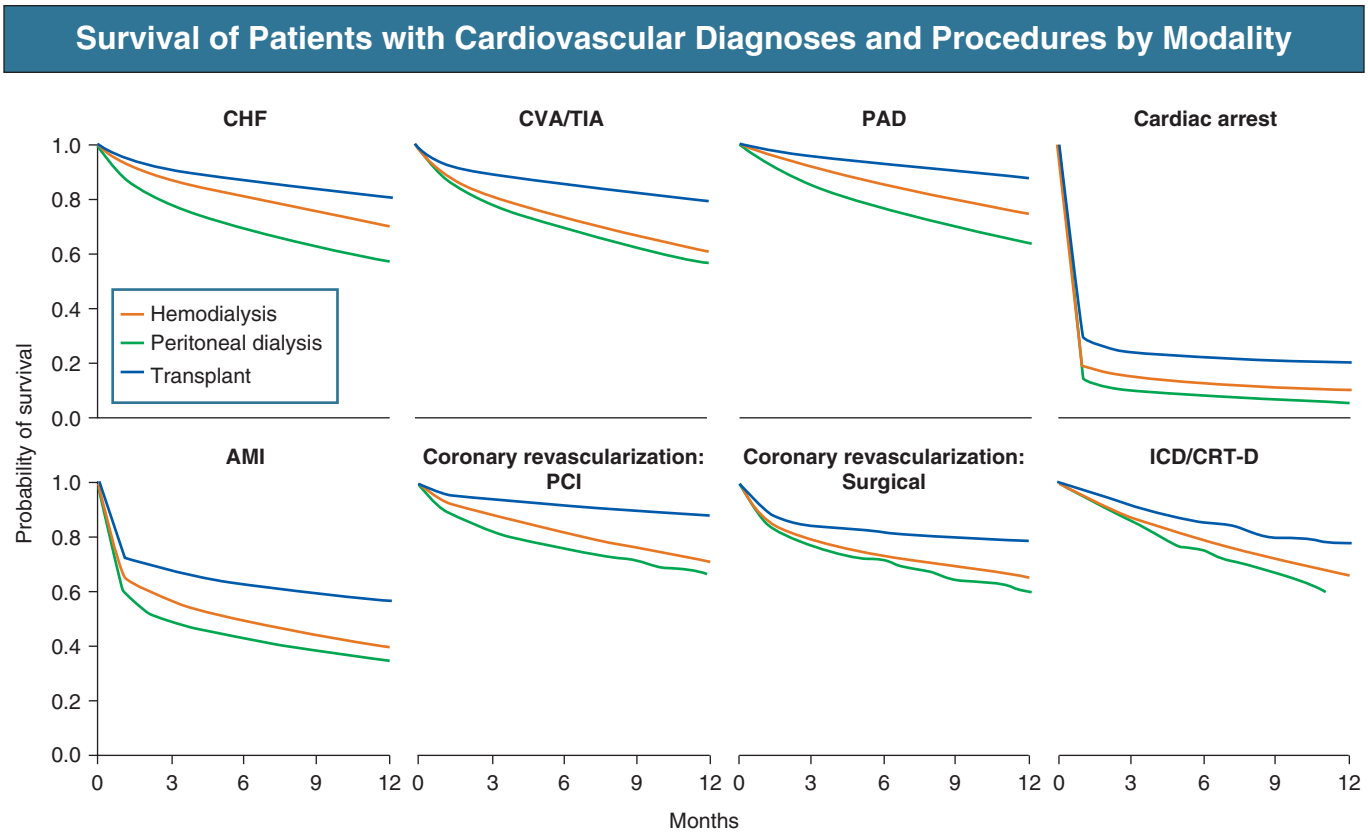

Figure 82-9 Survival of patients with cardiovascular diagnoses and procedures, by modality. January 1, 2005, point prevalent ESRD patients, age 20 and older, with a first cardiovascular diagnosis or procedure in 2005-2007. *AMI,* acute myocardial infarction; *CHF,* congestive heart failure; *CRT-D,* cardiac resynchronization therapy defibrillator; *CVA,* cerebrovascular accident; *ICD,* implantable cardioverter-defibrillator; *PAD,* peripheral arterial disease; *PCI,* percutaneous coronary intervention; *TIA,* transient ischemic attack. *(Modified from reference 166.)*

of patients according to underlying ESRD cause, age, and level of baseline comorbidity.[44] Such data are currently not available.

CLINICAL MANIFESTATIONS AND NATURAL HISTORY

Figure 82-9 shows survival of patients with cardiovascular diagnoses and procedures, by renal replacement therapy modality.

Chest Pain, Coronary Heart Disease, and Acute Myocardial Infarction

Acute myocardial infarction in dialysis patients is associated with poor long-term survival. The unadjusted 73% 2-year mortality rate has changed minimally in 25 years[45] despite dramatic improvements in AMI outcomes in the general population (Fig. 82-10). This heightened mortality is not restricted to ESRD patients; in-hospital deaths increase with decreasing GFR (Fig. 82-11).[46-48] Furthermore, the likelihood of prescribing evidence-based therapies, including aspirin and β-blockers, in CKD patients is historically diminished[46-49] (but recently increased),[1] although these therapies decrease mortality in such patients.

Prior speculations have attributed this poor outcome to underrecognition resulting from "atypical" presentations,[49] underuse of appropriate diagnostic investigations, and undertreatment (therapeutic nihilism).[49,50] The collaborative USRDS/National Registry of Myocardial Infarction study[50] of dialysis patients hospitalized for AMI found that:

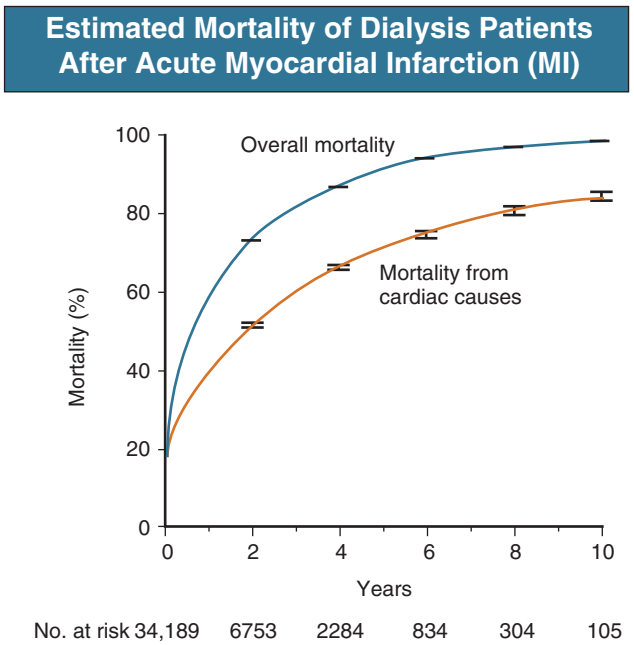

Figure 82-10 Estimated mortality of dialysis patients after acute myocardial infarction. *(Reprinted with permission from reference 167. Copyright © 2003 American Society of Nephrology.)*

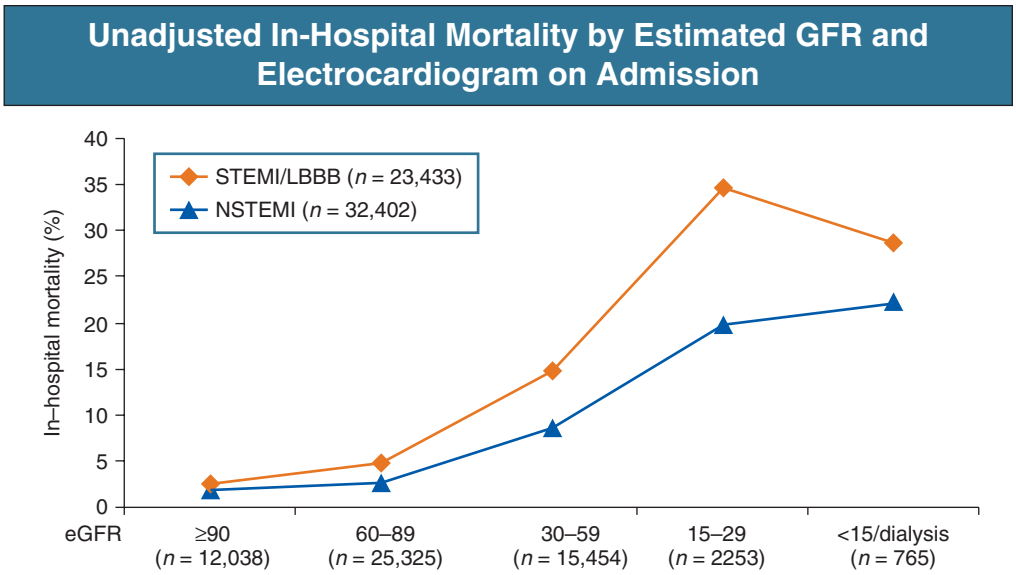

Figure 82-11 Unadjusted in-hospital mortality by estimated glomerular filtration rate (GFR) and electrocardiogram on admission. *LBBB,* Left bundle branch block; *NSTEMI,* non–ST-segment elevation myocardial infarction; *STEMI,* ST-segment elevation myocardial infarction. *(From reference 46.)*

- 45% of dialysis patients, versus 21% of nondialysis patients, were diagnosed incorrectly with respect to acute coronary syndrome.
- 44% of dialysis patients, versus 68% of nondialysis patients, experienced chest pain.
- 19% of dialysis patients, versus 36% of nondialysis patients, had ST-segment elevation.
- After other clinical exclusions, only 10% of dialysis patients, versus 25% of nondialysis patients, were eligible for acute coronary reperfusion.
- Of those who were eligible, 47% of dialysis and 75% of nondialysis patients actually received reperfusion.
- In-hospital death was 21% for dialysis and 12% for nondialysis patients. In-hospital cardiac arrest occurred twice as frequently in dialysis as in nondialysis patients (11% vs. 5%).

Similar findings occur across the CKD spectrum; the likelihood of increased mortality and lower prevalence of both ST-segment elevation myocardial infarction (STEMI) and chest pain are correlated with severity of non–dialysis-dependent CKD in patients with AMI.[47,48,51] Patients with eGFR below 45 ml/min/1.73 m^2 are three times as likely to present with AMI as with stable angina as the initial manifestation of CHD.[52]

Peripheral Arterial Disease

Risk of peripheral arterial disease (PAD) is highest for dialysis patients with diabetes or preexisting atherosclerosis. In HD patients, PAD is also associated with time on dialysis, hypoalbuminemia, low parathyroid hormone levels, and low predialysis diastolic blood pressure. Vascular medial calcification of large peripheral arteries may not indicate presence of occlusive disease, and peripheral gangrene is often caused by diabetic or other small-vessel disease or rarely by calcific uremic arteriolopathy (see Chapter 88). PAD is associated with increased mortality; outcomes after revascularization are worse than for the general population,[53] in part reflecting advanced vasculopathy. About one fourth of CKD patients and half of HD patients have PAD,[1,54] and the knowledge gaps regarding treatment of PAD in CKD patients are large.[13]

Cerebrovascular Disease and Atrial Fibrillation

Cognitive impairment is severe in more than a third of dialysis patients, and only 15% have normal cognition.[55] Cognitive impairment prevalence increases approximately 10% per 10 ml/min/1.73 m^2 of eGFR less than 60 ml/min/1.73 m^2.[56] Microalbuminuria and stage 3 CKD increased stroke risk 1.5-fold to 2-fold in a multivariate model.[57,58] Incident dialysis patients have a sixfold age-adjusted relative risk of stroke compared with the general population; the unadjusted rate for stroke hospitalization for dialysis patients was 48 per 1000 patient-years, and 11% of these hospitalizations were attributed to hemorrhagic stroke.[59] Dialysis initiation is associated with a fourfold to sevenfold increased stroke incidence compared with the rate 12 months before initiation.[60] Stroke accounts for 3% of ESRD deaths in the USRDS registry[1] (see Chapter 86 for more details).

Atrial fibrillation is the most common dysrhythmia in CKD patients; the prevalence among dialysis patients is 15% to 20%, and AF is associated with an increased stroke rate. Incident AF is an independent risk factor for development of ESRD in patients with CKD.[61] The incidence of AF is high and apparently increasing in older patients initiating dialysis in the United States.[12] Among warfarin-treated AF patients with stage 3 CKD, the hazard of stroke doubled versus lower CKD stages, and adjusted-dose warfarin was associated with a 76% reduction in the relative risk of ischemic stroke or systemic embolism.[63] In AMI patients with AF, warfarin treatment was associated with a lower 1-year risk for the composite outcome of death, AMI, and ischemic stroke without a higher risk of bleeding, irrespective of CKD severity was observed.[63a] In contrast, the usefulness of warfarin for primary prevention of stroke in dialysis patients with AF is controversial; because of observational studies suggesting harm, current KDIGO recommendations do not include routine warfarin therapy for primary prevention of stroke in AF patients with CKD stage 5D (however, warfarin for secondary prevention of stroke is recommended).[13,64]

Left Ventricular Remodeling and Hypertrophy

Left ventricular hypertrophy is a potent predictor of mortality in ESRD patients. LVH is associated with a 60% increased risk of sudden death and a more than twofold increased risk of stroke.[65] LVH occurs early in progressive CKD, probably because of high hypertension prevalence, including frequent nocturnal hypertension. Pressure overload, caused by hypertension and arterial stiffness, results in concentric hypertrophy. Volume overload manifests as eccentric hypertrophy. LV dilation strongly predicts poor outcome.

It may be an end result of severe LVH, diffuse ischemic damage, or recurrent volume overload; a high-output arteriovenous fistula may contribute. Diastolic dysfunction is strongly associated with LVH and with increased risk for intradialytic hypotension because relatively small reductions in left atrial filling have significant effects on cardiac output in these stiff, hypertrophied preload-sensitive hearts, together with Bezold-Jarisch reflex activation through stimulation of LV posterior wall stretch receptors in underfilled, hypercontractile, hypertrophied ventricles.

The term "uremic cardiomyopathy" is misleading; "cardiomyopathy of advanced CKD" more accurately describes the structural heart disease that occurs before ESRD onset. The Chronic Renal Insufficiency Cohort (CRIC) Study found no change in LV mass index in patients serially imaged with echocardiograms with eGFR below 20 ml/min/1.73 m^2 (not on dialysis) and subsequently imaged after dialysis initiation (i.e., after incident ESRD), a finding corroborated by the Initiating Dialysis Early and Late (IDEAL) trial.[66] In the CRIC study, dialysis initiation was associated with a small drop in left ventricular ejection fraction (LVEF; mean 53% to 50%), compared with no change in the IDEAL trial. In CRIC patients with stage 4 CKD (and no clinical heart failure), 75% had LVH and only about 10% had normal LV geometry.[67]

Conventional HD delivery can produce repetitive myocardial injury, leading to global and segmental reduction in LV systolic function[68]; the occurrence of HD-induced myocardial stunning is associated with 1-year mortality.[69] Even pediatric HD patients can experience HD-induced myocardial stunning, indicating that large-vessel obstructive CHD is not a prerequisite for this pathologic finding.[70] Biofeedback dialysis or reduced dialysate temperature both help reduce intradialytic hypotension and severity of HD-induced myocardial stunning.[71]

Extracellular Volume Overload

Extracellular volume overload resulting from loss of sodium excretory capacity is the major cause of hypertension in dialysis patients. Whether prevention of recurrent hypervolemia reduces cardiovascular morbidity and mortality remains unproved. If adjustments are made for comorbidity and advanced age, a strong, incremental risk of all-cause and cardiovascular mortality is associated with interdialytic weight gains.[72] Recurrent hypervolemia may result in LVH and LV dilation, peripheral or pulmonary edema, raised jugular vein pulse, or a third heart sound, or it may be largely asymptomatic. Tolerance of large ultrafiltration volumes may indicate that the dry weight target (see Chapter 94) has not been reached. Reaching an optimal dry weight, however, does not necessarily lead to immediate blood pressure correction; a lag phase of some weeks can precede improvement.

Pericarditis

Pericarditis from untreated uremia is rare today. Dialysis-associated pericarditis may be related to intercurrent illnesses (including viral infections), fistula recirculation leading to underdialysis, or underlying diseases such as systemic lupus, but the exact pathogenesis remains obscure. Fever with pericardial pain or a rub on heart auscultation, unexplained cardiomegaly on chest films, or hemodynamic instability should prompt echocardiography. An effusion causing overt hemodynamic compromise (i.e., pericardial tamponade) or large pericardial effusions judged unlikely to resolve with conservative measures require echocardiographically guided or computed tomography (CT)–guided pericardiocentesis or surgical drainage. Intensive dialysis is indicated for true uremic pericarditis; the optimal treatment of dialysis-associated pericarditis is much less clear in patients without hemodynamic compromise.[73] Aggressive anticoagulation should be avoided because of increased (but not well defined) risk for development of hemorrhagic pericarditis and pericardial tamponade.

Autonomic Dysfunction

Chronic kidney disease involves decreased baroreflex sensitivity, which has been linked to increased risk of sudden death.[74] Increased sympathetic nerve activity, including secondary to sleep apnea, is a common alteration in CKD patients and associated with adverse outcome.[75]

Valvular Disease

The rate of progression of calcific aortic stenosis is approximately three times faster in dialysis patients than in the general population.[76] Annual echocardiographic follow-up is recommended for asymptomatic dialysis patients who are suitable candidates for valve replacement with an aortic valve area of 1.0 cm^2 or less.[77] A USRDS study and a meta-analysis of dialysis patients undergoing valve replacement surgery found no difference in survival for patients receiving tissue versus mechanical valves and fewer valve-related complications with tissue valves.[78,79] The overall mortality is high, with in-hospital mortality of about 20% (four times higher than in non-CKD patients) and 2-year survival of 40%. In kidney transplant patients, in-hospital mortality was 11% for tissue and 15% for mechanical valve patients, and 2-year mortality rates were 62% and 60%, respectively. In the entire cohort of kidney transplant patients, the rate of endocarditis after valve surgery was 5% per year.[80]

Infective Endocarditis

Estimated incidence of infective endocarditis in U.S. dialysis patients is 267 cases per 100,000 patient-years.[81] Vascular access, including temporary and semipermanent catheters, is an important source of infection; heightened risk of bacteremia related to HD therapy is likely an important aspect of endocarditis risk. Dialysis patients with bacterial endocarditis have poor long-term survival. In-hospital mortality was 24% and 1-year survival only 38% for patients hospitalized in 1997 to 2000.[82]

A risk model for operative mortality may be helpful in managing these high-risk patients.[83]

Sudden Cardiac Arrest

In the USRDS database, two-thirds of all cardiac deaths and one quarter of all-cause mortality in dialysis patients are attributable to arrhythmias.[1] Although obstructive CHD is likely to be an important cause of sudden cardiac death, it is probably not the major one (unlike in the general population). Statin therapy has no impact on sudden death,[84] and a USRDS study found that coronary revascularization does not nullify the risk of sudden cardiac death for dialysis patients.[85] However, in the Hemodialysis (HEMO) trial the strongest multivariable predictors of sudden cardiac death were history of CHD, PAD, and diabetes.[86] Sudden cardiac death is independently associated with inflammatory biomarkers.[87] Myocardial fatty acid imaging might identify patients at risk for sudden death.[88] Factors probably contributing to the special vulnerability of ESRD patients to sudden cardiac arrest include LVH; rapid electrolyte shifts and hyperkalemia in HD; autonomic dysfunction and sympathetic

overactivity, including sleep apnea; and abnormalities in myocardial ultrastructure and function, including endothelial dysfunction, interstitial fibrosis, decreased perfusion reserve, and diminished ischemia tolerance.[49,89-91] Low-potassium dialysate (<2 mEq/L) is associated with a twofold independent risk for cardiac arrest and is thus a modifiable risk factor.[92] The rate of cardiac arrest is 50% higher for HD than for PD patients 3 months after initiation of dialysis but is higher for PD patients at 3 years.[93] The highest rate of sudden cardiac death occurs 2 months after HD initiation.[94] Reduced LVEF is a powerful independent predictor of cardiovascular death: ninefold for LVEF below 30% (versus 60% or higher) in incident HD patients.[94] Even a modest reduction in LVEF is prognostically important; in both HD (2.5-fold risk of cardiovascular death for LVEF 40% to 50%)[8] and PD patients, LVEF below 49% was the cutpoint for predicting sudden cardiac death in a prospective cohort of PD patients in Hong Kong.[95] One study of cardiac arrests occurring in HD centers found that the predominant rhythm was ventricular fibrillation (66%), followed by pulseless electrical activity (23%) and asystole (10%).[96]

Non–dialysis-dependent CKD is also associated with increased risk of sudden cardiac death. In women with CHD, eGFR below 40 ml/min/1.73 m^2 was associated with a 2.3-fold increased risk of sudden cardiac death. Despite a graded, incremental risk of arrhythmic death and impaired renal function, the overall magnitude of risk in stage 3 CKD patients is small compared with dialysis patients.

The reported rate of cardiac arrest in HD centers is 3.8 to 7.1 events per 100,000 dialysis sessions.[96-98] On-site defibrillation capability (preferably with automatic external defibrillators) was recommended as a U.S. practice guideline in 2005.[77]

The role that implantable cardioverter-defibrillators (ICDs) may play in reducing mortality in CKD patients is controversial, particularly regarding primary prevention of sudden death in patients with LVEF of 35% or lower (comparable general population patients receive ICDs under current U.S. implant guidelines). CKD may attenuate the survival advantage of ICDs for primary prevention of sudden cardiac death,[99,100] but older age and medical comorbidity should not routinely exclude patients from receiving ICDs. In dialysis patients who survived cardiac arrest, ICD implantation was associated with a 14% to 42% reduction in long-term mortality.[101,102] The role of ICDs in dialysis patients remains uncertain because they were never enrolled in clinical trials for either primary or secondary prevention of sudden death. The Wearable External Defibrillator in Hemodialysis Patients (WED-HED) trial, a large randomized controlled trial, will enroll patients who do not qualify for ICDs under current guidelines for primary prevention of sudden death (but who constitute the majority of patients at risk for it): dialysis patients with LVEF exceeding 35%.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Key issues in the diagnosis of CVD are under-recognition of symptoms, underuse of appropriate diagnostic investigations, and interpretation of those investigations.

Blood Pressure Measurements

Outcome prediction by ambulatory blood pressure monitoring is not necessarily better than by office blood pressure measurements. However, ambulatory monitoring is useful to identify high-risk nondippers and inverted dippers, allowing consequent treatment adjustments.

Electrocardiography and Echocardiography

Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines for CVD in dialysis patients recommend a baseline electrocardiogram at dialysis initiation and at annual intervals.[77] Diabetic HD patients presenting without sinus rhythm (11% of the cohort) were 89% more likely to die (based on multivariate analysis) and 164% more likely to sustain a stroke.[65] CKD patients (eGFR < 60 ml/min/1.73 m^2) with increased QRS duration had 15% greater risk of incident CHF, 13% greater risk of incident CHD, and 17% greater risk of mortality per 10-millisecond increase; prolongation of the QT interval was also independently associated with adverse outcome.[103]

KDOQI guidelines recommend routine echocardiograms in all dialysis patients after they achieve "dry weight" targets, preferably 1 to 3 months after dialysis initiation on an interdialytic day for HD patients and at 3-year intervals thereafter.[77] The rationale for this guideline is that diminished LV systolic function is independently associated with incident CHF, recurrent CHF, incident CHD, and increased mortality,[77] and it is not accurately diagnosed by history, physical examination, or chest radiography. Detection of unsuspected cardiomyopathy is also important, given that carvedilol therapy in such patients improved LV systolic function, decreased hospitalization, and reduced mortality.[104] As in the general population, CKD patients with LVEF below 40% should be evaluated for CHD (exceptions are pediatric or young adult patients with nondiabetic renal failure and other patients known to be at low risk for CHD).

Stress Tests and Screening Renal Transplant Candidates

End-stage renal disease patients are poorly suited for conventional exercise stress electrocardiography because of limited exercise tolerance and frequent resting electrocardiographic abnormalities. Accuracies of pharmacologic stress echocardiographic and nuclear scintigraphic techniques are remarkably variable over the world; they clearly are operator dependent, and the approach of individual sites to cardiac screening should rely on institutional expertise. Moreover, prediction of the likelihood of future events may differ considerably from prediction of coronary anatomy. In severe CKD, dobutamine stress echocardiography is an independent predictor of long-term mortality.[105] Sensitivities and specificities for detection of CHD in renal transplant candidates have been reported to range from 44% to 90%.[106] A meta-analysis[107] concluded that presence of inducible myocardial ischemia by any stress imaging test is independently predictive of increased AMI risk and cardiac death, whereas a fixed or resting defect or abnormality is predictive of cardiac death but not AMI. A subsequent meta-analysis by the Cochrane Collaboration concluded that dobutamine stress echocardiography is probably more accurate than myocardial stress nuclear scintigraphy for noninvasive detection of CHD in renal transplant candidates.[108]

The major problem with "screening" is use of test results for clinical management. The evidence for prophylactic revascularization of asymptomatic renal transplant candidates (or any other patient group) is weak.[49,109] The best observational data supporting the usefulness of preemptive coronary revascularization (in 184 of 657 renal transplant candidates screened with coronary angiography) showed 3-year cardiac event–free survival of 90% for wait-listed revascularized patients.[110] Optimal medical therapy (which should constitute the treatment strategy for all patients) may potentially attenuate the putative benefit of prophylactic coronary revascularization. One algorithm for screening and management of CHD in renal transplant candidates is presented in Figure 82-12. All patients undergo resting

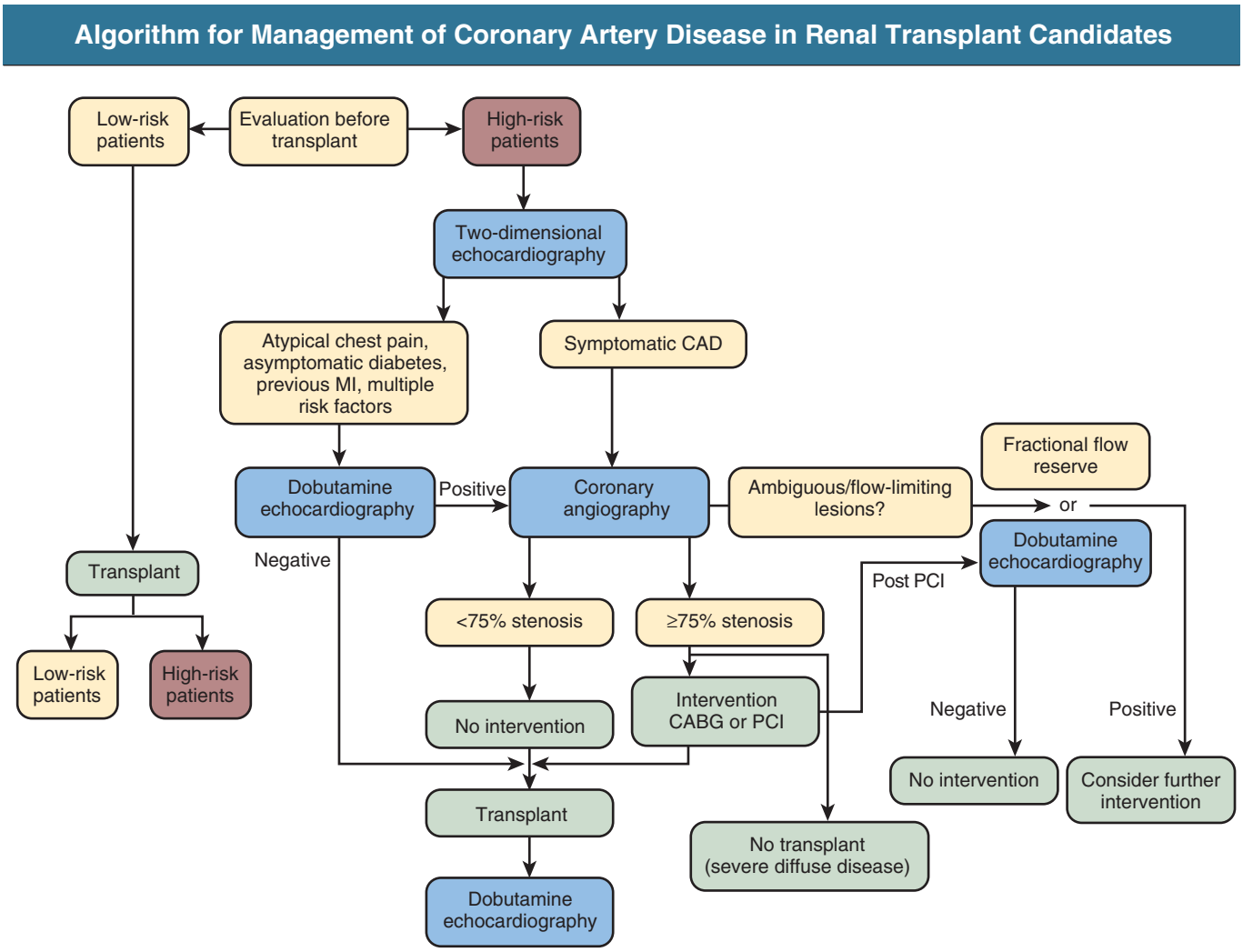

Figure 82-12 Algorithm for management of coronary heart disease (CHD) in renal transplant candidates. *CABG,* Coronary artery bypass graft surgery; *CAD,* coronary artery disease; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention. *(Modified from reference 168.)*

echocardiography, and high-risk patients (e.g., with diabetic ESRD, any age; history of CHD or angina; or two or more classic CHD risk factors [asymptomatic] and age older than 45 years) undergo stress echocardiography. For patients subsequently found to have angiographically indeterminate lesions, measurement of fractional flow reserve is used to make decisions about revascularization.[111]

Coronary Angiography

Coronary angiography, the gold standard in evaluating CHD in CKD, should be considered in stable ESRD patients with evidence for inducible myocardial ischemia, unstable patients with acute coronary syndrome (performed urgently for STEMI), and patients with LVEF below 40%. Some reports suggest a predilection for more proximal CHD in CKD patients, which may predict worse outcome.[112,113]

In CKD and ESRD patients with residual renal function, fear of contrast nephropathy may restrain use of coronary angiography (see Chapter 73 for preventive measures); one retrospective study of 76 nondialysis patients with mean eGFR of 12.5 ml/min/1.73 m^2 found no significant postangiographic deterioration in renal function.[114] However, patients sustaining acute kidney injury (AKI) after coronary angiography are at heightened risk for long-term mortality, ESRD, and hospitalization.[115] Echocardiography should be performed before any nonemergent coronary angiography in CKD patients to diagnose clinically unsuspected valvular disease or cardiomyopathy, to gauge preprocedure volume status, and to assess LV function (to avoid excessive exposure to radiocontrast media through unwarranted ventriculography).

Noninvasive coronary CT angiography may be problematic in dialysis patients because of medial calcification interfering with angiographic interpretation. Another problem may be the requirement for a large-bore intravenous line for rapid injection of radiocontrast media. Noninvasive gadolinium-based magnetic resonance angiographic imaging in patients with severe CKD remains problematic because of lingering concerns about nephrogenic fibrosing dermopathy; the usefulness of imaging without contrast media is uncertain.

Imaging of Vascular Calcification

Vascular calcification can be visualized by conventional x-ray techniques and by multislice spiral CT or electron-beam CT. Valvular and large-artery calcification can be visualized by ultrasound

techniques. Detection of any cardiovascular calcification predicts worse outcome in dialysis patients. The value of routine imaging of vascular calcifications in CKD patients is currently not defined. The diagnostic significance of coronary artery calcification in dialysis patients as a surrogate for CHD severity has been questioned.[116]

Biomarkers

Plasma brain natriuretic peptides (BNP and NT-proBNP), cardiac troponins (cTnT, cTnI), and high-sensitivity CRP are prognostic risk markers in the evaluation of heart disease in ESRD.[117-119] BNP reflects cardiac filling pressures (not limited to the left side of the heart), troponins reflect myocardial cell death (but not necessarily ischemia), and high-sensitivity CRP is an inflammatory marker. Elevation of cTnT occurs in pediatric CKD patients and is associated with cardiac dysfunction.[120] Elevation of plasma troponin levels in ESRD patients is not a false positive; the origin is myocardial, but the interpretation is incorrect if it is uncritically attributed to myocardial ischemia caused by obstructive coronary artery disease. Elevated levels of cTnT are associated with the presence and severity of HD-induced myocardial stunning.[121] The cardiac biomarker-based diagnosis of acute coronary syndrome requires a time-appropriate rise and fall of the biomarker. The most cost-effective combination of biomarkers for risk stratification in dialysis patients might be cTnT and high-sensitivity CRP, but this is controversial. In CKD, NT-proBNP and BNP are equivalent predictors of decompensated heart failure, but NT-proBNP is a better predictor of survival.[122] Figure 82-13 graphically displays the relationship of cTnT and cTnI levels in asymptomatic dialysis patients and long-term survival. On the basis of these data, the U.S. Food and Drug Administration approved the measurement of cTnT in dialysis patients for the indication of risk stratification (mortality prediction) in 2004.[77] FGF23 has also proven to be a strong outcome predictor in CKD patients,[123] but further studies are needed to demonstrate its role as an additional clinical biomarker.

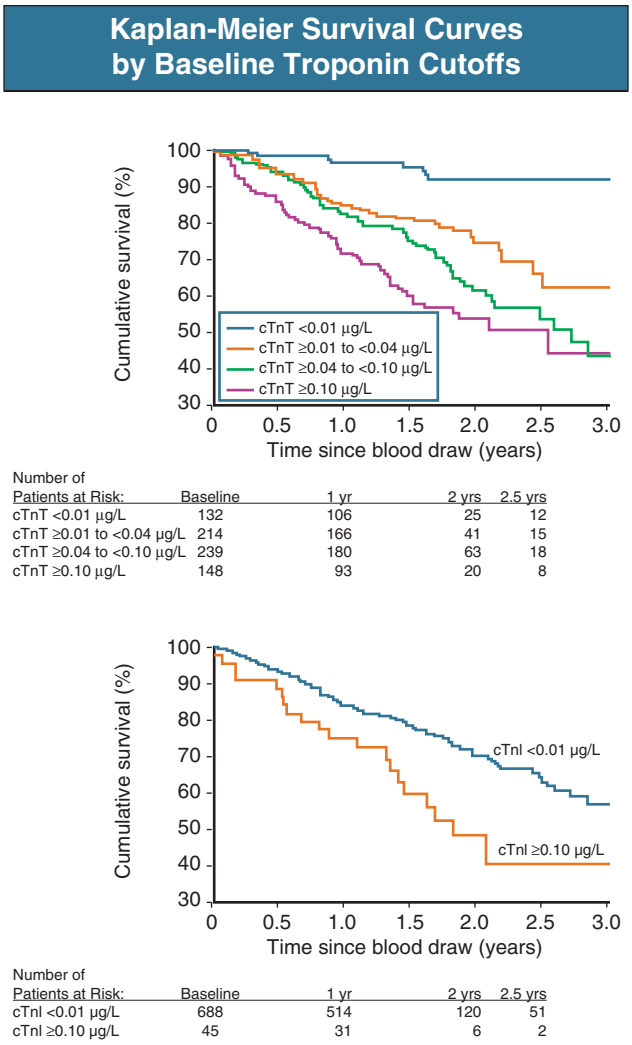

Figure 82-13 Kaplan-Meier survival curves by baseline troponin cutoffs. *cTnT,* Cardiac troponin T; *cTnI,* cardiac troponin I. *(From reference 117.)*

TREATMENT AND PREVENTION OF CARDIOVASCULAR DISEASE

Risk Factor Reduction

Lifestyle Factors and Smoking

Because physical inactivity is associated with albuminuria[124] and cardiovascular mortality,[125] CKD patients should be advised to stay as physical active as possible. It is clearly imperative to strongly encourage smoking cessation at any CKD stage.

Weight and Diet

Lifestyle changes, including balanced diets with regard to saturated fat and carbohydrates (in diabetic patients), probably reduce cardiovascular morbidity and should be encouraged. However, in all CKD stages, protein-energy wasting must be avoided; especially in dialysis patients, increased body mass index has been associated with improved outcomes,[126] possibly reflecting confounded epidemiology. Correction of obesity should be encouraged. Low-salt diet and phosphate restriction are discussed in Chapter 87.

Hypertension and Coronary Heart Disease

Arterial hypertension is undertreated in many CKD and ESRD patients, and despite controversial data about the risk prediction by diastolic and systolic blood pressure in dialysis patients, antihypertensive treatment is associated with improved survival. Blood pressure targets for CKD patients, in particular those with diabetes or proteinuria exceeding 1 g/day, are discussed in Chapter 80. Hallmarks of therapy are volume control (see Chapter 94) and prevention of sodium overload, particularly through dietary sodium restriction. Longer or more frequent HD sessions may be beneficial in controlling hypertension. Because of their parallel cardioprotective effects, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and vasodilating β-blockers (e.g., carvedilol) are the first-line drugs to treat CKD- and ESRD-related hypertension. Calcium channel blockers and most other antihypertensive drugs, including centrally acting sympathetic inhibitors, are useful when administered complementarily. Pure vasodilators (e.g., minoxidil) must be used with caution because they may increase volume overload or occasionally cause pericardial effusions. Novel approaches to drug-resistant hypertension, such as renal sympathetic denervation, potentially offer an alternative to patients with refractory hypertension; however, the recent and surprising negative results of the SYMPLICITY HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension) trial refutes the efficacy of renal sympathetic denervation therapy.[127] Because sleep-disordered breathing occurs in about 50% of CKD stage 4 and 5 patients and is associated

with hypertension, sleep apnea should be considered in therapy-resistant hypertension.

Coronary heart disease and CHD-related events should be treated with the same medications and active interventions indicated in the general population in the absence of convincing CKD-specific data to the contrary. Medical treatment includes use of antiplatelet agents, ACE inhibitors, ARBs, β-blockers, nitroglycerin, and statins. There is no rationale for a less aggressive therapeutic approach in CKD and ESRD patients than in the nonrenal population.

Diabetes Mellitus

Optimal glycemic control (see Chapter 32), reaching blood pressure target levels, and lipid monitoring (with subsequent dyslipidemia treatment) are crucial in managing diabetic CKD patients. CHD and other CVD should be treated aggressively in this high-risk group. Because recent data show that the harm associated with severe hypoglycemia might counterbalance the potential benefit of intensive glucose-lowering treatment, treating to a hemoglobin A1c (HbA1c) level below 7.0% is not recommended.[128]

Dyslipidemia

Because CKD, like diabetes and hypertension, is considered a cardiovascular risk equivalent,[28,29] CKD patients should be treated to secondary prevention LDL cholesterol target guidelines (<100 mg/dl or 2.6 mmol/l). However, this goal was unsupported by clinical trials targeting dialysis patients.[84,129] *Post hoc* subgroup analyses in the Heart Protection Study,[130] Cholesterol and Recurring Events (CARE) study,[131] and Treating to New Targets (TNT) study,[132] together with a meta-analysis,[133] provide inferential support for the role of statins in improving outcomes in CKD stage 1 or 2 patients. The Study of Heart and Renal Protection (SHARP) showed that reducing LDL cholesterol with simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events in patients with advanced CKD.[134] Thus, statin treatment is recommended in CKD patients older than 20 years, with LDL cholesterol level goals below 130 mg/dl (3.4 mmol/l) or below 100 mg/dl (2.6 mmol/l) for secondary prevention; however, the negative results from the 4D study and A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) do not support this guideline in dialysis patients.

Volume

In predialysis CKD, sodium restriction and diuretics are important to counteract fluid retention. In ESRD, longer and more frequent HD sessions may permit more effective volume control. In the HD center in Tassin, France, more than 90% of patients were normotensive with 8 hours of dialysis three times per week, with dietary salt restriction and no antihypertensive drugs. In the Frequent Hemodialysis Network (FHN) trial, frequent (six times per week) HD (versus conventional three times per week) led to better hypertension control, a drop in LV mass index over 12 months,[135,136] and less myocardial stunning.[135,136] Episodes of dialysis-related hypotension should prompt reevaluation of dry weight, antihypertensive treatment, and exclusion of pericardial effusions, valvular disease, cardiomyopathy, and silent myocardial ischemia (see Chapter 95).

Anemia

Partial correction of severe anemia with ESAs results in regression of LVH. Treatment of severe anemia is also associated with fewer ischemic symptoms in CHD patients. However, evidence for reduction of cardiovascular mortality by ESAs is based on observational data only. To date, randomized controlled trials in HD[137] and CKD patients[138] have shown no benefit of normalized anemia on mortality as a primary endpoint (see Chapter 83). Thus, anemia correction in CKD patients to a hemoglobin level of 11 to 12 g/dl appears logical.

Inflammation

Anti-inflammatory treatment strategies, such as statins and aspirin, have beneficial effects on cardiovascular mortality in the general population. Data from the 4D study[84] show that whereas CRP baseline levels were not significantly different between treated and placebo groups and remained stable at 6 months with atorvastatin, they increased significantly in the placebo group.[139] Although high-sensitivity CRP levels were elevated at baseline and were decreased by rosuvastatin in the AURORA study,[129] there was no reduction in cardiovascular events. Meanwhile, a careful search for infectious processes, such as periodontal disease, and use of ultrapure water are recommended in dialysis patients with inflammation. Restriction of catheter use is also important; short daily dialysis with better fluid status was associated with decreasing CRP levels compared with conventional HD.[140] Volume status should be carefully monitored to avoid inflammation. Altered intestinal microbial flora is a potential novel risk factor for systemic uremic inflammation, which merits further study.

Oxidative Stress

Oxidative stress probably plays a role in mediating CVD in CKD. Two placebo-controlled interventional studies showed that vitamin E[141] and *N*-acetylcysteine[142] decreased the number of cardiovascular events in HD patients. Unfortunately, both studies were small and of limited duration. Because *N*-acetylcysteine administration led to reduced atheromatous lesions in an apoE knockout model of CKD-enhanced atherosclerosis, adequately powered randomized trials with antioxidative treatment strategies are warranted. A recent meta-analysis showed that use of ultrapure dialysate results in decreased markers of inflammation and oxidative stress in HD patients.[143] However, administration of mixed tocopherols and α-lipoic acid did not influence biomarkers of inflammation and oxidative stress or the erythropoietic response in a recent randomized trial of 353 HD patients.[143a]

Chronic Kidney Disease–Mineral Bone Disorder

In a randomized Japanese trial, sevelamer, as compared with calcium carbonate treatment, slowed the increase in coronary artery calcification score.[144] Based on this and other studies, nephrologists should reduce oral calcium loading in CKD patients, in particular if cardiovascular calcifications have already been documented.[145] Because vitamin D treatment is associated with improved survival in dialysis patients,[146] vitamin D insufficiency should also be considered. However, results from the Dialysis Outcomes and Practice Patterns Study (DOPPS)[147] call into question the survival advantage for HD patients taking vitamin D. The PRIMO (Paricalcitol Capsules Benefits Renal Failure Induced Cardiac Morbidity in Subjects With Chronic Kidney Disease Stage 3/4) study showed that 48 weeks of paricalcitol therapy did not alter LV mass index or improve certain measures of diastolic dysfunction in CKD patients.[148] With respect to calcimimetics, the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) study[149] showed that cinacalcet did not significantly reduce the risk of death or major cardiovascular events in dialysis patients with moderate to severe secondary hyperparathyroidism unless the groups were adjusted for age. A randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in subjects with chronic kidney disease receiving hemodialysis (ADVANCE)[150] showed that cinacalcet plus low-dose

vitamin D sterols may attenuate vascular and cardiac valve calcification in HD patients with moderate to severe secondary hyperparathyroidism. KDOQI and KDIGO targets for parathyroid hormone, calcium, and phosphate are discussed in Chapter 85.

FGF23 is a bone hormone that has attracted much recent interest as a putative player in the calcification process. FGF23 is cardiotoxic and induces LVH[37] but does not induce vascular calcification.[151]

Revascularization

Chronic kidney disease is a strong risk factor for death after coronary revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).[152,153] Coronary revascularization complicated by AKI is associated with excess mortality; operative mortality for non-ESRD patients who require acute dialysis after cardiac surgery is 44%.[154]

Data comparing coronary revascularization with medical therapy in CKD are limited by their retrospective, observational nature and lack of optimal medical therapy, including β-blockers. Observational studies suggest lower mortality in CKD (including dialysis) patients undergoing coronary revascularization compared with no revascularization.[155,156] A *post hoc* analysis of CKD patients in the FRISC II (Fast Revascularization During Instability in Coronary Artery Disease) trial indicated a superior outcome with an early invasive strategy in acute coronary syndrome compared with conservative management.[157]

The optimal coronary revascularization method for CKD patients remains controversial because of absence of adequate clinical trial data. A *post hoc analysis* of CKD patients enrolled in ARTS (Arterial Revascularization Therapies Study)[158] found similar outcomes for CABG or multivessel PCI with non–drug-eluting stents (DESs) for death, myocardial infarction, or stroke; unsurprisingly, CABG was associated with less repeated revascularization. In elderly non–dialysis-dependent CKD patients, incidence of ESRD is lower after PCI (5.4% at 3 years vs. 6.8% for CABG), but long-term risk of death (28% 3-year mortality with CABG, 33% with PCI) or the combined event of death or ESRD is lower after CABG. The relative survival advantage of CABG (vs. PCI) occurs only more than 6 months after revascularization.[159] Dialysis patient survival after CABG is better than after PCI with non-DESs[160] and DESs,[161] but 2-year mortality remains high at 44% (vs. 52% for PCI).[160] Based on two large observational studies,[160,161] we recommend the following:

1. Patients with multivessel CHD (including the left anterior descending coronary artery [LAD]) who are anatomically suitable candidates for internal mammary artery grafts should undergo CABG surgery.
2. The CABG survival advantage occurs more than 6 months after revascularization. Patients with limited life expectancy or who are concerned about perioperative morbidity (higher with CABG) might choose PCI (better outcomes at less than 6 months).
3. If the left internal mammary graft (to the LAD) is not part of the surgical strategy, CABG likely provides no advantage.

In the general population, one proven advantage of DESs (compared with non-DESs) is lower incidence of in-stent restenosis. In dialysis patients, reliance on clinical surrogates (e.g., chest pain) for detection of restenosis can be problematic and lead to underestimation of the true incidence. The most complete angiographic follow-up of DESs (performed in Japanese dialysis patients) noted a 22% to 31% angiographically detected incidence of restenosis with DESs and 24% to 43% with non-DESs.[162-165] Clinically inapparent restenosis is a rationale for surveillance stress imaging to detect occult restenosis as part of our management strategy for dialysis patients undergoing PCI (see Fig. 82-12).

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CHAPTER 83

Anemia in Chronic Kidney Disease

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Anemia is an almost universal complication of chronic kidney disease (CKD). It contributes considerably to reduced quality of life of patients with CKD and has been associated with a number of adverse clinical outcomes. Before the availability of recombinant human erythropoietin (rHuEPO, or epoetin), patients on dialysis frequently required blood transfusions, exposing them to the risks of iron overload, transmission of viral hepatitis, and HLA sensitization, which reduced the chances of successful transplantation. The advent of rHuEPO in the late 1980s changed this situation completely. The ability to correct anemia has suggested that its consequences may go beyond general fatigue and reduced physical capacity to affect a broad spectrum of physiologic functions. Thus, there is a strong rationale for managing anemia in CKD patients, and yet the optimal treatment strategies are still incompletely defined. Apart from therapy with erythropoiesis-stimulating agents (ESAs), iron replacement is essential for anemia management. It is important to note that CKD patients require target thresholds of iron parameters different from those for normal individuals to ensure optimal rates of red cell production. The costs of anemia management are considerable, and it has also become apparent that full anemia correction may cause harm; therefore a rational and careful consideration of the risks and benefits is mandatory.

PATHOGENESIS

Renal anemia is typically an isolated normochromic, normocytic anemia with no leukopenia or thrombocytopenia. Both red cell life span and the rate of red cell production are reduced, but the latter is more important. The normal bone marrow has considerable capacity to increase the rate of erythropoiesis, and the reduction in erythrocyte life observed in association with CKD would normally be easily compensated for. However, this erythropoietin (EPO)–induced compensatory increase in erythrocyte production is impaired in CKD. Serum EPO levels remain within the normal range and fail to show the inverse exponential relationship with blood oxygen content characteristic of other types of anemia. EPO is normally produced by interstitial fibroblasts in the renal cortex, in close proximity to tubular epithelial cells and peritubular capillaries.[1,2] In addition, hepatocytes and perisinusoidal Ito cells in the liver can produce EPO (Fig. 83-1). Hepatic EPO production dominates during fetal and early postnatal life but does not compensate for the loss of renal production in adult organisms. Subtle changes in blood oxygen content induced by anemia, reduced environmental oxygen concentrations, and high altitude stimulate the secretion of EPO through a widespread system of oxygen-dependent gene expression.[2-4] Central to this process is a family of hypoxia-inducible transcription factors (HIFs). The two most important members of this family, HIF-1 and HIF-2, are composed of an oxygen-regulated α subunit (HIF-1α or HIF-2α) and a constitutive β subunit. The production of HIF-1α and HIF-2α is largely independent of oxygen, but their degradation is related to cellular oxygen concentrations. Hydroxylation of specific prolyl and asparagyl residues of HIF-α, for which molecular oxygen is required as a substrate, determines HIF proteasomal destruction and inhibits its transcriptional activity. Apart from EPO, far more than 100 HIF target genes have been identified. HIF-2, rather than HIF-1, is the transcription factor primarily responsible for the regulation of EPO production.[5,6]

The role of renal EPO production in the pathogenesis of renal anemia is supported by the observation that anemia is particularly severe in anephric individuals. However, the mechanisms impairing renal EPO production in diseased kidneys remain poorly understood. The production capacity for EPO remains significant, even in end-stage renal disease. Thus, patients with anemia and CKD can respond with a significant increase in EPO production to an additional hypoxic stimulus.[1] The main problem therefore appears to be a failure of EPO production in response to chronically reduced hemoglobin (Hb) concentrations. In line with this view, endogenous EPO production can be induced in CKD patients by pharmacologic inhibition of HIF degradation (see later discussion).

Erythropoietin is a glycoprotein hormone consisting of a 165–amino acid protein backbone and four complex, heavily sialylated carbohydrate chains.[1,2] The latter are essential for the biologic activity of EPO *in vivo* because partially or completely deglycosylated EPO is rapidly cleared from the circulation. This is also why rHuEPO has to be manufactured in mammalian cell lines; bacteria lack the capacity to glycosylate recombinant proteins.

Erythropoietin stimulates red cell production by binding to homodimeric EPO receptors, which are primarily located on early erythroid progenitor cells, the burst-forming units erythroid (BFU-e) and the colony-forming units erythroid (CFU-e). Binding of EPO to its receptors salvages these progenitor cells and the subsequent earliest erythroblast generation from apoptosis, thereby permitting cell division and maturation into red blood cells.[7] Inhibition of red cell production by uremic inhibitors of erythropoiesis may also contribute to the pathogenesis of renal anemia, although they have so far not been identified. Nevertheless, dialysis *per se* can improve renal anemia and the efficacy of ESAs. Moreover, the interindividual dose requirements for ESAs vary significantly among CKD patients, and the average weekly dose is much higher than estimated production rates of endogenous EPO in healthy individuals. An alternative view to the accumulation of inhibitors of erythropoiesis in CKD is that in many patients there is overlap between renal anemia and the anemia of chronic disease, which is characterized by inhibition of EPO production and EPO efficacy as well as by reduced iron availability, mediated through the effects of inflammatory cytokines.[8] The hepatic release of hepcidin, the key regulator of iron metabolism, is upregulated in states of inflammation; it simultaneously blocks iron absorption from the gut and promotes iron sequestration in macrophages.[9]

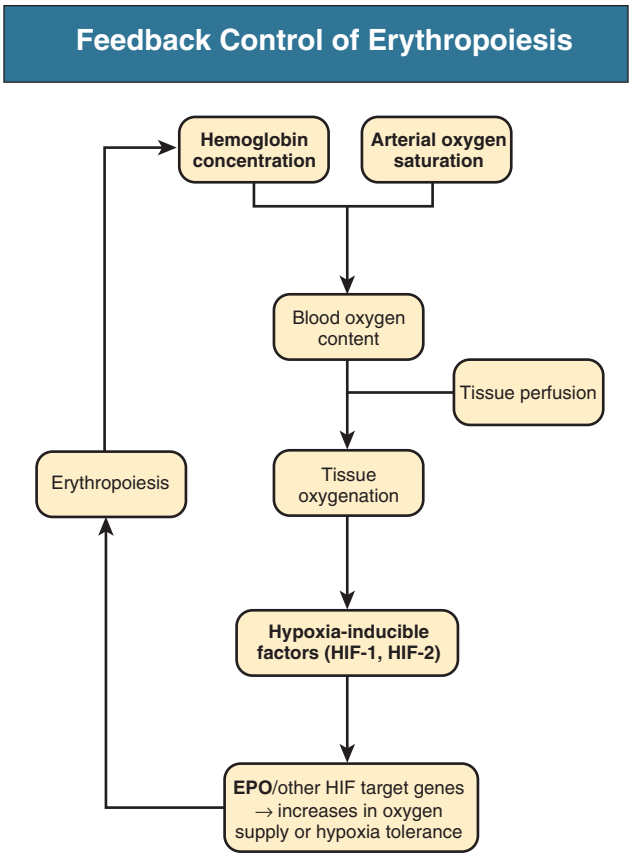

Figure 83-1 Feedback control of erythropoiesis. *EPO,* Erythropoietin.

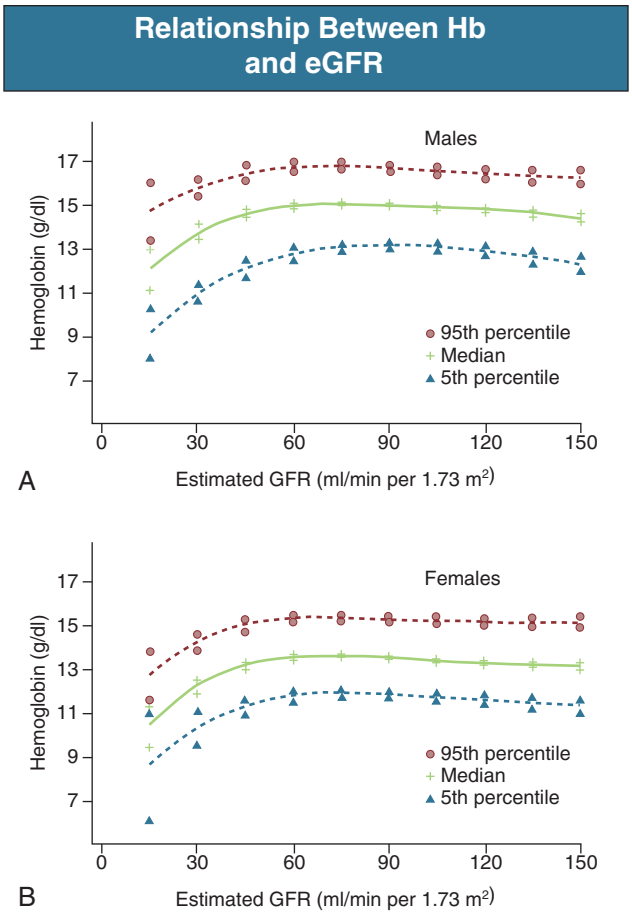

Figure 83-2 Relationship between hemoglobin (Hb) concentration and estimated glomerular filtration rate (eGFR). Data are from a cross-sectional survey of individuals randomly selected from the general U.S. population (Third National Health and Nutrition Examination Survey [NHANES III]). Results and 95% confidence interval are shown for males **(A)** and females **(B)** at each estimated GFR interval. *(From reference 11.)*

EPIDEMIOLOGY AND NATURAL HISTORY

In general, there is a progressive increase in the incidence and severity of anemia with declining renal function. The reported prevalence of anemia by CKD stage varies significantly and depends to a large extent on the definition of anemia and whether study participants are selected from the general population, are at high risk for CKD, are diabetic, or are already under the care of a physician. Data from the National Health and Nutrition Examination Survey (NHANES) showed that the distribution of Hb levels starts to fall at an estimated glomerular filtration rate (eGFR) of less than 75 ml/min/1.73 m^2 in men and 45 ml/min/1.73 m^2 in women (Fig. 83-2).[10] The prevalence of Hb values below 13 g/dl increases below a threshold eGFR of 60 ml/min/1.73 m^2 in men and 45 ml/min/1.73 m^2 in women in the general population. Among patients under regular care and known to have CKD, the prevalence of anemia was found to be much greater, with mean Hb levels of 12.8 ± 1.5 (CKD stages 1 and 2), 12.4 ± 1.6 (CKD stage 3), 12.0 ± 1.6 (CKD stage 4), and 10.9 ± 1.6 (CKD stage 5).[11] Although anemia develops largely independently of the cause of kidney disease, there are two important exceptions. Diabetic patients develop anemia more frequently, at earlier stages of CKD, and more severely at a given level of renal impairment.[12,13] Conversely, in patients with polycystic kidney disease, Hb is on average higher than in other patients with similar degrees of renal failure, and polycythemia may occasionally develop.[1]

With the advent of rHuEPO and its derivatives, Hb values in patients with CKD have changed. In particular, in patients on dialysis, average Hb values have steadily increased for many years, and then declined again in view of new evidence suggesting lower target levels.[12] The average Hb value, however, still varies considerably among countries, reflecting considerable variability in practice patterns (Table 83-1).[13] Moreover, Hb values vary considerably among patients in the same treatment setting as well as within patients over time, mainly reflecting persistent and time-dependent changes in responsiveness (see later discussion).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of anemia and the assessment of its severity are best made by measuring the Hb concentration rather than the hematocrit. Hb is a stable analyte that is measured directly in a standardized fashion, whereas the hematocrit is relatively unstable, indirectly derived by automatic analyzers, and lacking in standardization. Within-run and between-run coefficients of variation in automated analyzer measurements of Hb are one half and one third those for hematocrit, respectively.[12]

There is considerable variability in the Hb threshold used to define anemia. According to the most recent definition in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, anemia should be diagnosed at Hb concentrations of less than 13.0 g/dl in men and less than 12.0 g/dl in women.[14] These values represent the World Health Organization (WHO) definition of anemia. In children, age-dependent differences in the normal values have to be

Hemoglobin Levels in Patients on Dialysis						
	Among Patients on Dialysis for Longer Than 180 Days			Among Patients New to ESRD, at Start of Dialysis		
Country	n	Mean Hb (g/dl)	Hb <11 g/dl (% of patients)	n	Mean Hb (g/dl)	Hb <11 g/dl (% of patients)
Sweden	456	12.0	23	168	10.7	55
United States	1690	11.7	27	458	10.4	65
Spain	513	11.7	31	170	10.6	61
Belgium	442	11.6	29	213	10.3	66
Canada	479	11.6	29	150	10.1	70
Australia and New Zealand	423	11.5	36	108	10.1	70
Germany	459	11.4	35	142	10.5	61
Italy	447	11.3	38	167	10.2	68
United Kingdom	436	11.2	40	93	10.2	67
France	341	11.1	45	86	10.1	65
Japan	1210	10.1	77	131	8.3	95

Table 83-1 Mean hemoglobin (Hb) levels and percentage of patients with Hb levels below 11 g/dl who have been on dialysis therapy for more than 180 days and at the time of starting dialysis, by country. Data are from the Dialysis Outcomes and Practice Patterns Study, Phase II (DOPPS 2), and are derived from 308 randomly selected, representative dialysis facilities. Note that there are marked differences among countries, but at least one fourth and up to three fourths of dialysis patients, and, in most countries, more than two thirds of patients starting chronic dialysis have Hb values below the recommended lower target of 11 g/dl. *ESRD,* End-stage renal disease. *(Modified from reference 13.)*

taken into account. Normal Hb values are increased in high-altitude residents. It is important to note that thresholds for the diagnosis of anemia and evaluation of the causes should not be interpreted as being thresholds for treatment of anemia.[14]

In addition to the Hb value, the evaluation of anemia in CKD patients should include a complete blood count with red blood cell indices (mean corpuscular Hb concentration [MCHC], mean corpuscular volume [MCV]), white blood cell count (including differential), and platelet count. Although renal anemia is typically normochromic and normocytic, deficiency of vitamin B_{12} or folate may lead to macrocytosis, whereas iron deficiency or inherited disorders of Hb formation (such as thalassemia) may produce microcytosis. Macrocytosis with leukopenia or thrombocytopenia suggests a generalized disorder of hematopoiesis caused by toxins, nutritional deficit, or myelodysplasia. Hypochromia probably reflects iron-deficient erythropoiesis. An absolute reticulocyte count, which normally ranges between 40,000 and 50,000 cells/μl of blood, is a useful marker of erythropoietic activity.

Iron status tests should be performed to assess the level of iron in tissue stores or the adequacy of iron supply for erythropoiesis. Although serum ferritin is so far the only available marker of storage iron, several tests reflect the adequacy of iron for erythropoiesis, including transferrin saturation, the percentage of hypochromic red blood cells (PHRC), the content of Hb in reticulocytes (CHr), and the MCV and MCHC. Storage time of the blood sample may elevate PHRC, and MCV and MCHC are below the normal range only after longstanding iron deficiency.

It is important to identify anemia in CKD patients because it may signify nutritional deficits, systemic illness, or other conditions that warrant attention, and even at modest degrees, anemia reflects an independent risk factor for hospitalizations, cardiovascular disease, and mortality.[12] The diagnosis of renal anemia, that is, an anemia caused by CKD, requires careful judgment of the degree of anemia in relation to the degree of renal impairment and exclusion of other or additional causes. Because there is significant variability in the degree of anemia in relation to the impairment in renal function, no simple diagnostic criteria can be applied. Causes of anemia other than EPO deficiency should be considered when (1) the severity of anemia is disproportionate to the impairment of renal function, (2) there is evidence of iron deficiency, or (3) there is evidence of leukopenia or thrombocytopenia. Concomitant conditions such as sickle cell disease may exacerbate the anemia, as can drug therapy. For example, inhibitors of the renin-angiotensin system may reduce Hb levels by (1) direct effects of angiotensin II on erythroid progenitor cells,[15] (2) accumulation of *N*-acetyl-seryl-lysyl-proline (Ac-SDKP), an endogenous inhibitor of erythropoiesis in patients treated with angiotensin-converting enzyme (ACE) inhibitors,[16] and (3) reduction of endogenous EPO production, possibly because of the hemodynamic effects of angiotensin II inhibition. Myelosuppressive effects of immunosuppressants may further contribute to anemia.[17] The measurement of serum EPO concentrations is usually not helpful in the diagnosis of renal anemia because there is relative rather than absolute deficiency, with a wide range of EPO concentrations for a given Hb concentration that extends far beyond the normal range of EPO levels in healthy, nonanemic individuals. Abnormalities of other laboratory parameters should be looked for, such as a low MCV or MCHC (may indicate an underlying hemoglobinopathy), a high MCV (may indicate vitamin B_{12} or folate deficiency), or an abnormal leukocyte or platelet count (may suggest a primary bone marrow problem, such as myeloma or myelodysplastic syndrome), and further tests should be performed as indicated to explore these potential conditions. However, when there are no such pointers to other confounding causes of anemia, and iron deficiency has been excluded, a trial with rHuEPO or its derivatives is warranted, even when the eGFR is only moderately reduced.

CLINICAL MANIFESTATIONS

In the early clinical trials of rHuEPO performed in the late 1980s, the mean baseline Hb concentration was about 6 to 7 g/dl, and this progressively increased to about 11 or 12 g/dl after treatment.

Secondary Effects of Anemia Correction on the Cardiovascular System
Reduction in high cardiac output
Reduced stroke volume
Reduced heart rate
Increase in peripheral vascular resistance
Reduction in anginal episodes
Reduction in myocardial ischemia
Regression of left ventricular hypertrophy
Stabilization of left ventricular dilation
Increase in whole blood viscosity

Box 83-1 Secondary effects of anemia correction on the cardiovascular system.

Other Secondary Effects of Anemia Correction
Reduced blood transfusions
Increased quality of life
Increased exercise capacity
Improved cognitive function
Improved sleep patterns
Improved immune function
Improved muscle function
Improved depression
Improved nutrition
Improved platelet function
(Hypertension)
(Vascular access thrombosis)

Box 83-2 Other secondary effects of anemia correction. Parentheses indicate negative and adverse effects.

Patients subjectively felt much better, with reduced fatigue, increased energy levels, and enhanced physical capacity, and there were also objective improvements in cardiorespiratory function.[18] Thus, it is now clear that many of the symptoms previously attributed to the "uremic syndrome" may have been caused by severe anemia associated with CKD (Boxes 83-1 and 83-2). Although the avoidance of blood transfusions and improvement in quality of life are obvious early changes, there are also possible effects on the cardiovascular system (see Box 83-1). The physiologic consequences of longstanding anemia are an increase in cardiac output and a reduction in peripheral vascular resistance. Anemia is associated with the development of left ventricular hypertrophy in CKD patients and is thought to exacerbate left ventricular dilation. Sustained correction of severe anemia in CKD patients tends to reverse most of these cardiovascular abnormalities, with the notable exception of left ventricular dilation. Once the left ventricle is stretched beyond the limits of its elasticity, correction of anemia cannot reverse this.[19] It may, however, prevent further progression in some patients. Other effects of anemia correction reported in clinical trials include improvements in quality of life, cognitive function, sleep patterns, nutrition, sexual function, menstrual regularity, immune responsiveness, and platelet function. The majority of these trials, however, have not been placebo-controlled, so the spectrum and extent of possible benefits remain uncertain.

Over the years, there has also been considerable debate about the optimal target range of Hb in CKD patients. A presumed improvement in quality of life and expectations of positive effects on cardiovascular function and renal disease progression with increasing Hb concentrations led to suggestions of a level above 10 to 11 g/dl in all CKD patients,[12,13] but several studies have indicated increased risks associated with attempts to completely correct anemia. In particular, no survival benefit is evident at a higher level of anemia correction,[20-23] and attempts to normalize Hb concentrations have shown various risks, including increased rates of thromboembolic events, strokes, and possibly death. Thus there is a possible tradeoff among improved quality of life, reduced transfusion requirements, and risk for harm (see discussion later), and a target Hb level of above 13 g/dl should be avoided.[12, 14]

TREATMENT

Erythropoiesis-Stimulating Agents

Epoetin Therapy

Manufacture of rHuEPO is achieved by gene transfer into a suitable mammalian cell line such as Chinese hamster ovary (CHO) cells or induction of the human gene in a hepatoma cell line. The early clinical trials of rHuEPO were conducted with both EPO alfa and EPO beta, both produced in CHO cells. Like the endogenous hormone, rHuEPO consists of a 165–amino acid backbone with one *O*-linked and three *N*-linked glycosylation chains. Invariably, however, there are some differences in the glycosylation pattern among different preparations of rHuEPO and the endogenous hormone. Several formulations of EPO are now available, including "biosimilar" EPO preparations, which have been developed after patent expiry of the innovator compounds.[24] Other "copy" EPOs are available elsewhere in the world (e.g., China, India, Peru, Argentina, Russia, and Cuba) and are not necessarily produced to the same regulatory standards as the EPO preparations marketed in the United States and Europe. Another EPO that was initially developed for the European market was EPO delta, which differed from other EPOs in its glycosylation pattern because it was produced in a human fibrosarcoma cell line.

Before 1998, EPO alfa in Europe was formulated with human serum albumin, but because of a change in European regulations, this was replaced with polysorbate 80. EPO beta is formulated with polysorbate 20, along with urea, calcium chloride, and five amino acids as excipients. The importance of the formulation of the EPO products was highlighted in 2002 with an upsurge in cases of antibody-mediated pure red cell aplasia in association with the subcutaneous use of EPO alfa after its change of formulation. Patients affected by this complication develop neutralizing antibodies against both rHuEPO and the endogenous hormone, which result in severe anemia and transfusion dependence.[25] The cause of this serious complication in which there is a break in B cell tolerance remains obscure, although it seems likely that factors such as a breach of the cold storage chain are relevant, and the subcutaneous application route is a prerequisite; circumstantial evidence also suggests that rubber stoppers of prefilled syringes used in one of the albumin-free EPO alfa formulations may have released organic compounds that acted as immunologic adjuvants.[26] Although this unfortunate combination of adverse factors was specific for one compound, a low baseline rate of pure red cell aplasia also occurs with EPO beta and darbepoetin alfa.

The EPOs are administered either intravenously or subcutaneously. The bioavailability after intraperitoneal administration (in peritoneal dialysis patients) is too low. The earliest clinical trials of EPO used intravenous injections two or three times per week. This was partly because of the short half-life of EPO (6 to 8 hours after intravenous administration)[27] and partly because of the convenience

for the patient on dialysis. With use of this regimen, 90% of patients show a significant increase in Hb concentration. Good iron management is pivotal for the success of EPO therapy (see later discussion). Although the bioavailability of subcutaneous EPO is 20% to 30%, the prolonged half-life after subcutaneous compared with intravenous administration allows less frequent injections. Furthermore, the dose required to achieve the same Hb response is about 30% lower with subcutaneous than with intravenous administration.[27] There appears to be little difference between the thigh, arm, or abdomen as injection sites.

Darbepoetin Alfa

Darbepoetin alfa is a second-generation ESA that is a supersialylated analogue of EPO, possessing two extra *N*-linked glycosylation chains. This property confers greater metabolic stability and a lower clearance rate *in vivo*, and the elimination half-life of this compound in humans after a single intravenous administration is three times greater than that of epoetin alfa (25.3 hours vs. 8.5 hours). Thus, this agent can generally be given less frequently than the standard epoetins, with administration intervals of once weekly and once every alternate week.[28] In contrast to the epoetins, dosage requirements for darbepoetin alfa for the correction of anemia and maintenance of Hb concentration in CKD patients are the same for intravenous and subcutaneous administration. The conversion factor for switching patients from epoetin alfa or beta to darbepoetin alfa is usually quoted as 200:1, but there may be considerable variability in this, depending on the patient population, the dose, and the route of administration.

C.E.R.A. (Methoxy Polyethylene Glycol–Epoetin Beta)

Alternative bioengineering techniques to prolong the half-life of EPO further resulted in the development of C.E.R.A., which is a pegylated derivative of epoetin beta with an elimination half-life of around 130 hours when it is administered either intravenously or subcutaneously. A number of randomized controlled Phase III studies suggested that many patients are able to be maintained with once-monthly administration of C.E.R.A., and a superiority study (Comparator Study of C.E.R.A. and Darbepoetin Alfa in Patients Undergoing Dialysis [PATRONUS]) suggested greater efficacy with this frequency of administration compared with once-monthly dosing of darbepoetin alfa when it is administered intravenously to hemodialysis patients.[29]

Adverse Effects of the Erythropoiesis-Stimulating Agents

Adverse effects of ESA therapy include a moderate increase in blood pressure and an increased rate of thromboembolic events, including vascular access thrombosis. Whereas these effects are probably dependent to a large degree on the increase in Hb concentrations, there are some concerns that ESA therapy may enhance thrombogenicity and tumor growth in patients with malignant disease, as well as exacerbate vascular events in CKD independently of Hb concentrations. Thus, attempts should be made to use the lowest doses of ESA possible to avoid the presumed pleiotropic effects of this class of drugs. Similarly, because no "safe" upper dose level has been determined, it is advisable to avoid repeated dose escalations.[14] In the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), patients with a history of malignancy were found to have an increased rate of cancer-related deaths when treated with darbepoetin.[23] Although no study has investigated anemia management in patients with CKD and active cancer, ESAs should be used only with great caution in such patients, in particular when cure from cancer is the anticipated outcome.[14] Similarly, in patients with a history of stroke or recent venous thromboembolic event, careful consideration should be given to the benefit-risk ratio of using ESA therapy.

Other Erythropoiesis-Stimulating Agents

In addition to the original epoetins and the two long-acting derivatives, several other approaches to stimulating erythropoiesis have been explored,[24] and more recent ESAs include peginesatide and the HIF stabilizers.[24]

Peginesatide (previously called Hematide) is an EPO-mimetic peptide, the amino acid sequence of which is completely unrelated to native or recombinant EPO,[24] although it shares the same functional and biologic properties as EPO. It has been shown to be an effective treatment for anti-EPO antibody–mediated pure red cell aplasia because of a lack of cross-reactivity with anti-EPO antibodies.[30] Peginesatide was also shown to be equivalent to epoetin and darbepoetin in raising Hb concentrations in dialysis and nondialysis patients, respectively, but in nondialysis patients, a higher rate of cardiovascular events was observed.[31,32] Therefore it was approved in the United States for use in only dialysis patients. Approximately a year after its introduction, peginesatide had to be withdrawn from the market because of severe hypersensitivity reactions, including fatal anaphylactic events.

The HIF stabilizers are competitive inhibitors of HIF prolyl hydroxylases[24] and asparagyl hydroxylase, enzymes involved in the metabolism of HIF and its transcriptional activity. The HIF stabilizers therefore cause an increase in endogenous EPO production.[33] Such prolyl hydroxylase inhibitors are orally active, and several of these drugs, manufactured by different companies, are currently being tested in Phase II and III clinical trials.[24] There is much discussion about whether these agents will upregulate not only EPO gene expression but also the expression of other HIF target genes, such as those involved in iron metabolism and neoangiogenesis. Whereas some of these effects may facilitate an increase in Hb concentrations, the long-term consequences of these potential additional effects have not been established and merit careful monitoring.[24]

Initiation of and Maintenance Therapy with Erythropoiesis-Stimulating Agents

Before ESA therapy is considered in CKD patients, it is essential to exclude and to correct causes of anemia other than EPO deficiency, such as hematinic deficiencies (Fig. 83-3). If the ferritin concentration is below 100 µg/l, iron supplementation should be administered first. Iron is best given by intravenous administration, although oral iron can be considered in patients not yet on dialysis. Some patients may respond to intravenous iron alone (see later discussion). If the ferritin level is above 100 µg/l (in the absence of systemic inflammation) or there is a suboptimal response to iron, ESA therapy is an option. However, the Hb level at which ESAs should be initiated remains controversial, mainly because the topic has not been rigorously studied. TREAT, the largest ESA trial performed so far, compared darbepoetin therapy with a target Hb level of 13 g/dl versus placebo, with a rescue protocol when a patient's Hb dropped below 9 g/dl.[23] In the darbepoetin arm, the number of patients transfused was lower, and there was a small increase in quality of life, but the stroke rate was twice as high, so that the risk-benefit relationship was clearly negative. Whereas these data argue strongly against the initiation of ESA therapy in patients with mild anemia, there is only one, much smaller randomized controlled trial that tested two different target ranges of 9.5 to 11.0 g/dl and 11.5 to 13.0 g/dl against placebo in patients with severe anemia.[34] Patients in both EPO treatment arms experienced improved quality of life and exercise capacity, but

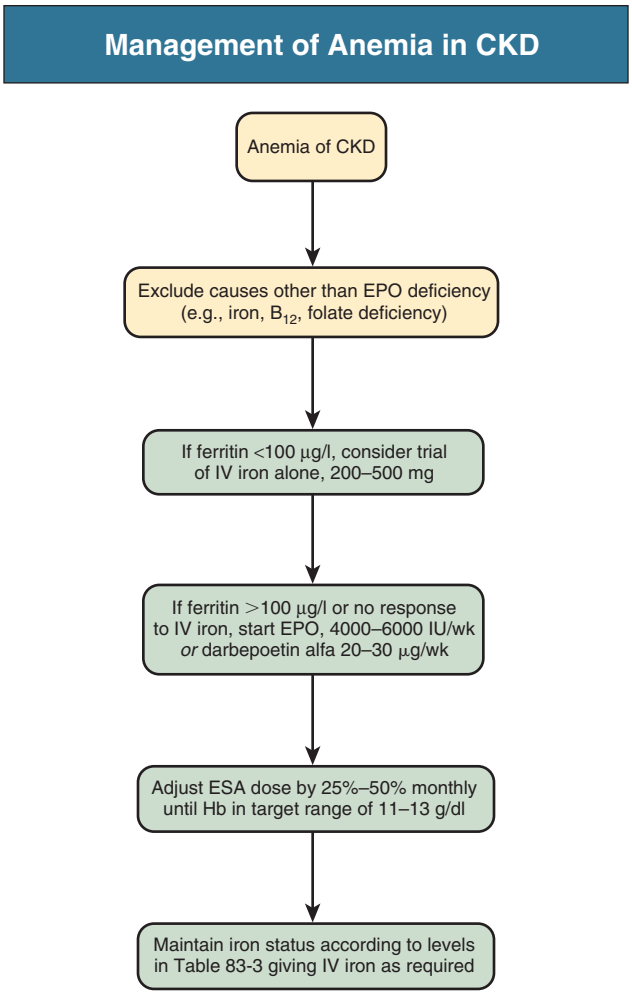

Figure 83-3 Management of anemia in patients with chronic kidney disease (CKD). *EPO,* Erythropoietin; *ESA,* erythropoiesis-stimulating agent; *Hb,* hemoglobin; *IV,* intravenous.

there was no difference between the arms. Based on these findings, the KDIGO guidelines recommend use of ESAs to prevent the Hb level from falling below 9 g/dl.[14] However, individualization is possible, acknowledging the fact that some patients have improved symptoms at higher Hb levels and are prepared to take increased risks.

The usual starting dose of epoetin is about 25 to 50 IU/kg (e.g., 2000 IU) two or three times weekly, either by intravenous or subcutaneous administration. A possible starting dose of darbepoetin alfa is 20 to 30 µg once weekly intravenously or subcutaneously; an appropriate starting dose of C.E.R.A. is 30 to 60 µg once every 2 weeks intravenously or subcutaneously. Within 3 to 4 days after treatment initiation, an increase in the reticulocyte count is seen, and within 1 to 2 weeks, there is a significant rise in the Hb concentration, usually on the order of 0.25 to 0.5 g/dl/wk. Thus, during the course of 1 month, a significant increase of 1 to 2 g/dl in the Hb concentration is usually achieved. If a patient fails to respond satisfactorily to ESAs, the dose is increased in stepwise upward titrations of 25% to 50%, and if there is still an inadequate response, causes of resistance to ESA therapy should be investigated (see later discussion).

Given the risks observed in trials aiming at Hb normalization, it is recommended that the Hb level should not be intentionally increased to 13 g/dl or higher and should generally not be maintained above 11.5 g/dl.

Causes of a Poor Response to Erythropoiesis-Stimulating Agent Therapy

Major (Frequent)	Minor (Less Common)
Iron deficiency	Poor compliance, poor adherence to ESA therapy
Infection, inflammation	Blood loss
Underdialysis	Hyperparathyroidism
	Aluminum toxicity (now rare)
	Vitamin B_{12} or folate deficiency
	Hemolysis
	Primary bone marrow disorders (e.g., myelodysplastic syndrome)
	Hemoglobinopathies (e.g., sickle cell disease)
	ACE inhibitors, angiotensin receptor blockers
	Carnitine deficiency
	Anti-EPO antibodies causing PRCA

Table 83-2 Causes of a poor response to erythropoiesis-stimulating agent (ESA) therapy. *ACE,* Angiotensin-converting enzyme; *EPO,* erythropoietin; *PRCA,* pure red cell aplasia.

Hyporesponsiveness to Erythropoiesis-Stimulating Agents

There is no absolute definition of hyporesponsiveness to ESA therapy, but according to the most recent guidelines, it is identified when the Hb concentration does not increase from baseline after the first month of ESA treatment on appropriate weight-based dosages or if after treatment with stable doses, patients require two increases in ESA doses up to 50% beyond the dose at which their condition had previously been stable.[14] Patients who are hyporesponsive have a worse prognosis than those who do respond.[35] The causes of resistance to ESA therapy are listed in Table 83-2, and it is important to correct them when possible. The major causes include iron deficiency (see later discussion), infection or inflammation, and underdialysis.[12,14] If the patient is self-administering (e.g., for peritoneal dialysis patients), poor adherence to or compliance with therapy must be excluded. If there is any doubt about the possibility of iron deficiency, a trial of intravenous iron may be useful. Vitamin B_{12}, folate, and thyroxine deficiency may be excluded easily by the appropriate laboratory tests, as may severe hyperparathyroidism. Aluminum toxicity is no longer a significant cause of ESA resistance. Depending on the ethnic origin of the patient, a hemoglobinopathy should be excluded by performance of Hb electrophoresis. Some patients taking ACE inhibitors or angiotensin receptor blockers may require higher doses of ESA therapy, although it is rarely necessary or indeed advisable to stop these drugs. The possibility of a primary bone marrow disorder, such as myelodysplastic syndrome, should be investigated by a bone marrow examination (aspirate and trephine) if all other causes have been excluded. A bone marrow test may also be necessary in the diagnosis of antibody-mediated pure red cell aplasia, although measurement of the reticulocyte count and anti-EPO antibodies may provide an earlier clue.[25] If a patient receiving ESA therapy has a high reticulocyte count, the bone marrow is generating more than adequate quantities of new red cells, and bleeding or hemolysis should be investigated by means of upper gastrointestinal endoscopy, colonoscopy, or hemolysis screen (Coombs test, serum bilirubin, lactate dehydrogenase, and haptoglobin levels).

There is no defined upper dose limit of ESA, and doses of 60,000 IU of EPO per week have not uncommonly been used in the United States, but there is recent concern that high doses of ESA may increase side effects independently of Hb concentrations, as described earlier. In patients with acute illness requiring hospitalization, Hb frequently falls despite continued ESA therapy, indicating increased

blood loss and temporary hyporesponsiveness. The optimal management of anemia under these conditions remains unclear. Whereas cost considerations may speak for withholding of ESA therapy until responsiveness is reestablished, it has also been proposed that doses should be increased in an attempt to overcome hyporesponsiveness. Very high doses can be effective even in critically ill patients in intensive care units, but a pivotal trial[36] failed to demonstrate a reduction in transfusion requirements and observed an increase in deep vein thrombosis. From a practical point of view, and pending evidence to the contrary, it seems sensible to continue the same dose of ESA.

Iron Management

Iron is an essential ingredient for heme synthesis, and adequate amounts of this mineral are required for the manufacture of new red cells. Thus, under enhanced erythropoietic stimulation, greater amounts of iron are used, and many CKD patients (particularly those on hemodialysis) have inadequate amounts of available iron to satisfy the increased demands of the bone marrow.[37] Even before the introduction of ESA therapy, many CKD patients were in negative iron balance as a result of poor dietary intake, poor appetite, and increased iron losses from occult and overt blood losses (see Chapter 87). Losses in hemodialysis patients are up to 5 or 6 mg/day, compared with 1 mg in healthy individuals, and this may exceed the absorption capacity of the gastrointestinal tract, particularly when there is any underlying inflammation. Iron absorption capacity in patients with CKD is considerably lower than in nonuremic individuals, particularly in the presence of systemic inflammation, and this is probably mediated by hepcidin upregulation (see earlier discussion).[9] For this reason also, oral iron is ineffective in many CKD patients, and parenteral iron administration is required, particularly in those receiving hemodialysis.[37] However, even with these limitations of oral iron absorption, the cheap costs of using this route, along with convenience for the patient, often persuade physicians to try oral iron supplementation first in nondialysis patients; if, however, there is insufficient response after 2 to 3 months, intravenous iron should be administered.

An inadequate supply of iron to the bone marrow may be caused by an absolute or a functional iron deficiency.[37] Absolute iron deficiency occurs when there are low whole-body iron stores, as indicated by a serum ferritin level less than 30 µg/l. Functional iron deficiency occurs when there is ample or even increased storage iron but the iron stores fail to release iron rapidly enough to satisfy the demands of the bone marrow. Several markers of iron status are available, but none of them is ideal (Table 83-3). Serum ferritin is a marker of storage iron but is spuriously raised in inflammatory conditions and liver disease. Transferrin saturation is a function of the circulating serum iron in relation to the total iron-binding capacity and is often regarded as a better measure of available iron; however, levels can be highly fluctuant because of significant diurnal variation in the measurement of serum iron.[37] The percentage of hypochromic red cells and the reticulocyte hemoglobin content (CHr) are red cell and reticulocyte parameters, respectively, that are indirect measures of how much iron is being incorporated into the newly developing or mature red cell. No one measure of iron status is usually adequate to exclude iron deficiency, and the recommended levels for these measures are based on limited scientific evidence. Functional iron deficiency is usually diagnosed when there is a normal or increased ferritin level and a reduced transferrin saturation (<20%) or increased hypochromic red cells (>10%). The KDIGO guidelines on renal anemia management suggest a trial of iron in CKD patients with anemia who are not on iron and ESA therapy and in whom an increase in Hb concentration is desired and in patients on ESA therapy in whom an increase in Hb concentration or a decrease in ESA dose is required when transferrin saturation (TSAT) is 30% or lower and ferritin level is 500 ng/ml or lower[14] (see Table 83-3). Levels of ferritin above this threshold usually do not confer any clinical advantage and may exacerbate iron toxicity. The optimal transferrin saturation is above 20% to 30% to ensure a readily available supply of iron to the bone marrow. No upper limits of ferritin or TSAT were specified in the KDIGO anemia guidelines, largely because there is no robust evidence to determine a threshold beyond which harm or loss of efficacy supervenes. However, until more informative data become available, the treating nephrologist would be well advised to exercise caution in administering intravenous iron to patients with ferritin levels above 800 ng/ml or TSAT levels above 30%. Several studies support the maintenance of the percentage of hypochromic red cells at levels of less than 6% and the CHr at levels greater than 29 pg/cell. Other measures of iron status, such as serum transferrin receptor levels and erythrocyte zinc protoporphyrin levels, are mainly research tools and have not been established in routine clinical practice.

Markers of Iron Status in Chronic Kidney Disease Patients

Test	Recommended Range
Serum ferritin	100-500 µg/l (CKD) 200-500 µg/l (HD)
Transferrin saturation	20%-40%
Hypochromic red cells	<10%
Reticulocyte hemoglobin content (CHr)	>29 pg/cell
Serum transferrin receptor	Not established
Erythrocyte zinc protoporphyrin	Not established

Table 83-3 Markers of iron status and the recommended target ranges in CKD. *HD,* Hemodialysis.

Oral iron is poorly absorbed in uremic individuals, and there is a high incidence of gastrointestinal side effects. Intramuscular administration of iron is not recommended in CKD, given the enhanced bleeding tendency, the pain of the injection, and the potential for brownish discoloration of the skin. Thus, intravenous administration of iron has become the standard of care for many CKD patients, particularly those receiving hemodialysis.[37] There are several intravenous iron preparations available worldwide, including iron dextran, iron sucrose, iron gluconate, and the newer iron preparations ferric carboxymaltose, ferumoxytol, and iron isomaltoside 1000. The last three iron preparations allow higher doses of intravenous iron to be administered more rapidly, without the need for a test dose. All of the iron preparations contain elemental iron surrounded by a carbohydrate shell, which allows them to be injected intravenously. The lability of iron release from these preparations varies, with iron dextran being the most stable and iron gluconate being the least stable. Iron is released from these compounds to plasma transferrin and other iron-binding proteins and is eventually taken up by the reticuloendothelial system.

In hemodialysis patients, it is easy and practical to give low doses of intravenous iron (e.g., 10 to 20 mg every dialysis session) or, alternatively, 100 mg weekly. In peritoneal dialysis and nondialysis CKD patients, however, such low-dose regimens are impractical, and larger doses may be administered. The more stable the iron preparation, the larger the dose administration rate that can be used. For example, 1 g of iron dextran may be given by intravenous infusion,

whereas the maximum recommended dose of iron gluconate is 125 mg. The usual dose of ferumoxytol is 510 mg, whereas up to 1 g of ferric carboxymaltose or iron isomaltoside 1000 may be given as a single administration. All intravenous iron preparations carry a risk for immediate hypersensitivity reactions, which may be characterized by hypotension, dizziness, and nausea. These reactions are usually short-lived and caused by too large a dose given in too short a time. Iron dextran also carries the risk for acute anaphylactic reactions because of preformed dextran antibodies, and although this risk may be less with the lower-molecular-weight iron dextrans, the potential for anaphylaxis still remains. Other, longer-term concerns about intravenous administration of iron include the potential for increased susceptibility to infections and oxidative stress. Much of the scientific evidence for this has been generated from *in vitro* experiments, the clinical significance of which is unclear.

There is emerging evidence that intravenous iron may improve the anemia of CKD in up to 30% of patients not receiving ESA therapy who have a low ferritin level.[38] In such patients, a response to intravenous iron alone may occur within 2 to 3 weeks of iron administration. In those already receiving ESAs, there is considerable evidence that concomitant intravenous iron may enhance the response to the ESAs and result in lower dose requirements.[12,14,37]

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CHAPTER 84

Other Blood and Immune Disorders in Chronic Kidney Disease

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PLATELET DYSFUNCTION AND COAGULATION DEFECTS

Normal hemostasis begins with platelet adhesion to vascular endothelium and requires a relatively vasoconstricted vessel wall, integrity of platelet glycoproteins (GPs), and a normal quantity of large-molecular-weight, multimeric von Willebrand factor (vWF) (Figs. 84-1 and 84-2). Main platelet GPs are GPIb, the platelet receptor for vWF, involved in platelet adhesion, and GPIIb/IIIa, the platelet receptor for fibrinogen, involved in platelet aggregation. Under static conditions, GPIb and vWF have no affinity for each other. However, these molecules develop a specific affinity for each other at high shear stress, resulting in arterial platelet adhesion. Aggregated fibrinogen-platelet mesh acts as a trap for binding and activation of other plasma clotting factors. The exposure of the preceding clotting factors to tissue factors, present on damaged endothelial cells, catalyzes the conversion of prothrombin to thrombin, which converts fibrinogen to fibrin. Subsequent cross-linking of insoluble fibrin results in a stable hemostatic plug.

BLEEDING DIATHESIS IN UREMIA

Uremic bleeding caused by acquired platelet dysfunction is a major cause of morbidity and mortality in end-stage renal disease (ESRD) patients. The bleeding problems are characterized by abnormal prolongation of bleeding time and hemorrhagic symptoms, manifesting usually as ecchymoses or petechiae in the skin, epistaxis, gastrointestinal or gingival oozing, or prolonged hemorrhage from needle puncture or postoperative sites. The cutaneous bleeding time (normal values are 1 to 7 minutes) is the best laboratory hallmark of clinical bleeding caused by uremia; however, it is very difficult to standardize and thus not widely used. Other coagulation screen tests, such as activated partial thromboplastin time (APTT), prothrombin time, and thrombin time, are generally normal in patients with uremia.[1] Hemorrhagic complications in ESRD patients may also manifest as hemorrhagic pericarditis and/or hemorrhagic pleural effusion as well as intracranial, retroperitoneal, ocular, or uterine bleeding.

PLATELET DYSFUNCTION

The pathogenesis of platelet dysfunction in uremia is multifactorial and includes diminished adherence of platelets to vascular endothelium (Box 84-1). In uremic patients, total platelet GPIb content is reduced, whereas the total content of GPIIb and GPIIIa is normal. Platelet membrane GPIb levels and GPIIb/IIIa expression have been described as normal, decreased, or increased in uremic platelets. Plasma vWF level is normal or elevated in uremia. However, the observation that the administration of agents that increase plasma vWF or the factor VIII–vWF complex results in a shortening of prolonged bleeding time and a transient reversal of bleeding tendency in uremia suggests abnormalities in vWF metabolism, structure, and/or function.

A variety of circulating plasma proteases, such as plasmin, cleave the α chain of platelet GPIb. The resulting proteolytic degradation product glycocalicin contains binding sites for thrombin and vWF. Elevated plasma glycocalicin levels in uremic patients may contribute to diminished binding of uremic platelets to subendothelium because of the vWF binding site of glycocalicin. Furthermore, glycocalicin contains the thrombin binding site of GPIb which may also contribute to diminished platelet function in uremia.

Low GPIb expression on resting platelets obtained from patients with chronic kidney disease (CKD) correlates with the severity of impaired kidney function. However, GPIb expression in uremic platelets increases after stimulation. In contrast, GPIIb/IIIa expression on resting uremic platelets is normal but reduced after stimulation, indicating hyporesponsiveness of the uremic platelets.

The ability to bind both vWF and fibrinogen to GPs is reduced in uremia because of a conformational change in the GPIIb/IIIa receptor. Improvement of fibrinogen binding to GPIIb/IIIa by hemodialysis (HD) treatment suggests that uremic toxins such as methylguanidine, guanidinosuccinic acid, phenolic acid, and hydroxyphenylacetic acid also contribute to platelet dysfunction. HD and peritoneal dialysis (PD) correct platelet abnormalities partially because both procedures do not remove all uremic toxins effectively. PD is more effective than HD in improving impaired platelet function and prolonged bleeding time in uremia, possibly because of better clearance of uremic middle molecules. In addition, platelet contact with older cellulose-based HD membranes caused defects in platelet membrane receptors for vWF and fibrinogen, thus preventing normal platelet-vessel wall and platelet-platelet interactions. This can be demonstrated by a more prolonged bleeding time, a more decreased platelet responsiveness to thrombin, and a decreased platelet agglutination in response to ristocetin immediately after the HD procedure. Heparin administered during HD treatment contributes to the prolonged bleeding time immediately after dialysis although not for the platelet alterations described earlier. Platelet contact with the artificial surfaces may result in GPIb internalization, which may also occur during platelet activation.

Molecules such as prostacyclin and nitric oxide (NO) inhibit platelet function, modulate vascular tone, affect platelet–vessel wall as well as platelet-platelet interactions, and have an important role in preventing platelet activation under normal conditions. However, uremic platelets generate more NO than platelets obtained from healthy patients, which may contribute to the increased bleeding

†Deceased.

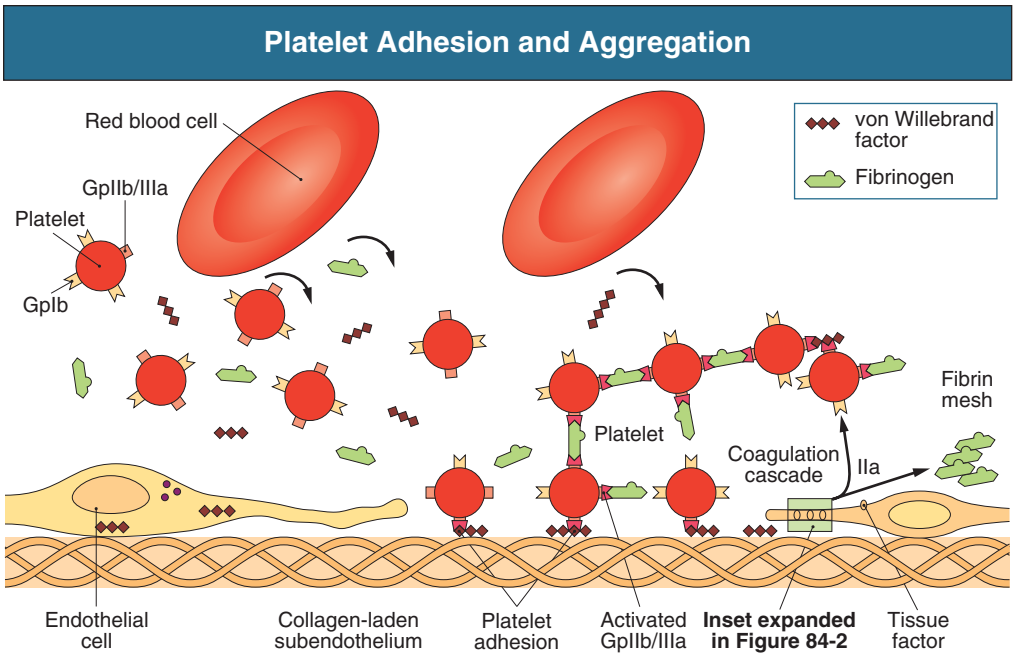

Figure 84-1 Platelet adhesion and aggregation. Platelets are pushed peripherally toward the vascular wall by red blood cells traversing centrally through the bloodstream. Damage to the vessel wall results in a disruption of the nonthrombogenic endothelial cell lining and exposure of subendothelial structures. Whereas collagen supports initial platelet adhesion (and subsequent aggregation), von Willebrand factor (vWF) deposition on the subendothelium serves as the main anchor for platelet adhesion through platelet GPIb receptor. Postadhesion conformational change in platelet GPIIb/IIIa receptor (fibrinogen or vWF receptor) results in interlinking platelet aggregation.

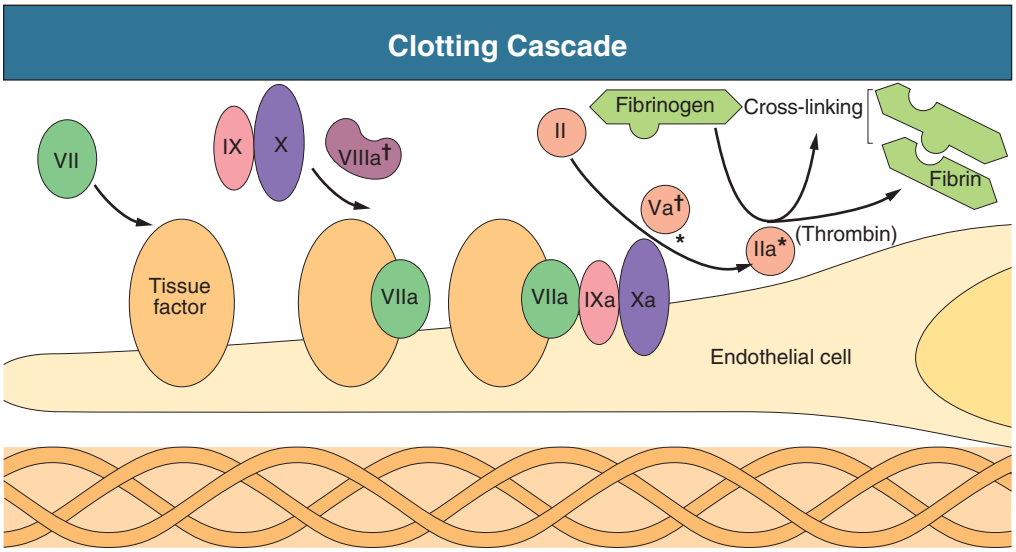

Figure 84-2 Clotting cascade. Expansion of the inset in Figure 84-1 shows the clotting cascade that takes place at the damaged vessel wall. Exposure of subendothelial tissue factor, present on pericytes and fibroblasts, allows eventual activation of prothrombin (factor II) to thrombin. Thrombin converts fibrinogen to fibrin, activates fibrin cross-linking, stimulates further platelet aggregation, and activates anticoagulant protein C. Naturally occurring anticoagulants antithrombin III, protein C, and protein S help maintain control and counterbalance on coagulation. *Site of anticoagulant effect for antithrombin III. †Site of anticoagulant effect for protein C–protein S complex. *(Courtesy James A. Sloand, MD, FACP, FASN, Baxter Healthcare Corporation, USA.)*

time in uremia. Uremic plasma induces NO synthesis in endothelial cells. Bleeding tendency in uremic patients is related to the increased platelet nitric oxide synthase (NOS) activity. The NOS substrate L-arginine inhibits platelet aggregation, whereas the NOS inhibitors NG-monomethyl-L-arginine (L-NMMA) and NG-nitro-L-arginine methylester (L-NAME) restore platelet adhesion and aggregation. Inhibition of NOS by L-NMMA restores the increased bleeding time in experimental uremia to normal. Elevated arginine transport in uremic platelets is mediated by the high-affinity amino acid transport system y^+L. Thus, increased L-arginine influx into uremic platelets is sustained and may contribute to platelet dysfunction even in the L-arginine–deprived uremic milieu.

Renal anemia is another determinant of the prolonged bleeding time in ESRD patients. Within the normal circulation red blood cells increase platelet–vessel wall contact by displacing platelets away from the axial flow and toward the vessel wall. Red blood cells also improve platelet function by releasing adenosine diphosphate (ADP) and inactivating prostacyclin. Vasodilating effects of prostacyclin and NO increase vessel luminal diameter and decrease peripheral dispersion of platelets and their contact with the vessel wall. Recombinant human erythropoietin (rHuEPO) improves platelet function mainly through increasing hematocrit, whereas an increase in blood viscosity may enhance the risk for thrombotic events. Platelet aggregation in uremia is ameliorated by rHuEPO therapy even at a dose that does not influence hemoglobin and hematocrit by the release of young platelets into the blood. Low-dose rHuEPO therapy in patients with uremia also improves impaired platelet aggregation stimulated by ADP and ristocetin.

PLATELET NUMBER IN UREMIA

Moderate thrombocytopenia (80 to 150×10^9/l) is a common finding in ESRD patients. The platelet number is reduced in 16% to 55% of uremic patients. However, the platelet count is rarely less than 80×10^9/L, a platelet number generally considered adequate for normal

Pathogenesis of Platelet Dysfunction in Uremia

- **Platelet abnormalities**
  - Alterations in membrane fluidity
  - Reduction in intracellular ADP and serotonin
  - Enhanced intracellular cAMP
  - Impaired release of β-thromboglobulin and ATP
  - Increased NO production
  - Increased intracellular Ca^{2+} (caused by secondary hyperparathyroidism)
  - Abnormal mobilization of platelet Ca^{2+}
  - Defective cyclooxygenase activity
  - Reduced thromboxane A_2 generation
  - Decreased platelet factor 3 availability
  - Reduced total GPIb content (with increased glycocalicin formation)
  - Reduced GPIIb/IIIa after stimulation
  - Diminished responsiveness to platelet agonists
  - Decreased clot retraction
  - Aggregation abnormalities (mostly hyperaggregation)
  - Abnormal platelet adherence
- **Uremic toxins**
- **Anemia**
- **vWF abnormalities**
- **Vessel abnormalities**
- **Drugs** (β-lactam antibiotics, nonsteroidal anti-inflammatory drugs, antiplatelet agents)

Box 84-1 Pathogenesis of platelet dysfunction in uremia. *ADP,* Adenosine diphosphate; *ATP,* adenosine triphosphate; *cAMP,* cyclic adenosine monophosphate; *NO,* nitric oxide; *vWF,* von Willebrand factor.

hemostasis. In the past, the interaction of blood with cellulose-based dialyzer membranes (e.g., cuprophane) resulted in complement activation and transient thrombocytopenia during the dialysis procedure. In contrast, relevant platelet reduction does not occur with the use of newer non–complement-activating dialyzer membranes. Heparin may induce thrombocytopenia via the emergence of antibodies. The principle antigen is a complex of platelet factor 4 and heparin (PF-4/H). Frequencies of anti–PF-4/H antibodies range from 0% to 12% in HD patients continuously exposed to heparin. In patients with heparin-induced thrombocytopenia (HIT) type II, platelet counts range from 50 to 80 $\times$ 10^9/l (see later). Increased numbers of circulating reticulated platelets in uremia suggest shortened platelet survival under these conditions. Reduced platelet half-life and low-normal platelet number in uremia suggest increased platelet turnover. Normal controls have a mean of 2.8% $\pm$ 0.2% reticulated platelets (a marker of platelet turnover), whereas PD and HD patients have a significantly higher percentage of 6.9% $\pm$ 0.7% and 8.2% $\pm$ 0.4%, respectively, suggesting enhanced platelet turnover in uremia. Shortened platelet survival in uremia may be the result of increased exposure of negatively charged phosphatidylserine. This signal is recognized by macrophages and promotes phagocytosis of the platelets.

THERAPEUTIC STRATEGIES

The bleeding disorder of uremic patients has been classically defined as an acquired defect of primary hemostasis, characterized by prolongation of bleeding time. Therapeutic strategies include both prevention of bleeding in patients at high risk because of invasive procedures or surgery, and treatment of patients with active bleeding. Several options are available to prevent or treat uremic bleeding.

Mechanisms by Which Erythropoiesis-Stimulating Agent (ESA) Therapy Improves Uremic Bleeding Tendency

Displacement of platelets closer to the vascular endothelium with the increase in circulating red blood cells

Increase in reticulated (metabolically active) platelets

Increase in platelet aggregation

Improvement of platelet signaling (and thereby better response to stimuli)

Scavenging of nitric oxide by hemoglobin, resulting in increased platelet adhesion

Box 84-2 Mechanisms by which ESA therapy improves uremic bleeding tendency. *(Data from reference 2.)*

Dialysis

Adequate dialysis (Kt/V > 1.2 in HD and Kt/V > 1.7 in PD patients; see Chapter 94) by removal of uremic toxins improves platelet functional abnormalities. Hemorrhagic problems are fewer with PD than with HD. Deep-tissue biopsies or invasive surgical procedures that require improved hemostasis should ideally be scheduled 12 to 24 hours after dialysis in HD patients. The residual anticoagulant effect of unfractionated heparin (UFH) used during HD lasts as long as 2.5 hours or even longer with the use of low-molecular-weight heparin (LMWH). In case of clinical urgency or high risk of postoperative bleeding, heparin use should be minimized, stopped (using predilutional saline, 100 to 200 ml every 15 or 30 minutes, and a dialysis membrane with low thrombogenicity such as polysulfone), or replaced by regional anticoagulation with citrate during HD. Protamine sulfate administration (1 mg/100 U of heparin infused over 10 minutes) should be considered if there is marked, HD-induced prolongation of the partial thromboplastin time (PTT) and severe bleeding.

Correction of Anemia

The severity of anemia in uremic patients correlates with the prolongation of bleeding time. Beneficial effects of red cell transfusion on prolonged bleeding time are independent of changes in platelet function tests or in the level of vWF. Erythropoiesis-stimulating agent (ESA) therapy improves uremic bleeding tendency by several mechanisms (Box 84-2),[2] and this has diminished hemorrhagic problems in uremic patients. Increased intraoperative bleeding complications have been reported in ESRD patients with low preoperative hematocrit levels. Unfortunately, in ESRD patients, intraoperative transfusion of packed red blood cells may cause or aggravate hyperkalemia. If surgery is elective, ESA therapy (in combination with intravenous iron) may be administered preoperatively to raise hemoglobin and hematocrit to the upper acceptable values (see Chapter 83). In uremic patients on ESA therapy, a threshold hematocrit of 27% to 32% effectively normalized bleeding time.[1]

Cryoprecipitate

Cryoprecipitate is a blood product rich in factor VII, vWF, and fibrinogen. In uremic patients at high risk of bleeding or with active

bleeding, the effect of cryoprecipitate is apparent 1 hour after infusion, but maximal effects on the bleeding time are obtained 4 to 12 hours after the infusion. By 24 to 36 hours, the effect of cryoprecipitate is no longer detected. As many as 50% of patients fail to respond to cryoprecipitate.[1] Disadvantages include the risk of exposure to various blood-borne pathogens and allergic reaction.[2] It has therefore largely been replaced by other approaches.

Desmopressin

Desmopressin acetate (1-deamino-8-D-arginine-vasopressin, DDAVP) is a synthetic derivative of the antidiuretic hormone vasopressin. The compound has been shown to be useful in a variety of inherited and acquired hemorrhagic conditions, such as uremia, and in patients with hemostatic defects induced by therapeutic use of antithrombotic drugs, such as aspirin, dipyridamole, clopidogrel or ticlopidine. Moreover, DDAVP shortens bleeding time and APTT of patients receiving heparin. It is therefore helpful for the management of hemorrhagic complications during treatment with heparin. Desmopressin shortens the prolonged APTT and bleeding time by an increase in plasma levels of factor VIII and vWF. The increase in larger vWF–factor VIII multimers after infusion of DDAVP is associated with shortening of bleeding time. It also increases platelet GPIb expression.

Desmopressin is the most common agent used in uremic patients. The recommended doses range from 0.3 to 0.4 μg/kg administered intravenously in 50 ml normal saline over 20 to 30 minutes as a single infusion. Subcutaneous (0.3 μg/kg) or intranasal (2-3 μg/kg) routes of administration are also effective. One important advantage of DDAVP is its rapid onset of action in the setting of acute bleeding. Desmopressin decreases bleeding time within approximately 1 hour after administration. This advantage is important for CKD patients with prolonged bleeding time who require biopsies or major surgery. Disadvantages of DDAVP include tachyphylaxis caused by depletion of vWF from endothelial stores even after one single dose, headache, facial flushing, and rare thrombotic events. Because of the short duration of DDAVP activity (4 to 6 hours), bleeding time tends to return toward baseline within 24 hours, indicating patients are once again at risk of bleeding.[2] DDAVP can be given repetitively, but its effect may diminish in some patients as a result of tachyphylaxis if given at short time intervals.

Conjugated Estrogens

Conjugated estrogens can be given intravenously, orally, or transdermally. The intravenous route of administration at a cumulative dose of 3 mg/kg divided over 5 consecutive days produces a long-lasting reduction in the bleeding time of uremic patients. At least 0.6 mg/kg of a conjugated estrogen is needed to reduce bleeding time. A single oral dose of 25 mg normalizes the bleeding time for 3 to 10 days. Low-dose transdermal application of a conjugated estrogen (50 to 100 μg of estradiol per 24 hours) as a patch twice weekly also improves bleeding time and reduces bleeding complications. Conjugated estrogens are safe and well tolerated.[1] Side effects include flush, increase in blood pressure, and abnormal liver function tests.

Tranexamic Acid

Tranexamic acid (TXA) is an antifibrinolytic lysine analog that shortens bleeding time in uremic patients. TXA prevents the binding of plasminogen to fibrin and the activation of plasminogen to plasmin. Bleeding time improves or normalizes in uremic patients within 6 days of treatment with TXA (20 to 25 mg/kg/day) administered intravenously or orally. Improvement of bleeding time is already observed as soon as 24 to 48 hours after initiation of TXA therapy. TXA may be combined with DDAVP to prevent or treat bleeding in uremic patients, if other treatment options do not elicit the desired response.

PLATELET HYPERAGGREGABILITY IN UREMIA

Uremic patients also have a thrombophilic tendency and an increased incidence of thrombotic events because of platelet hyperaggregability and hypercoagulability. Binding of activated factor V to platelet surface exposed phosphatidylserine induces coagulation. In uremic patients who received muromonab-CD3 infusion for prophylaxis of graft rejection, platelet procoagulant activity increased by binding of anti–factor V/Va as a result of increased exposure of anionic phospholipids in platelets.

Platelet activation also results in shape change; activation of surface receptors for fibrinogen and other adhesion proteins; secretion of PF-4, β-thromboglobulin, thromboxane B_2, and serotonin; and induction of procoagulant activity. In HD patients, a relationship between recurrent vascular access failure and increase in CD62P-positive platelets and an increase in fibrinogen receptor (PAC-1 antigen)–positive platelets has been demonstrated.

Chronically activated circulating platelets seen in ESRD patients interact with leukocytes and erythrocytes, resulting in platelet-erythrocyte aggregates and platelet-leukocyte aggregates. Platelet-erythrocyte aggregates enhance platelet reactivity measurable by thromboxane B_2 formation and the release of β-thromboglobulin. Low levels of platelet-erythrocyte aggregates are found in healthy patients (1.2% ± 0.1%). This percentage increases approximately sixfold in ESRD patients but approximately 8-fold or 10-fold during HD. Platelet-leukocyte aggregates trigger neutrophil oxidative burst.

Platelets release small particles, so-called "platelet microparticles" (PMPs), after they are activated. PMPs express procoagulant proteins such as tissue factor and contain a membrane receptor for coagulation factor V. In addition, PMPs provide a highly catalytic surface for the prothrombinase reaction as a result of high amounts of negatively charged phospholipids at the outer membrane. PMP counts are significantly increased in predialysis patients as well as in patients undergoing regular PD or HD as compared with healthy patients.[3] The HD procedure does not affect PMP counts. However, rHuEPO therapy increases PMP release. Some studies suggest higher PMP counts in uremic patients with thrombotic events, but not all studies have confirmed these findings.

INDICATIONS FOR ANTIPLATELET AGENTS IN END-STAGE RENAL DISEASE

Despite the increased risk for bleeding in ESRD patients receiving antiplatelet agents, current evidence suggests that dialysis access thrombosis or loss of patency is reduced by antiplatelet agents, but only in native fistulas and not in grafts.[4] In contrast, access maturation or the need for intervention to attain patency or assist maturation tended to be improved or reduced, respectively, but this did not reach significance in a meta-analysis (see also Chapter 91).[4] There is no role for the routine use of warfarin, particularly in view of its adverse effects in HD patients (see later).

A recent Cochrane meta-analysis concluded that in CKD patients, myocardial infarction but not all-cause mortality was reduced by antiplatelet agents but that this came at the price of a 30% to 50%

increase in minor and major bleeding episodes.[4] The risk reduction of acute myocardial infarction was not major, and the number needed to treat to prevent one infarction was estimated as 77, which needs to be balanced against a number needed to harm of 115 to observe one major bleeding episode. The risks associated with antiplatelet therapy in the Cochrane analysis may, however, be an overestimate with respect to low-dose aspirin. Of importance, the Cochrane analysis yielded no evidence for increased mortality from antiplatelet agents, in particular aspirin, in CKD patients. For further discussion of this issue, refer to Chapter 82.

Because antiplatelet agents such as aspirin (low and full dose), dipyridamole, clopidogrel, or ticlopidine increase bleeding time, these drugs should not be given within 72 hours before biopsies and major surgery. Other drugs that may increase the risk of intraoperative bleeding in uremic patients include warfarin and coumadins, β-lactam antibiotics, nonsteroidal anti-inflammatory drugs, and diphenhydramine.

ANTICOAGULATION AND ASSOCIATED COMPLICATIONS IN UREMIA

Heparin-Induced Thrombocytopenia

Unfractionated heparin is the most commonly used anticoagulant in the United States. Risks of UFH use include bleeding, heparin-induced thrombocytopenia, hypertriglyceridemia, anaphylaxis, and possible bone mineral disease, hyperkalemia, and catheter-associated sepsis caused by the development of a biofilm.[5] HIT type II is a serious immune-mediated complication of heparin therapy. Severe thrombocytopenia (mean platelet number 60,000/mm^3) caused by platelet consumption usually occurs 4 to 14 days after the administration of heparin and is associated with arterial ("white clot syndrome") and, particularly, venous thromboembolism in 20% to 50% of the patients. HIT type II should be considered whenever the platelet count falls by 50% in a patient receiving heparin. HIT may develop when novel epitopes of PF-4 present on the platelet surface membrane are exposed because of cross-linking with heparin, resulting in autoantibody formation. These antibodies activate PF-4, resulting in peripheral thrombocytopenia. Patients with HIT antibodies without clinical complications need to be differentiated from those with HIT antibodies in whom active thrombosis (heparin-induced thrombotic thrombocytopenia syndrome [HITTS]) or hemorrhage exist. HITTS can be life-threatening. These patients not only require complete avoidance of all heparins but also need systemic anticoagulation. The direct thrombin inhibitors, such as argatroban, synthetic heparinoids, and danaparoid, are the current treatment options (Fig. 84-3). After heparin withdrawal, thrombocytopenia typically resolves within 5 to 7 days.[6,7] A negative HIT antibody test does not exclude the diagnosis of HIT type II syndrome. In HIT type II patients, warfarin should not be used until the platelet count has recovered.

In contrast, HIT type I presents with a nonimmune mild transient decrease in the platelet count (rarely <100,000/mm^3) 1 to 4 days after initiation of heparin therapy. It occurs in 10% to 20% of patients

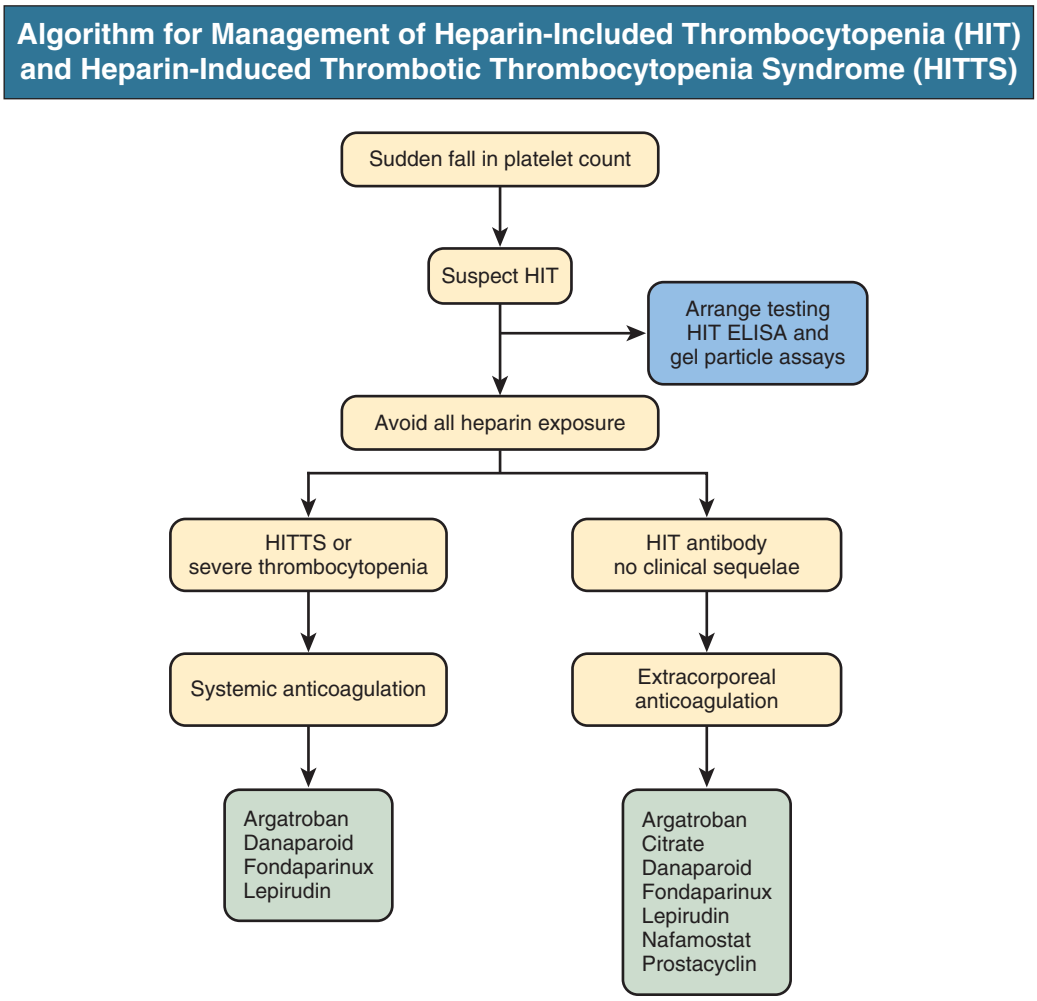

Figure 84-3 Algorithm for management of heparin-included thrombocytopenia (HIT) and heparin-induced thrombotic thrombocytopenia syndrome (HITTS). *ELISA,* Enzyme-linked immunosorbent assay. *(Modified from reference 6.)*

without appreciable clinical consequences and usually resolves spontaneously even though heparin therapy is continued.

In a summary of six trials performed in HD patients, 2.6% of patients had a positive test result for the HIT antibody, with a lower percentage in those using LMWH as compared with UFH.[8] Less than 1% of the HD patients were thrombocytopenic, and none had severe thrombotic complications. A recent survey reported a prevalence of 0.26 per 100 patients and an incidence of 0.32 per 100 patients of HIT II syndrome in the United Kingdom HD population. Only 17% of the patients have had complications of HIT II syndrome. Thirty-six percent of renal units used danaparoid as an alternative anticoagulation therapy in these patients.[9]

Danaparoid

Danaparoid is a mixture of glycosaminoglycans and acts by activating antithrombin. Danaparoid is a heparinoid with a molecular weight of 5.5 kDa and consists of heparin sulfate (83%), dermatan sulfate, and chondroitin sulfate. It is used as an alternative anticoagulant in HD patients with HIT type II in Canada and the European Community. Danaparoid reduces PF-4–containing immune complexes and therefore can prevent activation of platelets by HIT antibodies. It inhibits factor Xa more selectively than LMWH.[7] In 6.5% of patients with HIT, cross-reactivity against danaparoid may result in thrombocytopenia. For monitoring of danaparoid therapy, anti-Xa activity has to be measured. The half-life of the anti-Xa activity of danaparoid is 31 hours in patients with normal kidney function and is further prolonged in uremia. When treating patients with HITTS, systemic anticoagulation is required. It is recommended to start with a bolus of 2500 IU (1250 if <55 kg and 3750 IU if >90 kg), followed by an infusion of 200 IU/h, subsequently adjusted to maintain anti-Xa activity between 0.5 and 0.8 IU/ml.[6] An antidote is not available.[7]

Argatroban

Argatroban is a potent arginine-derived synthetic thrombin inhibitor. It is metabolized primarily by the liver. Its half-life is only moderately extended in patients with impaired kidney function. Argatroban does not cross-react with HIT antibodies. It reversibly binds to thrombin and thus requires continuous intravenous infusion. A loading dose of 250 μg/kg before HD and a maintenance dose of 1.7 to 3.3 μg/kg/min are recommended. Target APTT of argatroban-treated HD patients is 1.5 to 3.0 × mean of normal range.[7] Much lower doses are required for patients with liver disease. Over time, argatroban and the primary metabolite (with an anticoagulation effect) tend to accumulate, and excessive anticoagulation is a major risk. Because of protein binding, argatroban is not significantly cleared during HD. In patients with HIT antibodies without thrombosis, argatroban can be used for extracorporeal anticoagulation during HD, although the infusion should be stopped 20 to 30 minutes before the end of the dialysis session.[6] Currently, no antidote is available.

Lepirudin

Lepirudin is a recombinant hirudin preparation. It is mainly eliminated by the kidney. Thus, its half-life is markedly prolonged in patients with ESRD. After a single loading dose (0.1 mg/kg), therapeutic anticoagulation may persist for 1 week or even longer. Hirudin does not cross-react with HIT antibodies, but 44% to 74% of patients treated with hirudin for more than 5 days develop antihirudin antibodies. Antilepirudin antibodies are not necessarily associated with a decrease in efficacy. Only in 2% to 3% of patients with antilepirudin antibodies is an inhibitory effect seen, and dose adjustments are required. Target APTT is 1.5 to 2.5 times the normal value.

Fondaparinux

Fondaparinux is a fully synthetic pentasaccharide with high anti-Xa activity. Its half-life is prolonged in patients with impaired kidney function. Preliminary data suggest that administration of fondaparinux (2.0 to 3.5 mg for at least 5 days) is safe.[6] In patients with HITTS requiring systemic anticoagulation, 2.5 mg subcutaneously on nondialysis days and 2 mg intravenously predialysis provide systemic anticoagulation (anti-Xa 0.5 to 0.8 IU/ml). In patients not requiring systemic anticoagulation, 2.5 mg predialysis provides adequate extracorporeal anticoagulation. Fondaparinux is currently not approved in the United States.[6]

Regional Anticoagulation with Citrate

Citrate infused into the arterial line during HD inhibits the coagulation cascade in the extracorporeal circulation by the chelation of calcium and magnesium. The local deficit in ionized calcium is corrected by calcium substitution into the venous line before the blood is reinfused to the patient. In HD patients, regional citrate anticoagulation reduces bleeding complications and improves biocompatibility of dialysis membranes as compared with systemic anticoagulation with UFH or LMWH.

Careful reading of the information provided by the manufacturers and the dose recommendations is a prerequisite before alternative anticoagulation is initiated in patients with HIT type II.

THROMBOTIC EVENTS IN PATIENTS WITH END-STAGE RENAL DISEASE

Hemodialysis patients frequently experience thrombotic events at the site of vascular access, as well as in the coronary, cerebral, and retinal arteries. Pathogenetic mechanisms include enhanced platelet aggregability, diminished protein C anticoagulant activity, deficient release of tissue plasminogen activator (tPA), and elevated plasma levels of antiphospholipid (APL) antibodies, anti–protein C and anti–protein S antibodies, anticardiolipin antibodies, factor VIII, prothrombin fragments 1+2, fibrinogen, homocysteine, and lipoprotein(a). ESRD patients also develop thrombotic complications as the result of changes in secondary hemostasis and of impaired fibrinolytic system activity. APL antibodies can trigger activation of the coagulation cascade at the endothelial surface. These antibodies cross-react with protein C and S, rendering them functionally deficient. Reduced anti-thrombin III activity in uremia results in increased thrombin formation. Activated factor V (factor Va) serves as a cofactor for the conversion of prothrombin to thrombin. Its inactivation occurs by activated protein C. The factor V Leiden mutation alters factor C cleavage site by a single amino acid substitution, rendering it resistant to degradation by activated protein C. Heterozygosity for factor V Leiden mutation occurs in 2% to 5% of the Western population. Its prevalence is not increased in CKD patients, but factor V Leiden increases the risk of thrombotic complications.

Approximately 6% of ESRD patients at risk of thrombosis or thromboembolic events may be treated with oral anticoagulants, which increase the frequency of hemorrhages. Other potential adverse effects of long-term therapy with vitamin K antagonists, in particular in the dialysis population, are accelerated vascular and

valvular calcifications[10] (see Chapter 82), as well as a 10-fold increase in the risk of calcific uremic arteriolopathy (calciphylaxis) (see Chapter 88). Standard oral anticoagulation with an international normalized ratio (INR) of 2 to 3 is not sufficient to prevent clotting during HD. Additional low-dose LMWH or UFH is needed to facilitate adequate extracorporeal treatment.

The emergence of anticardiolipin antibodies in patients with systemic lupus erythematosus is a serious occurrence with regard to a high risk for thrombosis and thromboembolic complications. Immunoadsorption therapy may be an effective method to reduce anticardiolipin antibody levels rapidly and keep them at a low level in the long term.[11]

IMMUNE DYSFUNCTION IN UREMIA

End-stage renal disease is simultaneously associated with immune activation, marked by systemic inflammation, and immune deficiency, characterized by impaired response to vaccination, and increased incidence and severity of microbial infections. Uremia-associated immune deficiency is caused by a large number of alterations in leukocytes (Box 84-3).[12] ESRD-associated systemic inflammation and oxidative stress are commonly associated with atherosclerosis, cardiovascular disease (CVD), cachexia, and anemia, among other morbidities. Bacterial infections remain the most common cause of hospitalization and the second most common cause of death in patients with ESRD.

Vaccination against hepatitis B virus (HBV) decreased the incidence of chronic HBV carriers in ESRD patients. However, only 50% to 75% of dialysis patients develop protective antibodies (>10 IU/l) against HBV surface antigen as compared with greater than 90% in the healthy population. High failure rates have also been reported for vaccinations against the influenza virus, *Clostridium tetani,* and *Corynebacterium diphtheriae.* Because the antigens in all these vaccines are proteins, the antibody response is T lymphocyte dependent. In contrast, the response to polysaccharide antigens is normal in dialysis patients. Therefore antibody production after vaccination against pneumococci is normal in ESRD. Thus the disturbance of acquired immunity of uremic patients concerns mainly the T lymphocyte and not the B lymphocyte. This assumption is supported by the fact that serum IgG isotypes and both IgM and IgA production are normal in ESRD patients. Nevertheless, nonspecific B lymphocyte activation may be responsible for the enhanced autoantibody production observed in this population.[13]

Premature aging of the immune system in patients with ESRD might be related to a permanent skewing of the hematopoietic stem cell population toward myeloid-generating subsets, similar to that seen in healthy elderly individuals.[14] In uremia, a diminished immune defense contributes to the high prevalence of infections, whereas preactivation and priming of immune cells lead to inflammation and consequently to CVD (see also Chapter 82). Whereas the coordinated removal via apoptosis of activated immune cells is crucial for the resolution of inflammation, inappropriately high apoptotic rates lead to a diminished immune response. In uremia, the balance between proinflammatory and anti-inflammatory and between pro-apoptotic and antiapoptotic factors is disturbed. CVD and infections are directly or indirectly associated with a disturbed immune response and account for the high incidence of morbidity and mortality among patients with kidney dysfunction. Besides uremic toxins accumulating in CKD patients as a result of impaired glomerular filtration, deranged metabolic activities in ESRD interfere with the immune defense in uremia.[15] A variety of additional factors such as iron deficiency, iron overload, or vitamin D deficiency may also contribute to cardiovascular and infectious complications in patients with ESRD.

Causes of Uremia-Associated Immune Deficiency

Polymorphonuclear Leukocytes (PMNLs) and Monocyte-Macrophage Abnormalities

- Decreased granulocyte and monocyte-macrophage phagocytic function and microbial killing activity
- Reduced numbers and decreased antigen-presenting capacity of dendritic cells
- Upregulation of Toll-like receptors TLR-2 and TLR-4
- Upregulation of integrin expression
- Increased production of reactive oxygen radicals
- Marked degranulation
- Increased polymorphonuclear neutrophil apoptosis

B and T Cell Abnormalities

- Significant B lymphopenia
- Reduced antibody-producing capacity of B lymphocytes
- Diminished population of $CD5^+$ innate B cells and $CD27^+$ memory B cells as a result of enhanced apoptosis and impaired maturation induced by uremia
- Reduction and dysfunction of regulatory T cells
- Depletion of memory $CD4^+$ and $CD8^+$ T lymphocytes
- Reduced CD4/CD8 ratio, increased Th1/Th2 ratio and depletion of memory $CD4^+$ and $CD8^+$ T cells because of increased apoptosis

Box 84-3 Causes of uremia-associated immune deficiency. *(Data from reference 12.)*

VACCINATIONS IN UREMIA

Hepatitis B Vaccination

Patients receiving maintenance HD are at increased risk of acquiring HBV infection. Therefore, HBV vaccination is recommended for CKD patients negative for hepatitis B surface antigen (HBsAg) and antibody to hepatitis B core antigen (anti-HBcAg), with antibody to hepatitis B surface antigen (anti-HBsAg) below 10 IU/l. Because attenuated response in ESRD, patients usually receive a three- or four-dose vaccination schedule with a higher dose of a recombinant HBV vaccine (40 µg/dose) than immunocompetent adults (20 µg/dose) and intramuscularly into the deltoid muscle (Fig. 84-4). Seroconversion rates of ESRD patients after HBV vaccination are quite variable. Anti-HBsAg levels above 10 IU/l are usually accepted as an adequate response. Older age and diabetes mellitus but not hepatitis C virus (HCV) infection attenuate the immunologic response to the HBV vaccine in both predialysis and dialysis patients.[16,17] Because seroconversion rates correlate with the CKD stage, vaccination of patients with CKD should ideally be performed before they become dialysis dependent. Successful vaccinations in nonresponders have been achieved by simultaneous administration of HBV vaccine with one of tetanus, diphtheria, oral or inactive polio, pertussis, or *Haemophilus influenzae* type B vaccine. Similarly, immunization with combined hepatitis A and B virus vaccine results in better seroprotection against hepatitis B compared with HBV monovalent vaccine in HD patients.[18] Seroprotection persisted in 92% of strong responders but only in 44% of weak responders after 1 year of immunization against HBV.[19] Whereas the current recommendation is to

Hepatitis B Vaccination Scheme in End-Stage Renal Disease Patients

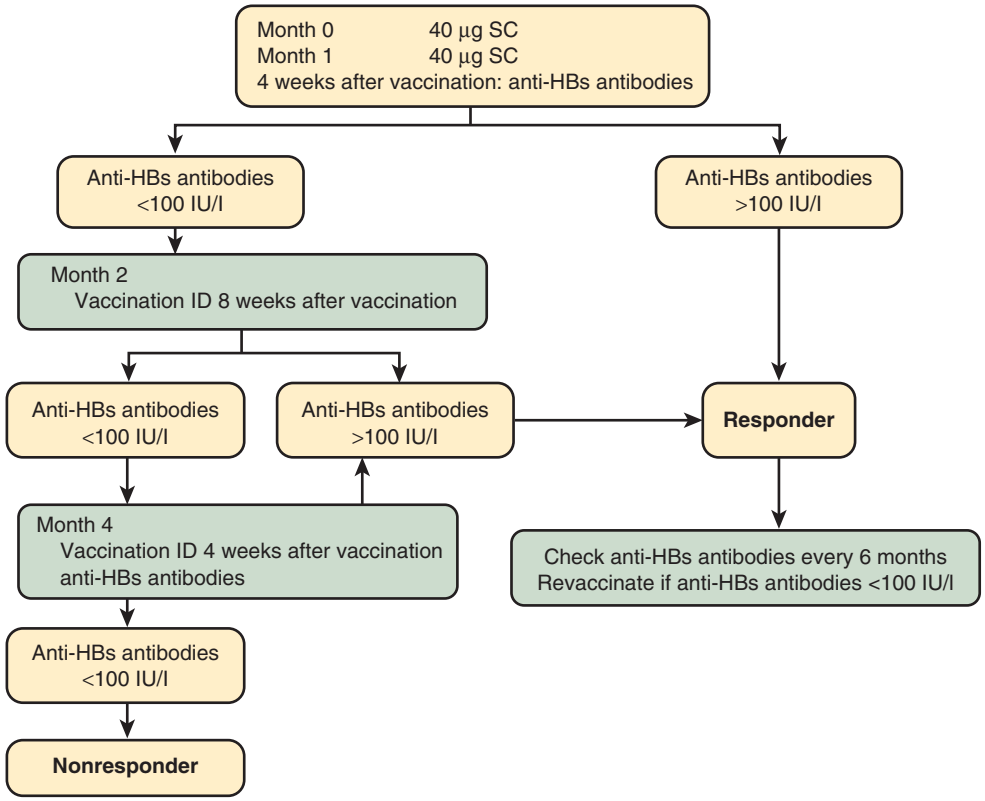

Figure 84-4 Hepatitis B vaccination scheme in patients with end-stage renal disease. *HBs,* Hepatitis B surface; *ID,* intradermal.

administer subsequent booster doses if protective antibody titers are below 10 IU/l, trials are needed to determine whether the threshold should be 100 IU/l or higher in immunocompromised individuals to maximize the duration of seroprotection.[20]

Hepatitis A Vaccination

The hepatitis A vaccine has been shown to be safe and effective in dialysis patients when given in standard doses. Seroconversion rates were also satisfactory in kidney transplant recipients when compared with healthy controls, but the majority of these patients will lose seroprotection after 2 years, probably because of immunosuppressive therapy.[20]

Vaccination Against Influenza and Pneumococcal Disease

Patients with ESRD are considered a high-risk population for hospitalization and death from seasonal influenza and pneumococcal disease. Dialysis patients who received influenza vaccination, vaccination against pneumococcal disease, or both had improved survival. The adjusted odds ratio of all-cause mortality for influenza vaccine alone was 0.79, and the adjusted odds ratio for coadministration of influenza and pneumococcal vaccine was 0.70 compared with no vaccination, suggesting that both influenza and pneumococcal vaccines prevent death and likely have a synergistic effect.[21]

Response rates of influenza vaccination have been reported to be similar to or lower than those in the general population. A single immunization using a higher than usual vaccine dose may be preferable in dialysis patients, because the effects of booster vaccinations were not uniform.[20]

Immunologic response to pneumococcal vaccine is lower in dialysis patients compared with the general population. The antibody levels are considerably lower than those of healthy vaccinated adults and decline rapidly (within 6 months to 5 years), whereas they usually remain sufficient in healthy patients after 5 years. Therefore vaccination every 2 years or an even more frequent regimen of annual vaccination in CKD patients is recommended.[20]

Tetanus and Diphtheria

The seroresponse to tetanus vaccination in HD patients is suboptimal because of impaired T cell–specific immunity. Protective antitetanus titers (≥0.1 IU/ml) develop at an about 20% lower frequency in HD patients compared with healthy individuals. Seroprotection against tetanus in HD patients has been shown to decline over time.[20]

Diphtheria immunization also results in lower protection rates and poor long-term immunity in ESRD patients as compared with healthy patients. In HD patients, long-term immunity against tetanus is better than against diphtheria. In ESRD patients, there is a need for regular monitoring of individual antibody levels and revaccination if required.[20]

Varicella Zoster Virus Vaccination

A relatively high prevalence of herpes zoster has been reported in the CKD and ESRD populations. The live attenuated vaccine has been shown to be highly effective in reducing the risk of zoster

among older adults or ESRD patients. A single dose of zoster vaccine has been recommended for persons aged 60 years or older with ESRD.

Vaccination against pneumococcal disease and varicella vaccination should not be performed at the same time because the combination has been shown to reduce the efficacy of the varicella vaccine.[20]

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CHAPTER 85

Bone and Mineral Metabolism in Chronic Kidney Disease

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DEFINITION

Disturbances of mineral metabolism are common if not ubiquitous during the course of chronic kidney disease (CKD) and lead to serious and debilitating complications unless these abnormalities are addressed and treated. The spectrum of disorders includes abnormal concentrations of serum calcium, phosphate, and magnesium and disorders of parathyroid hormone (PTH), fibroblast growth factor 23 (FGF-23), and vitamin D metabolism. These abnormalities as well as other factors related to the uremic state affect the skeleton and result in the complex disorders of bone known as *renal osteodystrophy;* it is now recommended that this term be used exclusively to define the bone disease associated with CKD. The clinical, biochemical, and imaging abnormalities heretofore identified as correlates of renal osteodystrophy should be defined more broadly as a clinical entity or syndrome called *chronic kidney disease–mineral and bone disorder* (CKD-MBD).[1] The spectrum of skeletal abnormalities seen in renal osteodystrophy includes the following (Fig. 85-1):

- Osteitis fibrosa, a manifestation of hyperparathyroidism characterized by increased osteoclast and osteoblast activity, peritrabecular fibrosis, and increased bone turnover.
- Osteomalacia, a manifestation of defective mineralization of newly formed osteoid most often caused by aluminum deposition; bone turnover is decreased.
- Adynamic bone disease (ABD), a condition characterized by abnormally low bone turnover.
- Osteopenia or osteoporosis.
- Combinations of these abnormalities termed *mixed renal osteodystrophy.*
- Other abnormalities with skeletal manifestations (e.g., chronic acidosis, β_2-microglobulin amyloidosis).

EPIDEMIOLOGY

The prevalence of the various types of renal bone disease in patients with end-stage renal disease (ESRD) is illustrated in Figure 85-2.[2] In patients on hemodialysis, osteitis fibrosa and ABD now occur with almost equal frequency. In contrast, in patients on peritoneal dialysis, the adynamic bone lesion predominates. Osteomalacia represents only a small fraction of cases in either group but is more common in certain ethnic groups, particularly Indo-Asians. The abnormalities of the skeleton start relatively early in the course of CKD.

PATHOGENESIS

Several biochemical and hormonal abnormalities that are encountered during the course of CKD contribute to renal bone disease and can be affected by efforts at prevention and therapy. The major factors that are operative in early CKD may vary as CKD progresses (Fig. 85-3). Similarly, the predominance of one particular pathogenetic mechanism over another may contribute to the heterogeneity of bone disorders. We therefore discuss separately the two major entities, namely, high- and low-turnover osteodystrophy.

Osteitis Fibrosa: Hyperparathyroidism—High-Turnover Renal Bone Disease

Elevated levels of PTH in blood, hyperplasia of the parathyroid glands, and elevations in FGF-23 are seen early in CKD. Whereas the level of free (i.e., non–protein bound) calcium in blood is normally the principal determinant of PTH secretion, during the course of CKD, several metabolic disturbances also alter the regulation of the secretion of PTH.

Abnormalities of Calcium Metabolism

There are three main body pools of calcium: the bony skeleton (mineral component), the intracellular pool (mostly protein bound), and the extracellular pool (see Chapter 10). The calcium in the extracellular pool is in continuous exchange with that of bone and cells and is altered by diet and excretion. Calcium metabolism depends on the close interaction of two hormonal systems: PTH and vitamin D. Perturbations of both of these systems occur during the course of CKD, with adverse consequences on the skeleton. Total serum calcium tends to decrease during the course of CKD as a result of phosphate retention and decreased production of 1,25-dihydroxyvitamin D (calcitriol) from the kidney, decreased intestinal calcium absorption, and skeletal resistance to the calcemic action of PTH, but the levels of free calcium remain within the normal range in most patients[3] as a result of compensatory hyperparathyroidism. Because calcium is a major regulator of PTH secretion, persistent hypocalcemia is a powerful stimulus for the development of hyperparathyroidism and also contributes to parathyroid growth.

Abnormalities of Phosphate Metabolism

With progressive CKD, phosphate is retained, at least, transiently, by the failing kidney. However, hyperphosphatemia usually does not become evident before CKD stage 4. Until then, compensatory hyperparathyroidism and increases in circulating FGF-23 result in increased phosphaturia, maintaining serum phosphate levels in the normal range.[4]

One mechanism by which phosphate retention may lead to hyperparathyroidism is by a decrease in serum free calcium, which in turn stimulates the secretion of PTH (Fig. 85-4). Thus, a new steady state is achieved in which serum phosphate is restored to normal at the expense of a sustained high level of PTH. This cycle is

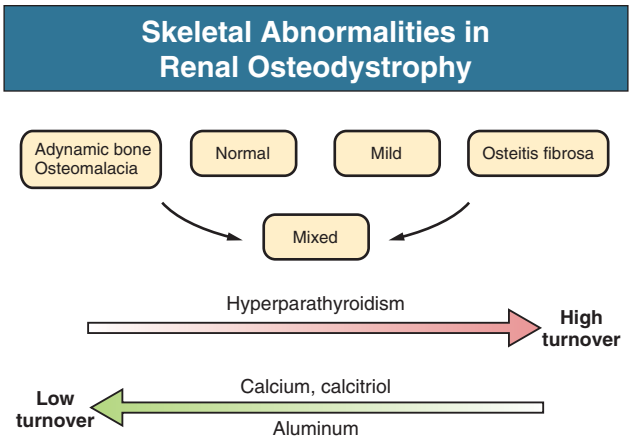

Figure 85-1 The spectrum of renal osteodystrophy. The range of skeletal abnormalities in renal bone disease encompasses syndromes with both high and low bone turnover.

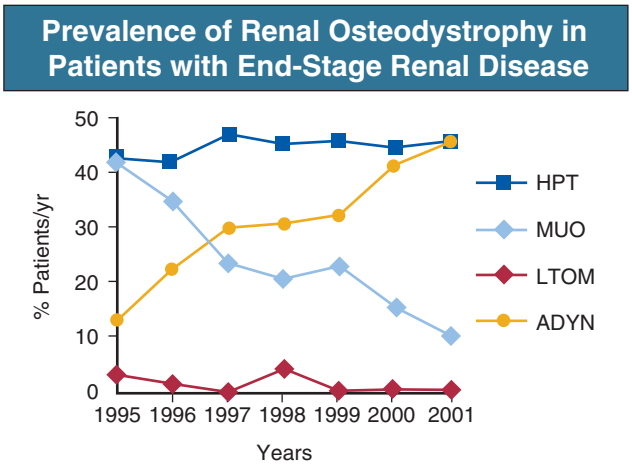

Figure 85-2 Prevalence of renal osteodystrophy in patients with end-stage renal disease. *ADYN,* Adynamic bone disease; *HPT,* high-turnover renal osteodystrophy; *LTOM,* low-turnover osteomalacia; *MUO,* mixed uremic osteodystrophy. *(From reference 40.)*

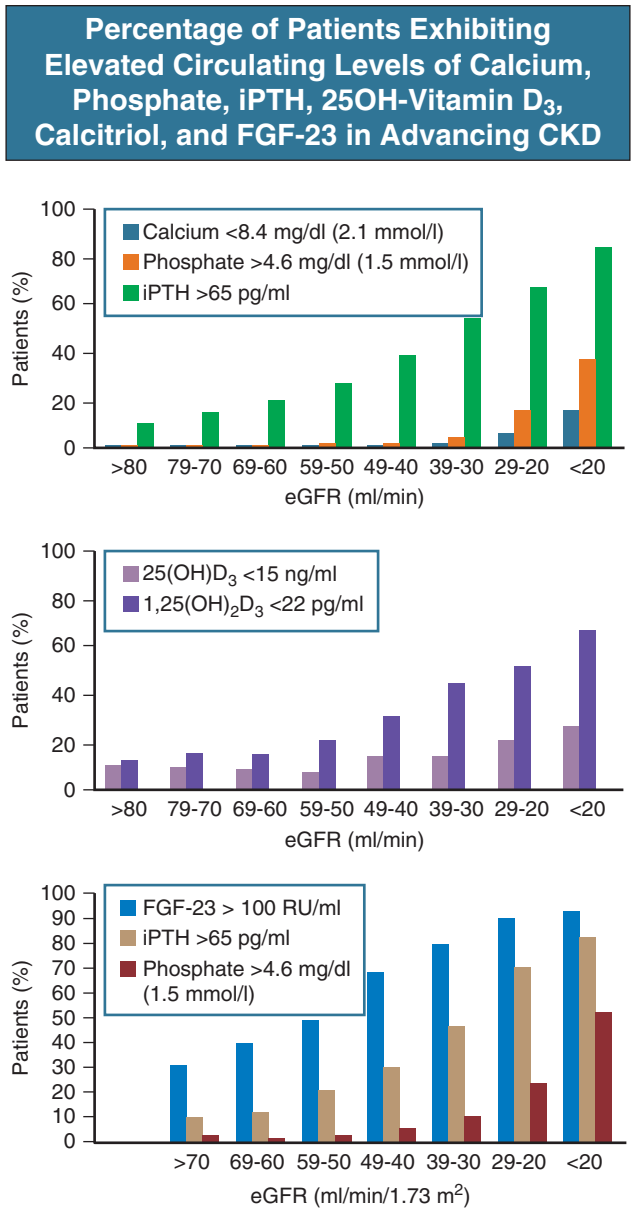

Figure 85-3 Percentage of patients exhibiting elevated circulating levels of calcium, phosphate, iPTH, 25OH-vitamin D_3, calcitriol, and FGF-23 in advancing CKD. In particular in early CKD stages there is wide variability at the individual level, and some patients, for example, may exhibit increased FGF-23 and normal iPTH, whereas others may have elevated iPTH levels with normal FGF-23 or elevations of both. *FGF-23,* Fibroblast growth factor 23; *iPTH,* intact PTH. *(Data from references 65 and 66.)*

repeated as renal function declines until sustained and severe hyperparathyroidism is present. Second, phosphate retention leads to decreased production of calcitriol by the kidney, either directly or by increasing the levels of FGF-23 (which decreases the activity of 1α-hydroxylase). The decrease in calcitriol allows increases in PTH gene transcription by direct action and also decreases intestinal calcium absorption, leading to hypocalcemia, which in turn stimulates PTH secretion. Third, hyperphosphatemia is associated with resistance to the actions of calcitriol in the parathyroid glands, which also favors the development of hyperparathyroidism and also induces resistance to the actions of PTH in bone. Finally, phosphate *per se* appears to affect PTH secretion independently of changes in serum calcium or serum calcitriol.[5,6] Phosphate may also have an effect on parathyroid growth independent of serum calcium.[7,8] Regardless of the mechanism by which phosphate retention causes hyperparathyroidism, restriction of dietary phosphate in proportion to the decrease in glomerular filtration rate (GFR), in experimental animals, can prevent the development of hyperparathyroidism. Current evidence suggests that FGF-23 also acts directly on the parathyroid gland and has inhibitory effects on PTH secretion and parathyroid growth.[9,10] This would suggest that the main effects of FGF-23 on the pathogenesis of hyperparathyroidism appear to be indirect as a result of the potent effect of FGF-23 to decrease calcitriol production. These various actions may explain the association of the levels of FGF-23 with patient outcome.[11]

Abnormalities of Vitamin D Metabolism

The conversion of 25-hydroxyvitamin D to its active metabolite 1,25-dihydroxyvitamin D occurs mainly in the kidney by the enzyme 1α-hydroxylase. Extrarenal production of calcitriol also occurs and contributes to the circulating levels of calcitriol. Renal calcitriol production progressively declines during the course of CKD as a result of several mechanisms (Fig. 85-5).

Calcitriol production is compromised in the setting of CKD by a reduction in 25-hydroxyvitamin D levels[12] and the decrease in GFR,

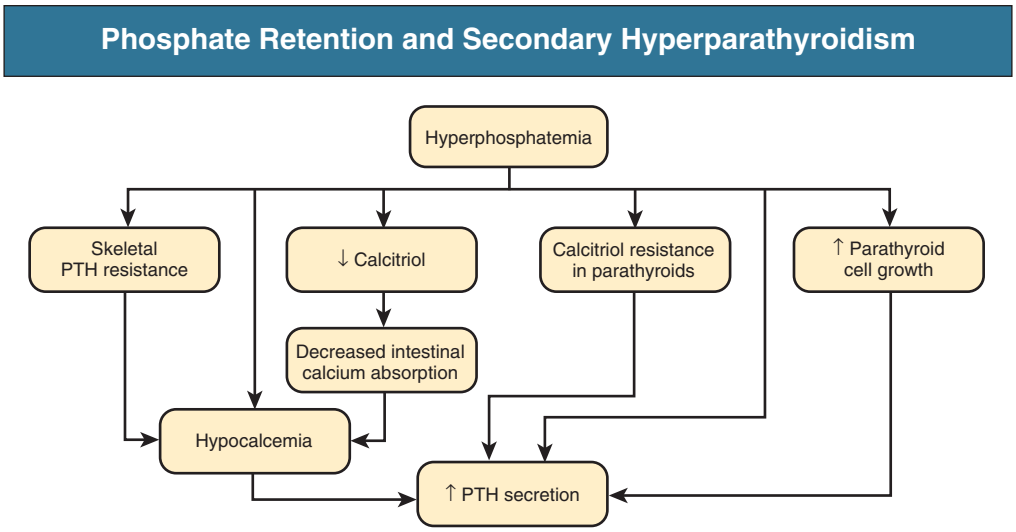

Figure 85-4 Role of phosphate retention in the pathogenesis of secondary hyperparathyroidism. Hyperphosphatemia stimulates parathyroid hormone *(PTH)* secretion indirectly by inducing hypocalcemia, skeletal resistance to PTH, low levels of calcitriol, and calcitriol resistance. Hyperphosphatemia also has direct effects on the parathyroid gland to increase PTH secretion and parathyroid cell growth.

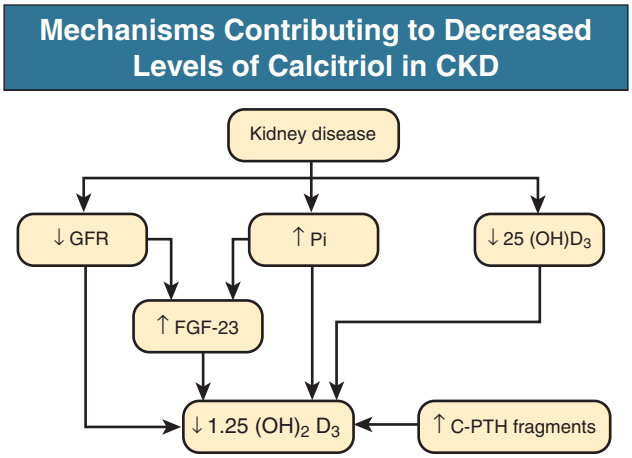

Figure 85-5 Mechanisms contributing to decreased levels of calcitriol in chronic kidney disease (CKD). *C-PTH,* Carboxyl-terminal parathyroid hormone; *FGF-23,* fibroblast growth factor 23; *GFR,* glomerular filtration rate; *Pi,* inorganic phosphate.

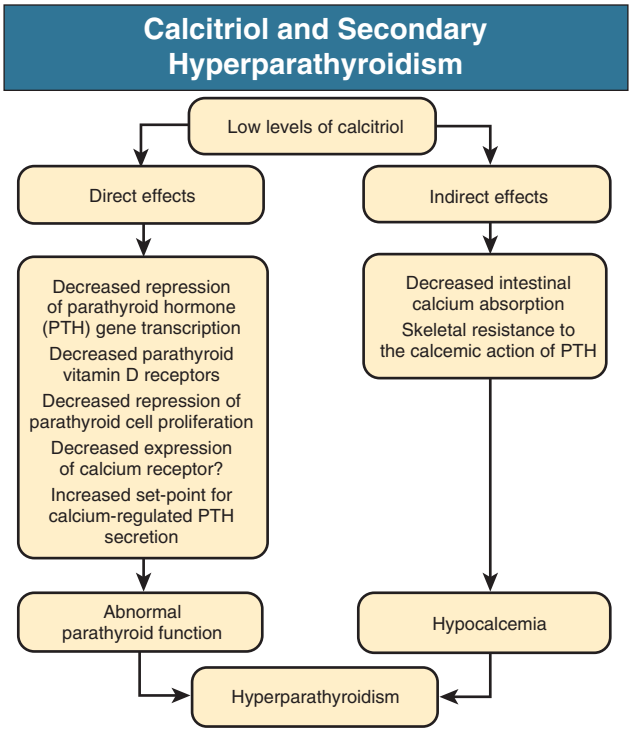

Figure 85-6 Role of low levels of calcitriol in the pathogenesis of secondary hyperparathyroidism.

which further limits the delivery of 25-hydroxyvitamin D to the site of the 1α-hydroxylase in the proximal tubule. Phosphate retention either directly or by inducing an increase in FGF-23 also decreases the activity of 1α-hydroxylase. Finally, it appears that circulating PTH fragments may also directly decrease calcitriol production. The resultant decreased levels of calcitriol contribute to the pathogenesis of hyperparathyroidism by several direct and indirect mechanisms (Fig. 85-6). Low levels of calcitriol directly release the gene for PTH from suppression by the vitamin D receptor and allow increased PTH secretion. In many tissues, vitamin D regulates its own receptor by positive feedback; the vitamin D receptor content is decreased in parathyroid tissue in CKD. Administration of calcitriol has been shown to increase the vitamin D receptor content in the parathyroid glands coincident with the suppression of PTH secretion. Studies *in vitro* have shown that calcitriol is a negative growth regulator of parathyroid cells; therefore, calcitriol deficiency in patients with CKD may facilitate parathyroid cell proliferation. Other direct consequences of low levels of calcitriol that contribute to the pathogenesis of secondary hyperparathyroidism include an increase in the parathyroid set-point for calcium-regulated PTH secretion and possibly a decrease in the expression of calcium receptors.

Low levels of calcitriol may also promote the development of hyperparathyroidism indirectly. First, decreased calcitriol production as renal function decreases can lead to progressive reductions in intestinal absorption of calcium, leading to hypocalcemia and stimulation of PTH release. Second, low levels of calcitriol have been implicated in skeletal resistance to the calcemic actions of PTH, which may also contribute to the development of hyperparathyroidism.

Parathyroid Abnormalities in Chronic Kidney Disease

- Parathyroid gland hyperplasia: diffuse, nodular
- Decreased expression of vitamin D receptors
- Decreased expression of calcium receptors
- Increased set-point of calcium-regulated parathyroid hormone secretion

Box 85-1 Parathyroid abnormalities in chronic kidney disease.

Abnormalities of Parathyroid Gland Function

There are intrinsic abnormalities in parathyroid gland function in the course of CKD in addition to those caused by hypocalcemia, low levels of calcitriol, and skeletal resistance to the actions of PTH (Box 85-1).

Parathyroid hyperplasia is an early finding in CKD. In experimental models, hyperplasia begins within a few days after the induction of CKD and can be prevented by dietary phosphate restriction or by the use of calcimimetic agents.[7,13] Resected parathyroids from patients with severe hyperparathyroidism have nodular areas throughout the gland, which represent monoclonal expansions of parathyroid cells.[14] Within these nodules, there is decreased expression of vitamin D receptors as well as of calcium receptors.[15,16] The decreased expression of calcium receptors renders efforts to therapeutically affect these enlarged hyperplastic glands difficult.

The parathyroid calcium receptor is centrally involved in the regulation of PTH secretion by calcium.[17] Its expression and synthesis are decreased in parathyroid glands from hyperparathyroid patients,[16] leading to altered calcium-regulated PTH secretion. Increased concentrations of calcium are required *in vitro* to suppress PTH release from the parathyroid cells of uremic patients compared with those of normal controls. Thus, the set-point for the concentration of calcium required to decrease PTH release by 50% appears to be increased.

Abnormal Skeletal Response to Parathyroid Hormone

In patients with CKD, there is an impaired response of serum calcium to the administration of PTH and a delay in the recovery from induced hypocalcemia in the presence of larger increments in PTH levels. Thus, in CKD the skeleton is relatively resistant to the calcemic actions of PTH. The resultant decrease in serum calcium levels stimulates PTH secretion and contributes to the pathogenesis of secondary hyperparathyroidism. Factors involved in the skeletal resistance to PTH in CKD include decreased levels of calcitriol, downregulation of the PTH receptor, and phosphate retention. In addition, circulating fragments of PTH, truncated at the *N*-terminus, which still react in the older, second-generation two-site PTH assays, may serve to oppose the calcemic actions of PTH, probably acting at a receptor for the C-terminal region of PTH.[18,19]

CLINICAL MANIFESTATIONS OF HIGH-TURNOVER RENAL OSTEODYSTROPHY

Clinical manifestations of hyperparathyroidism are usually nonspecific and are often preceded by biochemical or imaging abnormalities. Aches and pains are common manifestations, often nonspecific in nature; occur in the lower back, hips, and legs; and are aggravated by weight bearing. Acute, localized bone pain can also manifest and may be suggestive of acute arthritis. Pain around joints may be caused by acute periarthritis, which is associated with periarticular deposition of calcium phosphate crystals, especially in patients with marked hyperphosphatemia. The symptoms may be confused clinically with gout or pseudogout and often respond to nonsteroidal anti-inflammatory drugs (NSAIDs). The gradual onset of muscle weakness is also common in patients with ESRD. Many factors are probably involved in its pathogenesis, including hyperparathyroidism and abnormalities of vitamin D. The arthropathy associated with β_2-microglobulin amyloidosis (see later discussion) should be considered in the differential diagnosis in very-long-term dialysis patients.

Bone deformities may occur in patients with severe hyperparathyroidism, particularly in children. In adults, deformities arise as a consequence of fractures, sometimes induced by brown tumors (see later discussion); the axial skeleton is most commonly affected. This can lead to kyphoscoliosis or chest wall deformities. Slipped epiphysis may occur in children, and frank rachitic features are occasionally evident. Growth retardation is also common in children, and although some improvement has been shown with calcitriol, this has not been the universal finding.

Extraskeletal calcifications are frequently encountered in patients with advanced CKD and are aggravated by persistent elevation of the calcium-phosphate product. Most commonly, vascular calcifications are seen, but calcifications may also occur in other sites, such as the lung, myocardium, and periarticular areas (see Fig. 85-7).

In the skin, hyperparathyroidism can manifest as pruritus (discussed in detail in Chapter 88). Rarely, it can also underlie the development of calciphylaxis, or calcific uremic arteriolopathy (discussed in detail in Chapter 88; see Figs. 88-6 and 88-7).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In addition to the clinical manifestations of renal osteodystrophy, a variety of biochemical and radiographic techniques are helpful to establish the specific diagnosis and to serve as a guide for the initiation and adjustment of therapeutic interventions. Although bone biopsy is not widely used in clinical practice, it remains the gold standard for the diagnosis of renal osteodystrophy.

Serum Biochemistry

The levels of free calcium and phosphate in serum are usually normal in patients with mild to moderate CKD. Usually in stage 4 CKD, the levels of serum calcium tend to fall and hyperphosphatemia manifests. Hypercalcemia may result from the administration of large doses of calcium-containing antacids or the administration of vitamin D metabolites. Patients with severe hyperparathyroid bone disease may develop hypercalcemia. It is important to differentiate among the different causes of hypercalcemia in the setting of CKD (see Chapter 10) because the management will vary greatly according to the cause. Also, the levels of serum calcium and phosphate, when used alone, are not useful in predicting the specific type of bone disease.

Parathyroid Hormone

Measurements of PTH are important for diagnostic purposes and for therapeutic guidance in the management of renal osteodystrophy. With renal impairment, there is accumulation of circulating PTH

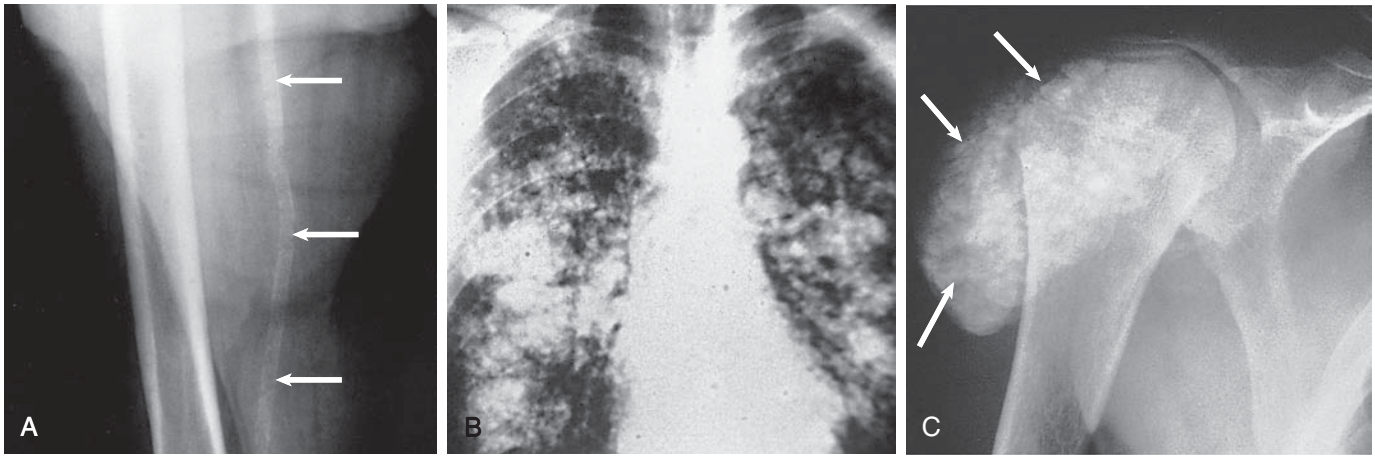

Figure 85-7 Extraskeletal calcification in chronic renal failure. A, Arterial calcification *(arrows).* **B,** Pulmonary calcification. **C,** Periarticular calcification *(arrows).*

fragments, which complicates the interpretation of PTH assays, including the two-site immunometric assays, which were thought to measure "intact" PTH (iPTH). Refinements in PTH assays have demonstrated that these iPTH assays also measure some large fragments of PTH, which are truncated at the *N*-terminus and may have important biologic activity. Although more specific assays for so-called "biointact" PTH (PTH 1-84) have been developed that exclude these fragments from measurement, work continues to define the clinical usefulness of such more specific assays.[20-22] Recent demonstration of the presence of oxidized PTH, which is biologically inactive, in patients with ESRD may further complicate PTH measurements.[23] It is hoped that continued efforts will lead to improved standardization among different PTH assays from various laboratories and various manufacturers of assay reagents. With existing iPTH assays (upper limit of the reference range, approximately 60 pg/ml), only values at the extremes are useful in the noninvasive diagnosis of renal osteodystrophy. In dialysis patients, iPTH levels above approximately 600 pg/ml are characteristic of patients with osteitis fibrosa. It is well accepted that there is an element of skeletal resistance to PTH in patients with CKD; therefore supranormal levels of PTH appear to be required to maintain normal bone turnover. Serial measurements of PTH are useful in the initial evaluation of patients with renal bone disease and are essential during the management of these disorders to assess response to therapy and to avoid overtreatment and undertreatment because either can have detrimental effects on bone histology. There are marked differences between commercial PTH assay results so that precise recommendations of desired ranges cannot reliably be provided.[24]

Vitamin D Metabolites

The levels of calcitriol in patients with CKD are not helpful in differentiating the histologic lesions of renal osteodystrophy. Measurements of calcitriol are not used routinely for diagnostic purposes unless extrarenal production of this metabolite is suspected, as in granulomatous disorders (see Chapter 10).

Vitamin D deficiency in CKD rarely results in osteomalacia in the United States and Europe but may contribute to hyperparathyroidism. In patients with CKD with proteinuria, there is loss of vitamin D–binding protein in the urine, which may result in decreased levels of 25-hydroxyvitamin D. Vitamin D deficiency may be encountered in patients with limited sun exposure, in those with intestinal malabsorption or malnutrition, and in susceptible racial groups, particularly Indo-Asians. Assessment of vitamin D nutrition is by measurement of serum 25-hydroxyvitamin D_3.

Markers of Bone Formation and Bone Resorption

Levels of circulating alkaline phosphatase offer an approximate index of osteoblast activity in patients with CKD. High levels are commonly present in hyperparathyroid bone disease. The discriminatory power of alkaline phosphatase measurements is enhanced by measurement of bone-specific alkaline phosphatase (BAP) isoenzyme and in particular in conjunction with PTH values. Serial measurements of alkaline phosphatase may be useful in assessing the progression of bone disease. Osteocalcin is another marker of osteoblastic activity, but it is not superior to alkaline phosphatase. Tartrate-resistant acid phosphatase and collagen degradation products are both markers of osteoclastic activity but are considered investigational at present.

Radiology of the Skeleton

Routine x-ray examination of the skeleton is relatively insensitive for the diagnosis of renal osteodystrophy, and radiographs can appear virtually normal in patients with severe histologic evidence of renal bone disease. However, subperiosteal erosions are often present in severe secondary hyperparathyroidism, detected in the hands (Fig. 85-8), clavicles, and pelvis. Skull radiographs may show focal radiolucencies and a ground-glass appearance, known as "pepper pot" skull. Osteosclerosis of the vertebrae is responsible for the "rugger-jersey" appearance of the spine (Fig. 85-9). Very rarely, brown tumors, focal collections of giant cells and typical of severe hyperparathyroidism, are seen as well-demarcated radiolucent zones in long bones, clavicles, and digits. They may be confused with osteolytic metastases. Looser zones or pseudofractures are characteristic of osteomalacia. Routine skeletal radiographs are not indicated unless there are symptoms.

Measurements of Bone Density

Dual-energy x-ray absorptiometry is widely used to assess bone density. However, there is no clear usefulness for this technique in the assessment of renal bone disease (see later discussion) because bone density measurements do not correlate with bone histology in

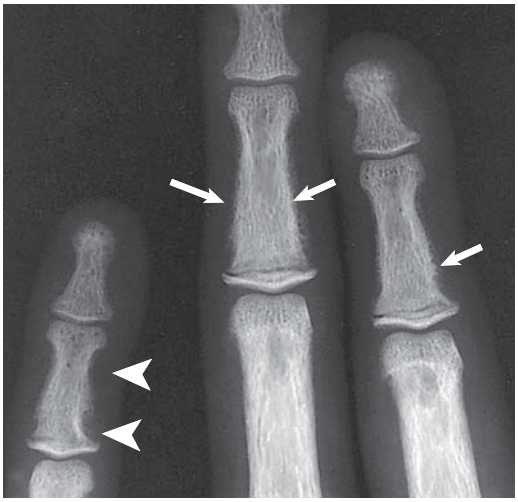

Figure 85-8 Subperiosteal erosions in hyperparathyroidism. Severe subperiosteal erosions as a manifestation of hyperparathyroidism *(arrows)*. The extensive scalloped appearance of the middle phalanx on the left *(arrowheads)* represents a small brown tumor.

Figure 85-9 "Rugger-jersey spine" in hyperparathyroidism. Vertebral bodies show the increased density of the ground plates and central radiolucency, which gives the striped appearance of a rugger jersey.

renal bone disease. Vascular and soft tissue calcifications may contribute to errors in bone density measurements.

Bone Biopsy

Biopsy of bone and the microscopic analysis of undercalcified sections after double tetracycline labeling provide definitive and quantitative diagnosis of renal bone disease.[25] To standardize reports on bone histology, the Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD work group proposed the TMV classification, an assessment of turnover (T), mineralization (M), and bone volume (V).[1] Bone mineralization is assessed by the administration of two different tetracyclines spaced apart (e.g., tetracycline 500 mg three times daily for 2 days, followed by a 10-day interval, then demeclocycline 300 mg three times daily for 3 days) and biopsy 4 days later; the quantitation of bone mineralization rate is achieved by measuring the distance between the two fluorescent tetracycline bands.

Bone biopsy is not routinely performed in clinical practice because of the invasive nature of the procedure. Although noninvasive testing is useful to distinguish normal from high bone turnover, there is considerable overlap, and therefore biopsy might be required for definitive diagnosis when biochemistry is not conclusive (e.g., PTH in recommended range but bone alkaline phosphatase elevated, hypercalcemia with PTH only modestly elevated, or bone pain).

Osteitis fibrosa (hyperparathyroid bone disease) is characterized by increased bone turnover, increased number and activity of osteoblasts and osteoclasts, and variable amounts of peritrabecular fibrosis (Fig. 85-10, *A*). Osteoid may be increased but usually has a woven pattern distinct from the normal lamellar appearance. Osteomalacia is characterized by increased osteoid seam width, increase in the trabecular surface covered with osteoid, and decreased bone mineralization as assessed by tetracycline labeling (Fig. 85-10, *B*). The presence of aluminum can be detected on the mineralization front by specific staining (Fig. 85-10, *C*). Aluminum-related bone disease is defined by aluminum staining exceeding 15% of the trabecular surface and a bone formation rate of less than 220 mm^2/day. Features of osteitis fibrosa may occur together with features of osteomalacia; the combination is termed *mixed renal osteodystrophy.*

TREATMENT OF HIGH-TURNOVER BONE DISEASE

Prevention is the primary goal in the management of renal osteodystrophy. Therapy for hyperparathyroidism should ideally be initiated in CKD stage 3 so that parathyroid gland hyperplasia can be prevented. Because renal osteodystrophy is usually asymptomatic early in the course of CKD, attention is often not paid to secondary hyperparathyroidism. By the time CKD is advanced, patients may have already developed significant skeletal abnormalities or nodular parathyroid hyperplasia, and more aggressive therapy is required to prevent the long-term consequences of renal bone disease. The successful approach to the prevention and management of this disorder involves the integration of a variety of measures directed toward the suppression of PTH secretion and the prevention of parathyroid hyperplasia.

Prevention of Hypocalcemia

Hypocalcemia, if present, should be corrected because it is a potent stimulus for PTH secretion. In patients with hypoalbuminemia, free calcium should be measured. The initial approach to therapy for hypocalcemia in patients with mild to moderate CKD is the administration of calcium supplements such as calcium carbonate, taken between meals with increasing doses as required. Assessment of vitamin D status should be undertaken by measurement of 25-hydroxyvitamin D, and this should be corrected if it is below 30 ng/ml. The determination of 1,25-dihydroxyvitamin D levels is not helpful in this respect, given its 8-hour half-life. Assessment of efficacy of therapy is by follow-up determinations of serum calcium and PTH. Adjunctive therapy with active vitamin D sterols should be considered if hyperparathyroidism or hypocalcemia persists. In patients with ESRD, active vitamin D sterols are often required. In dialysis patients, the goal is to achieve levels of iPTH that are approximately two to nine times above the upper limit of the assay used.[26] Also, iPTH trends over time should be closely monitored. In CKD stages 3 to 5, progressive rises in iPTH above the normal range should be abrogated by correction of hypocalcemia, vitamin D deficiency, and hyperphosphatemia.

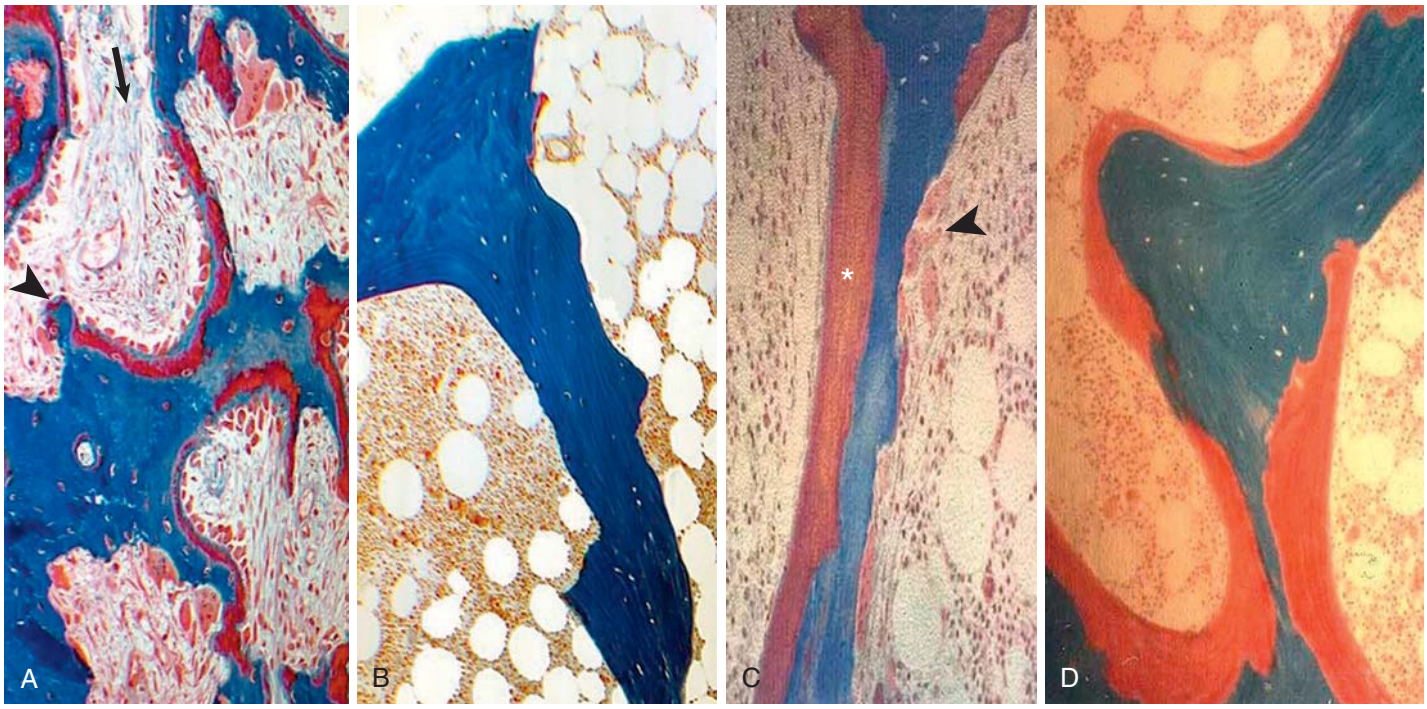

Figure 85-10 Bone histology in renal osteodystrophy. A, Osteitis fibrosa: Characteristic manifestations of severe hyperparathyroidism with increased osteoclast and osteoblast activity and peritrabecular fibrosis (stained blue; *arrow*). **B,** Adynamic bone disease: There is no cellular activity along the bone surface and no osteoid visible. **C,** *(arrowhead)* Mixed renal osteodystrophy: There is evidence of active osteoclasts on one bone surface *(arrowhead)* and evidence of thickened osteoid (stained red; *asterisk*). Indicating a mineralization defect on the other. **D,** Osteomalacia: Marked excess of unmineralized osteoid *(stained red)* surrounding the mineralized bone *(stained blue)*.

Control of Phosphate

Control of phosphate is the cornerstone of effective management of secondary hyperparathyroidism. In mild to moderate CKD, a normal serum phosphate concentration does not necessarily indicate normal parathyroid status, and except for the late stages of CKD, normophosphatemia may be maintained at the expense of elevated serum PTH and FGF23. Therefore, efforts to control phosphate, including dietary phosphate restriction and the use of phosphate binders, should not be delayed until frank hyperphosphatemia develops.

Dietary Phosphate Restriction

In experimental animals with mild CKD, dietary phosphate restriction can prevent excessive PTH synthesis and secretion, as well as parathyroid cell proliferation, independently of changes in serum calcium and calcitriol concentrations. Accordingly, restriction of dietary phosphate intake might be considered in patients with CKD stage 2 or 3. The input of a dietician is essential. Protein restriction and avoidance of dairy products but in particular processed foods containing high amounts of added phosphate are the mainstays of the regimen. In addition to reducing CKD progression, phosphate-protein restriction has been shown to increase the serum levels of calcitriol in patients with mild to moderate CKD. Restriction of phosphate by severe dietary protein restriction should be avoided because it may lead to protein-calorie malnutrition. Restriction of the daily dietary protein intake to 0.8 g/kg should be sufficient to provide phosphate restriction without the risk for malnutrition.

Phosphate Binders

Whereas dietary phosphate restriction is usually sufficient in early CKD, the control of phosphate becomes more difficult as renal function deteriorates. It then becomes necessary to also use agents that bind ingested phosphate in the intestinal lumen to limit its absorption. Compounds used for this purpose include calcium-containing antacids, magnesium salts, aluminum hydroxide, and, in recent years, non–calcium-containing, non–aluminum-containing phosphate binders (Fig. 85-11).

Aluminum-containing antacids are effective phosphate binders, but in patients with CKD, their use can no longer be recommended because of the risk for aluminum toxicity. There are certain circumstances that limit the use of calcium-containing phosphate binders, such as hypercalcemia, extensive vascular calcification, and calciphylaxis. In such patients, aluminum-containing antacids may be used for a short period, but the dose should be restricted to no more than 40 to 45 mg/kg/day, and frequent reassessments should be made to institute alternative therapy as soon as possible. Ingestion of aluminum-containing antacids together with foods containing citric acid (such as fruit juices and foods with sodium, calcium, or potassium citrate) may significantly increase aluminum absorption and therefore should be avoided.

Calcium carbonate or calcium acetate taken with meals effectively binds phosphates and limits their absorption. They are effective phosphate binders in 60% to 70% of patients on hemodialysis. The doses required to prevent hyperphosphatemia may vary according to the patient's compliance with dietary phosphate restriction as well as the CKD stage. Hypercalcemia and calcium loading are the major potentially serious side effects. Calcium citrate potentiates aluminum uptake and should be avoided in CKD. Current recommendations are to limit the ingestion of elementary calcium to 1500 mg/day. Consideration of overall calcium balance may be important with the use of calcium-containing phosphate binders.

Magnesium salts are also effective phosphate binders for patients who become hypercalcemic with calcium-containing phosphate binders, but they should be administered with caution in CKD patients not on dialysis because hypermagnesemia may have serious adverse effects. In patients on dialysis, magnesium carbonate (200 to 500 mg elemental magnesium per day) has been used successfully,

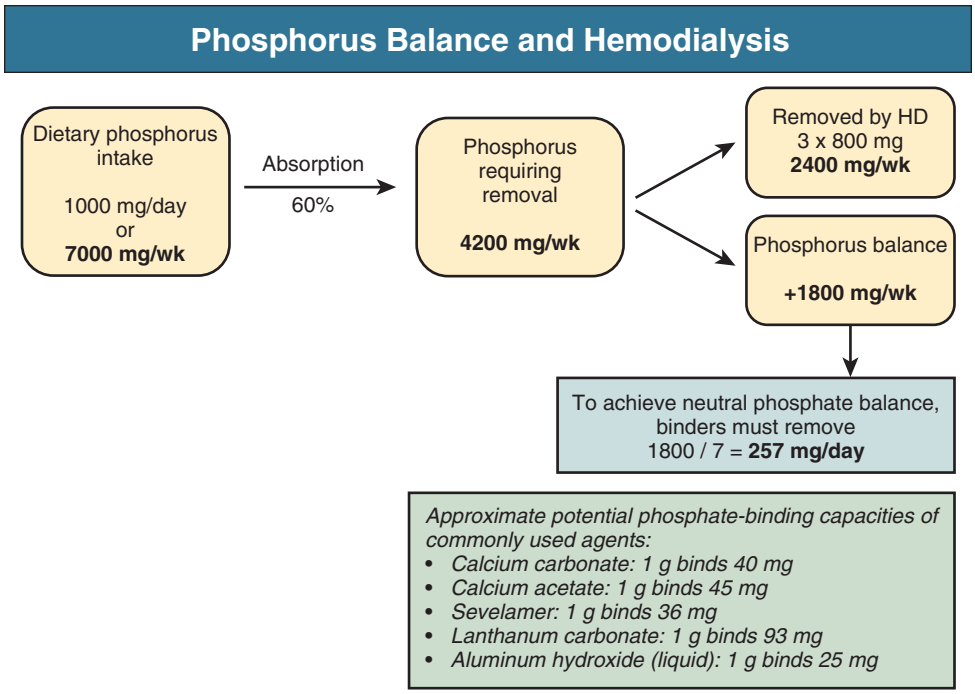

Figure 85-11 **Phosphate balance and phosphate binders used in hemodialysis patients.**

with prevention of hypermagnesemia through a reduction in dialysate magnesium concentration. The use of magnesium carbonate also allows reduction of the dose of calcium carbonate required by about half, but its use is frequently complicated by diarrhea.

The risks for hypercalcemia because of the high calcium load of calcium-containing phosphate binders can be prevented by the use of nonabsorbable polymers. Sevelamer hydrochloride in a dose range of 2.4 to 4.8 g daily provides effective phosphate control without hypercalcemia and also produces a significant reduction in total and low-density lipoprotein cholesterol. Agents such as sevelamer may offer great advantage over calcium-containing phosphate binders in terms of limiting the calcium load, although they are significantly more expensive. Studies have suggested that the use of sevelamer is associated with decreased progression of vascular calcification.[27,28] Sevelamer hydrochloride has largely been replaced by sevelamer carbonate, which has similar properties.[29] Sevelamer may be combined with both calcium- and magnesium-containing phosphate binders if necessary. Lanthanum carbonate also is an effective phosphate binder.[30] No significant toxicity has been observed, although some lanthanum appears to accumulate in bone and liver.[31] Finally, iron-containing phosphate binders have just entered the market.

Use of Vitamin D Metabolites

Calcitriol and other 1α-hydroxylated vitamin D sterols, such as 1α-hydroxyvitamin D_3 (alfacalcidol), 1α-hydroxyvitamin D_2 (doxercalciferol), and 19-nor-1α,25-dihydroxyvitamin D_2 (paricalcitol), are effective in the control of secondary hyperparathyroidism. Calcitriol lowers PTH levels and improves bone histology. In patients with very high levels of PTH and markedly enlarged glands with severe nodular hyperplasia, the effectiveness of vitamin D metabolites may be limited because the levels of vitamin D receptor are low in such tissue. Accordingly, it would appear rational to initiate treatment of secondary hyperparathyroidism with vitamin D metabolites early in CKD when the parathyroid glands are more sensitive to such therapy and thereby prevent the progression to a refractory stage. A beneficial effect of vitamin D metabolite therapy in the treatment of secondary hyperparathyroidism in patients with mild to moderate CKD has been shown, but the concern with initiation of vitamin D therapy at this stage of CKD is acceleration of the progression of renal disease should hypercalcemia occur. Because of the effect of calcitriol to increase intestinal phosphate absorption, hyperphosphatemia and elevations in calcium-phosphate product may predispose patients to the development of metastatic calcification; however, it appears that doses of 1α-hydroxyvitamin D_3 or calcitriol up to 0.5 μg/day are not commonly associated with hypercalcemia, hyperphosphatemia, or worsening renal impairment. Another concern with the use of vitamin D metabolites before dialysis is that oversuppression of hyperparathyroidism may increase the risk for adynamic bone. Accordingly, vitamin D therapy should be monitored carefully and should not be instituted without documentation of hyperparathyroidism, correction of 25-hydroxyvitamin D deficiency, and prior control of serum phosphate.

In patients with ESRD, indications for therapy with vitamin D metabolites are better defined; however, hypercalcemia and aggravation of hyperphosphatemia are frequent complications of therapy. Vitamin D metabolites are increasingly used as oral or intravenous pulses given intermittently (e.g., three times weekly) rather than as continuous oral therapy. In recent years, analogues of calcitriol that have less calcemic activity than the parent compound and yet retain the ability to suppress PTH release *in vivo* have been developed. Such analogues of vitamin D studied in patients with ESRD are 22-oxacalcitriol (OCT), 1α-hydroxyvitamin D_2, and 19-nor-1α,25-dihydroxyvitamin D2 (paricalcitol).[32-34] Direct comparisons between these compounds are not available. It is likely that a wider therapeutic window may be offered by these analogues. Several but not all studies have suggested that there may be a survival advantage associated with active vitamin D administration in patients with CKD as well as with ESRD.[35,36]

Role of Calcimimetics

An additional approach to the treatment of hyperparathyroidism in ESRD is the use of a calcimimetic agent, such as cinacalcet, which targets the calcium-sensing receptor and increases its sensitivity to calcium. In dialysis patients, cinacalcet results in a significant fall in PTH levels and when administered daily can facilitate the control of hyperparathyroidism. The addition of cinacalcet to standard therapy in patients with iPTH serum levels exceeding 300 pg/ml while receiving standard therapy allowed significantly more dialysis patients to achieve guideline targets for calcium, phosphate, and iPTH.[37] Cinacalcet is especially useful in patients with marginal or frank hypercalcemia or with hyperphosphatemia and can be used in conjunction with other therapies. Central side effects include hypocalcemia and nausea and vomiting; the latter can be somewhat improved by administering cinacalcet at night. Studies investigating the effect of cinacalcet on progression of vascular calcification demonstrate that progression of cardiovascular calcification may be attenuated.[38] A large randomized controlled trial—Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE)—to examine the effect of cinacalcet therapy on cardiovascular events and survival in hemodialysis patients with secondary hyperparathyroidism was nondefinitive because of, at least in part, significant migration from the control arm to commercial cinacalcet and an age difference between the two arms, whereby the cinacalcet patients were older on average and thus at higher cardiovascular risk.[39] In that trial, however, cinacalcet significantly reduced rates of parathyroidectomies and of calciphylaxis.[39] In CKD patients not on dialysis, the use of calcimimetics is accompanied by significant phosphate retention and is currently not recommended.

Role of Parathyroidectomy

Although the strategies discussed previously are effective for the control of hyperparathyroidism in many patients, there are occasions when these steps fail or are contraindicated, and surgical removal of the parathyroids should be considered (Box 85-2). Parathyroidectomy is indicated for patients with severe hyperparathyroidism that cannot be controlled medically (phosphate binders, vitamin D sterols, or calcimimetic). Severe hyperphosphatemia in these patients precludes the use of vitamin D metabolites because of the risk for metastatic calcification. Some control of iPTH levels may be obtained with calcimimetics, but even these compounds may fail in severe hyperparathyroidism because of downregulated calcium-sensing receptors in the parathyroid glands. Some patients with severe hyperparathyroidism may become hypercalcemic in the absence of calcitriol therapy; consequently, calcitriol and calcium-containing phosphate binders cannot be administered. In this circumstance, calcimimetic and non–calcium-containing phosphate binders should be administered. It is important to be certain that hypercalcemia represents severe hyperparathyroidism and is not caused by adynamic bone or other disease. For hypercalcemia to occur because of hyperparathyroidism in CKD, the levels of iPTH generally exceed 1000 pg/ml, and BAP is usually elevated. Surgical parathyroidectomy might also be considered in patients with very severe hyperparathyroidism who may receive a renal transplant in the near future, particularly if they are female and have significant osteopenia. Parathyroidectomy in these patients can help avoid posttransplantation hypercalcemia and hypophosphatemia (caused by PTH-induced phosphaturia) as well as osteopenia. By avoiding hypercalcemia, this may lead to improved graft function and possibly to less intragraft calcification. Parathyroidectomy might also be considered in patients with severe hyperparathyroidism who have evidence of metastatic calcification. The development of calciphylaxis is an urgent indication for parathyroidectomy if PTH levels are elevated (see Chapter 84). Before parathyroidectomy, consideration should also be given to the possibility of coexisting aluminum accumulation, with deferoxamine testing and bone biopsy performed if necessary, because this might predispose to osteomalacia after parathyroidectomy.

Indications for Parathyroidectomy

- Severe hyperparathyroidism
  - With persistent hyperphosphatemia
  - Unresponsive to calcitriol and calcium
  - With hypercalcemia
  - With intolerance or unresponsiveness to calcimimetics
  - In renal transplantation candidate
  - With evidence of metastatic calcification
- Calciphylaxis with evidence of hyperparathyroidism
- Severe pruritus, only if additional evidence of hyperparathyroidism

Box 85-2 Indications for parathyroidectomy.

The choice of surgical procedure for parathyroidectomy has been controversial. The most commonly used procedures are subtotal removal of the parathyroids and total removal of the parathyroids with reimplantation of parathyroid tissue in the forearm. Recurrence of hyperparathyroidism occurs in about 10% of patients. Total parathyroidectomy alone is less commonly performed; although this is an appropriate procedure for patients remaining on dialysis, there is concern that hypoparathyroidism after a renal transplantation may be a disadvantage of this approach if there is no residual parathyroid tissue. Unregulated tumor-like growth of parathyroid tissue implants has been described and may be related to the monoclonal nature of the nodular hyperplasia of severe hyperparathyroidism. Total parathyroidectomy with forearm implantation (our preference) or subtotal parathyroidectomy in the neck, marking remaining tissue with clips, may be performed.

Recurrence of hyperparathyroidism may respond to further medical therapy, but more surgery to remove the forearm implant or further neck exploration to search for additional glands is often necessary and may be guided by parathyroid imaging.

Synthesis of Therapeutic Strategies

The general recommendations for the prevention and therapy of renal osteodystrophy are summarized in Figure 85-12, in which therapeutic maneuvers are stratified according to the degree of CKD.

Therapy should be initiated if possible in stage 2 or 3 CKD (GFR, 30 to 90 ml/min), and dietary phosphate intake may be restricted once patients enter CKD stage 3. Levels of iPTH should be measured; if elevated above the normal range, the levels of 25-hydroxyvitamin D should be measured and corrected if less than 30 ng/ml. If hyperparathyroidism persists, calcium-based or other phosphate binders may be initiated. As CKD progresses within stage 3, dietary phosphate restriction should be continued or intensified, and the doses of calcium-containing phosphate binders should be adjusted on the basis of serial measurements of iPTH, with careful attention to avoid hypercalcemia or excessive calcium load. Acidosis, if present, should be treated with oral sodium bicarbonate because persistent acidosis has deleterious effects on the skeleton. The additional sodium load may require further salt restriction or increases in diuretics. Aluminum-based phosphate binders should be avoided. If hyperparathyroidism (iPTH > approximately 2-3 times above the upper normal range of the assay) persists despite these measures,

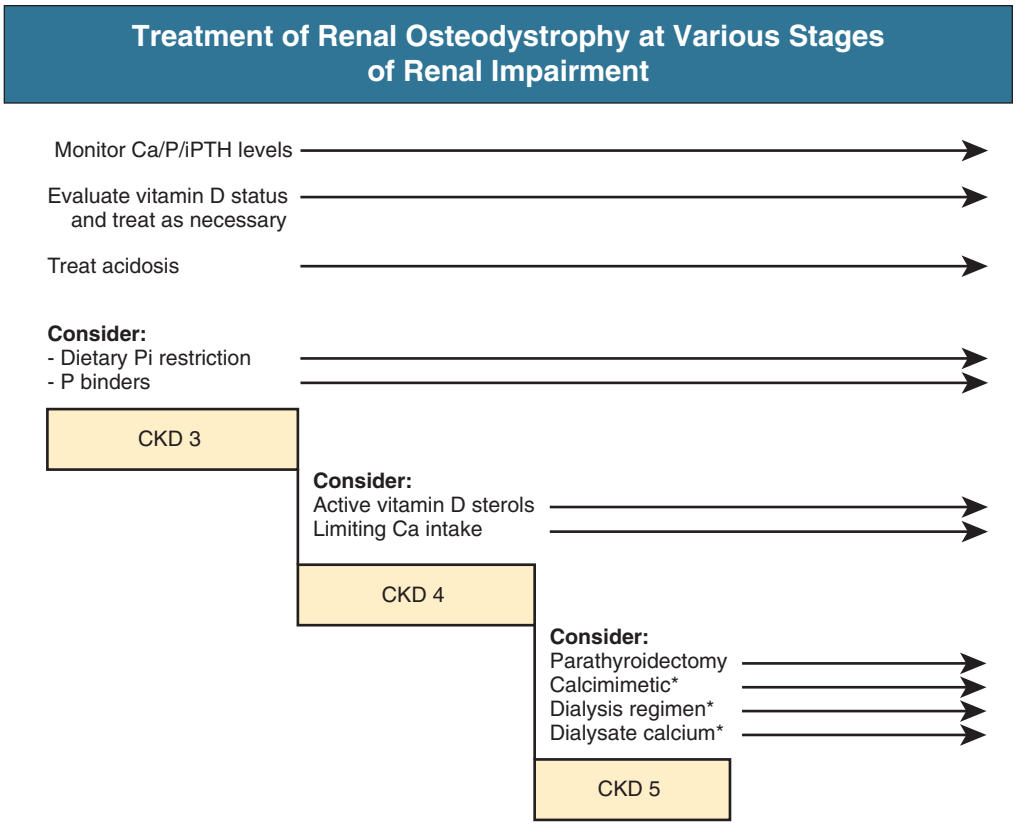

Figure 85-12 Treatment of renal osteodystrophy at various stages of renal impairment. *, Consider in CDK5D (i.e., dialysis dependent) only; *Ca,* calcium; *CKD,* chronic kidney disease; *iPTH,* intact parathyroid hormone; *P,* phosphate; *Pi,* inorganic phosphate. *(Modified from reference 67.)*

consideration should be given to the addition of calcitriol (0.25 to 0.5 µg/day), vitamin D analogues, or vitamin D prohormones to the regimen. Such therapy should be monitored carefully to avoid hypercalcemia and acceleration of progression of CKD.

In CKD stages 4 and 5, the preceding therapies may need to be intensified, and larger amounts of phosphate binders may be required to avoid hyperphosphatemia. The use of aluminum-containing phosphate binders is particularly undesirable at this stage in view of the increased risk for aluminum accumulation with worsening renal function. In patients on dialysis, calcitriol therapy can be intensified, with attention to the serum levels of calcium and phosphate and monitoring of iPTH levels. In CKD stage 5, iPTH levels should be maintained approximately two to nine times above the upper limit of the assay used to maintain normal bone turnover.[26] Calcitriol may be administered orally either daily or intermittently (pulse therapy) or administered intravenously to patients on hemodialysis. During therapy with calcitriol, it is imperative to ensure that serum phosphate remains controlled and that elevations of serum calcium do not occur to prevent metastatic calcification. Vitamin D analogues, which are less calcemic and phosphatemic than calcitriol and yet retain the ability to suppress the levels of PTH, may be useful. The calcimimetic cinacalcet provides additional effective control of hyperparathyroidism in patients with ESRD and may be used alone or in combination with the other strategies if iPTH levels do not fall into the target range. Parathyroidectomy needs to be considered in selected circumstances. Bone biopsy may be indicated in selected patients, particularly if aluminum overload is suspected. Aluminum overload may require chelation therapy with deferoxamine in selected circumstances, especially if it is symptomatic, but in most patients the prevention of further aluminum exposure is sufficient to allow a gradual reduction in the serum levels of aluminum. During therapy with potent vitamin D metabolites, attention should be given to the dialysate calcium concentrations because high concentrations may aggravate hypercalcemia. However, the increasingly frequent use of lower dialysate calcium levels, such as 1.25 mmol/l, requires careful monitoring of the patient to ensure compliance with calcium-containing phosphate binders and vitamin D metabolites to avoid progressive negative calcium balance. Dialysate calcium should not be taken outside the range of 1.25 to 1.75 mmol/l and, when possible, should be individually prescribed.

LOW-TURNOVER RENAL BONE DISEASE

Adynamic bone disease describes the morphologic consequences of low-turnover osteopathy in CKD. As CKD progresses, high-turnover renal osteodystrophy initially develops as an adaptive response to counteract the increasing skeletal PTH resistance and phosphate overload. ABD probably results from too rigorous suppression of this adaptive response. ABD is increasingly important in CKD-MBD because of the high percentage of affected individuals (>40% in CKD stage 5) and because of its association with cardiovascular calcification and mortality.[40,41] Furthermore, fracture incidence is estimated to be twice as high in individuals with low than in those with high bone turnover. ABD prevalence is markedly increasing in bone biopsy registries of dialysis patients, which may relate to the increasing prevalence of its central risk factors, namely, advanced age and diabetes mellitus. Peritoneal dialysis also represents a risk factor, possibly because of a continuous exposure of the patient to high dialysate calcium as opposed to hemodialysis, in which calcium exposure is cyclic.

Pathogenesis of Adynamic Bone Disease

As pointed out earlier, the bone develops a relative resistance of the PTH-1 receptor to its ligand PTH as CKD progresses. Therefore,

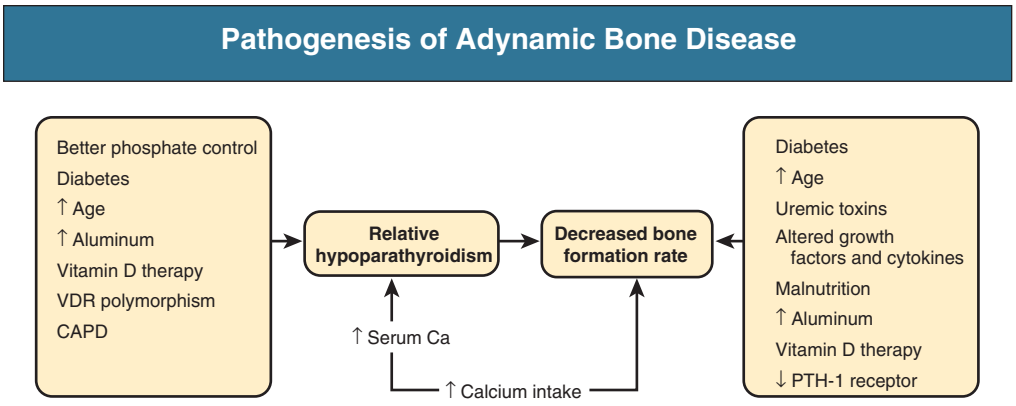

Figure 85-13 Pathogenesis of adynamic bone disease. *Ca,* Calcium; *CAPD,* continuous ambulatory peritoneal dialysis; *PTH,* parathyroid hormone; *VDR,* vitamin D receptor. *(Modified from reference 68.)*

PTH levels above the normal range are required to maintain adequate bone turnover. Unfortunately, there are no definite ranges of elevated PTH levels that can reliably differentiate an adaptive response (normal bone turnover) from a maladaptive response (increased bone turnover) because PTH resistance individually varies and because it depends on the stage of CKD. Accordingly, ABD is a consequence of inadequately low PTH levels, which cause suppression or cessation of both osteoblast and osteoclast activities, resulting in a reduced bone formation rate and low bone mass. Iatrogenic oversuppression of PTH in CKD mostly results from high-dose active vitamin D metabolite treatment, from calcium loading (high doses of calcium-containing phosphate binders, high dialysate calcium concentration), or after parathyroidectomy. The effects of intensified calcimimetic treatment on bone turnover have recently been prospectively evaluated in hemodialysis patients (Bone Histomorphometry Assessment for Incident Dialysis Patients with Secondary Hyperparathyroidism of End Stage Renal Disease [BONAFIDE]), but final results are not available yet, and patients in this cohort had significant high-turnover osteopathy at baseline (average iPTH >1200 pg/ml). Finally, diabetes, uremic toxins, malnutrition, and a disproportionate appearance of C-terminal PTH fragments may be additional factors favoring a state of low bone turnover (Fig. 85-13).

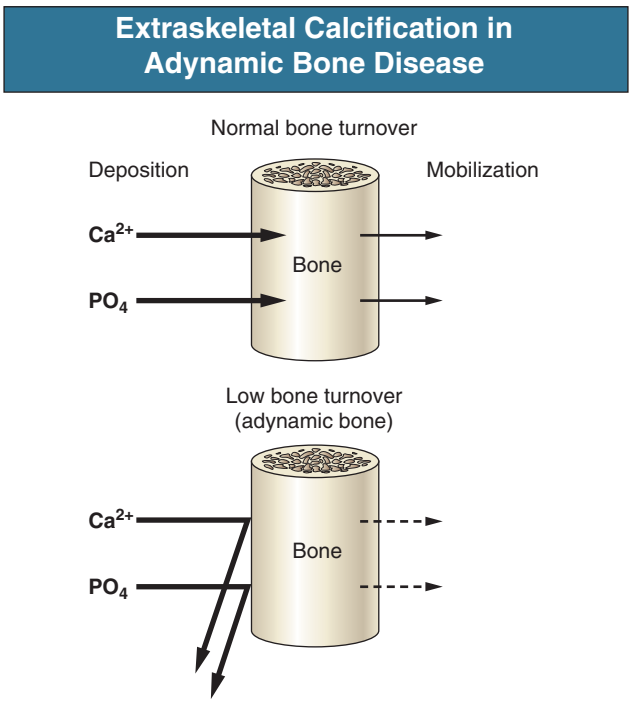

Figure 85-14 Bone turnover in adynamic bone disease. Reduced bone turnover leads to increased extraskeletal calcification. *Ca^{2+},* Calcium ion; *PO_4,* phosphate.

Diagnosis and Differential Diagnosis

Serum Biochemistry

Low iPTH levels (<100 pg/ml) are almost always indicative of low bone turnover in CKD stage 5D. However, histologically proven ABD may occur in many dialysis patients with iPTH levels of up to 300 pg/ml and, in exceptions, of up to 600 pg/ml.[42,43] Therefore, PTH levels alone are not a sensitive biomarker of ABD. Serum levels or activities of alkaline phosphatase or BAP are usually normal or low; downward trends may indicate the development of ABD. Serum calcium and phosphate can be normal or elevated, dependent on the choices of co-treatment (phosphate binders, vitamin D metabolites) and on the nutritional status. Particularly in instances of calcium and phosphate loading, hypercalcemia and hyperphosphatemia may be pronounced because adynamic bone is unable to buffer calcium and phosphate loads by osseous deposition (Fig. 85-14).

In CKD stages 3 and 4, there are uncertainties with regard to the diagnosis of ABD and its clinical consequences. It is unclear which PTH levels are required to maintain adequate bone turnover in these stages. It seems reasonable to correct vitamin D deficiency, hyperphosphatemia, and hypocalcemia when PTH levels start to rise, but beyond that, no firm recommendations can be given at this time.

Bone Biopsy

The gold standard for diagnosis of ABD is bone biopsy. According to the TMV classification (see earlier discussion),[1] ABD is characterized by low turnover, normal (or high secondary) mineralization, and low bone (osteoid) volume. The individual indication to perform bone biopsy should be considered in symptomatic patients on the basis of inconsistencies of biochemical parameters associated with unexplained fractures, bone pain, progressive extraosseous calcifications, or hypercalcemia. The KDIGO initiative recently investigated more than 600 bone biopsies (South America, Portugal, Turkey) and concomitant serum samples to identify biomarker patterns that may allow noninvasive testing of bone turnover status. These data are still unpublished, but preliminary reports suggested a predominance of ABD that was quite strongly associated with low-normal to low BAP levels. Aluminum toxicity is a relevant differential diagnosis versus ABD. Thus, if the patient's history suggests significant aluminum exposure, aluminum bone deposition should be excluded by specific staining.

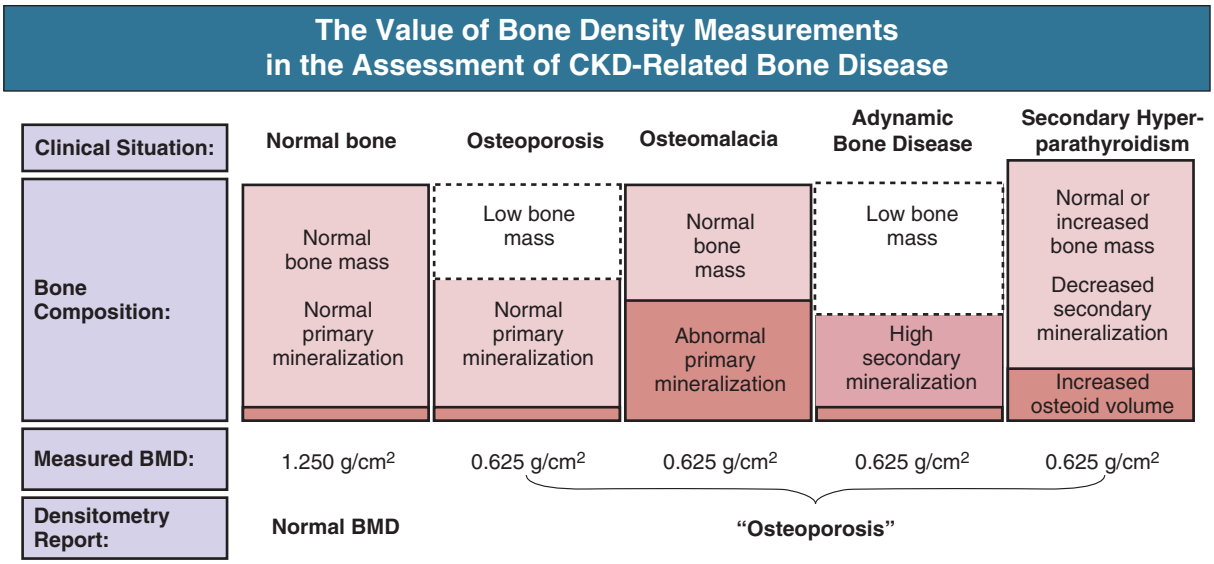

Figure 85-15 The value of bone density measurements in the assessment of chronic kidney disease (CKD)–related bone disease. *Pink boxes* indicate mineralized bone; *red boxes* indicate osteoid. *BMD,* Bone mineral density. *(Courtesy Prof. M.H. Lafage-Proust, St. Etienne, France.)*

Radiology and Measurements of Bone Density

There are no typical features of ABD in conventional bone radiographs or in dual-energy x-ray absorptiometry. In the latter, bone density may be low, normal, or high, depending on the primary or secondary mineralization state, but it never reflects the actual turnover and is therefore not a helpful diagnostic test (Fig. 85-15). A very high cardiovascular calcification burden on conventional radiographs may raise the suspicion of a low bone turnover state if accompanying biochemical parameters are compatible with this diagnosis. Biopsy-proven ABD is associated with the highest magnitude of vascular calcification in dialysis patients.[41]

Treatment of Adynamic Bone Disease

The key therapeutic approaches in the treatment of ABD are to avoid PTH overexpression and to restore adequate PTH levels, without triggering the progressive development of secondary hyperparathyroidism. Such a stepwise treatment approach may include reduction or withdrawal of active vitamin D metabolites, reduction or withdrawal of calcium-containing phosphate binders, and reduction of the dialysate calcium concentration (usually to 1.25 mmol/l). Any aluminum should be withdrawn. After these interventions, biochemical parameters (PTH, calcium, phosphate, perhaps alkaline phosphatase, and especially BAP) should be monitored more frequently than usual.

The best study data on this issue are available from studies comparing calcium-containing versus non–calcium-containing phosphate binders in dialysis patients.[42,44] In comparing baseline with follow-up bone biopsies in such cohorts, the administration of calcium-containing phosphate binders was associated with a higher percentage of individuals who developed ABD. This development was associated with a fall in serum PTH because of the higher calcium load. In an observational study, it was also shown that high-dose calcium-containing phosphate binder intake was associated with both low bone turnover and increased aortic calcification.[45] Other therapeutic approaches to ABD have not been systematically studied. They include optimized diabetes control, a change from peritoneal dialysis to hemodialysis to facilitate a more flexible dialysate calcium prescription, the administration of recombinant PTH (e.g., for patients after total parathyroidectomy), and calcilytics.[46] At present, many patients with ABD remain refractory to treatment.

OSTEOPOROSIS IN CHRONIC KIDNEY DISEASE

Whereas abnormal bone is common and fracture risk is increased in CKD patients, the relative contribution of classic osteoporosis (as defined by World Health Organization criteria) to the CKD-MBD complex is not well defined. Data from studies of antiosteoporosis agents are available only for patients in CKD stages 1 to 3. Nevertheless, postmenopausal women and elderly men nowadays are highly prevalent in late-stage CKD populations, and it is thus likely that classic osteoporosis also contributes to their bone disease.

Pathogenesis of Osteoporosis in Chronic Kidney Disease

Osteoporosis may be associated with low, normal, or high bone turnover and is characterized by thin and disconnected trabeculae and the loss of the platelike bone structure. Many patients with CKD have abnormal mineralization and increased osteoid, which is quite atypical for osteoporosis. Typical pathogenetic factors of osteoporosis, including hypoestrogenemia, immobilization, and corticosteroid use, are frequent in CKD patients, although some postmenopausal women with late-stage CKD may have relatively normal estrogen levels. However, the sum of CKD-MBD–related biochemical disturbances probably represents the decisive factors as to which bone phenotype predominates. Secondary hyperparathyroidism, relative hypoparathyroidism (as in ABD), and 25-hydroxyvitamin D as well as 1,25-dihydroxyvitamin D deficiencies may dominate and "overrule" the bone phenotype of osteoporosis even if classic risk factors are present.

Diagnosis and Differential Diagnosis

In patients with advanced CKD, bone turnover biomarkers and measurements of bone mineral density by dual-energy x-ray

absorptiometry are useless tools (see Fig. 85-15) in the differential diagnosis of classic osteoporosis versus other CKD-MBD–related bone disease. Assays for biomarkers, such as β-CrossLaps (C-terminal cross-linked, CTX; marker of bone collagen degradation), procollagen type I *N*-terminal propeptide (PINP; marker of bone collagen synthesis), and tartrate-resistant alkaline phosphatase 5b (TRAP5b; marker of osteoclast activity) are insufficiently validated in CKD patients, and low bone mineral density can be found in CKD-MBD–induced high-turnover bone disease, ABD, and osteomalacia (see Fig. 85-15). Furthermore, bone mineral density (as measured by dual energy x-ray absorptiometry [DXA]) does not predict fracture risk in CKD patients as it does in the general population, implying that abnormal bone quality rather than density is the major disturbance in such patients. Peripheral quantitative tomography (pQCT) of the radius may be a superior methodology for assessment of CKD patients in the future but awaits validation in sufficiently large patient cohorts.[47] The only reliable methodology to diagnose osteoporosis and to discriminate it from other bone manifestations in CKD patients is bone biopsy. In a large bone biopsy study, including 1429 samples from dialysis patients, osteoporosis was diagnosed in 52% of individuals, and 49% of them also had ABD.[48] These percentages may be quite different in patients in earlier CKD stages, but there are no systematic data available on such cohorts.

Treatment of Osteoporosis in Chronic Kidney Disease

Post hoc analyses of large prospective treatment studies using antiosteoporotic medications demonstrated that it seems safe and efficacious to treat postmenopausal women in stages CKD 1 to 3 if they have a high risk of fractures (according to World Health Organization criteria) and no features of CKD-MBD.[49-52] In such populations, bisphosphonates, raloxifene, and teriparatide appear to be feasible therapeutic options. A recent subanalysis from the Following Rehabilitation, Economics and Everyday-Dialysis Outcomes Measurements (FREEDOM) trial identified patients in CKD stages 2 to 4 and demonstrated a significantly reduced fracture risk with denosumab treatment versus placebo, independent of the stage of CKD.[53] In contrast, for patients in CKD stages 3 to 5 with features of CKD-MBD, there are no data available on the safety and efficacy of any of these antiosteoporotic medications. In CKD patients with ABD, bisphosphonates may aggravate osteoclast paralysis. In CKD patients with secondary hyperparathyroidism, bisphosphonates may upregulate PTH secretion. None of these antiosteoporotic compounds can thus be recommended in patients with CKD-MBD to date, unless bone biopsy proves the exclusive presence of osteoporosis.

β_2-MICROGLOBULIN–DERIVED AMYLOID

β_2-Microglobulin–derived ($A\beta_2M$) amyloidosis, also termed *dialysis-associated amyloidosis,* exclusively affects patients with stage 5 CKD. It is a systemic amyloidosis. Clinical manifestations are largely confined to the musculoskeletal system. In recent years the disease has become notably infrequent. $A\beta_2M$ amyloidosis in CKD stage 5 should not be confused with a rare hereditary systemic amyloidosis derived from the Asp76Asn variant of β_2-microglobulin, which manifests in the absence of CKD.

Pathogenesis

Fibrils of $A\beta_2M$ amyloid are derived from the circulating precursor protein β_2-microglobulin, the nonvariable light chain of the human leukocyte antigen (HLA) class I complex. The pathogenesis appears to involve three events:

1. Pronounced renal retention of β_2-microglobulin (11.8 kd), leading to plasma levels that can be elevated up to 60-fold in dialysis patients[54]; however, even massive overproduction of β_2-microglobulin in mice was not sufficient to induce amyloid deposits, and thus further steps must be important.[55]
2. Modifications of the β_2-microglobulin molecule that render it more amyloidogenic, such as limited proteolysis or the formation of different sugar-protein cross-links.[56]
3. Local factors that contribute to and determine the particular spatial localization of the amyloidosis.

Epidemiology

Histologic studies from the 1990s observed amyloid deposits in 100% of dialysis patients treated for more than 13 years.[57] Most amyloid deposits never cause clinical problems. Main risk factors for $A\beta_2M$ amyloid deposition are age at onset of renal replacement therapy and the duration of (nontransplant) renal replacement therapy.[54,56] $A\beta_2M$ amyloid–related symptoms presently are largely confined to patients who have been dialyzed for more than 15 years.

Clinical Manifestations and Diagnosis

$A\beta_2M$ amyloidosis mainly manifests at osteoarticular sites, particularly synovial membranes; visceral manifestations are rare.[54,56] Carpal tunnel syndrome typically worsens at night and during hemodialysis. It is often bilateral and usually requires surgery. Osteoarthropathy of peripheral joints, resulting from amyloid deposition in periarticular bone and the synovial capsule (Fig. 85-16), is characterized by recurrent or persistent arthralgias, stiffness of large and medium-sized joints, and swelling of capsules and adjacent tendons. Recurrent joint effusions and synovitis, often in the shoulders and knees, may occur. The clinical presentation may vary from frank, acute arthritis to slow, progressive destruction of the affected joints. Destructive spondyloarthropathy (Fig. 85-17) resulting from $A\beta_2M$ amyloidosis can manifest as asymptomatic deposits, radiculopathy, stiffness, "mechanical ache," and, finally, medullary compression with resulting paraplegia or cauda equina syndrome.[54,55] Other manifestations include camptodactyly (a flexion deformity resulting in bent fingers that cannot completely extend or straighten) resulting

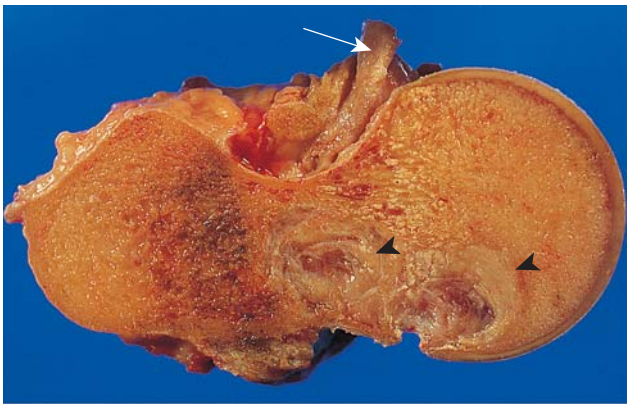

Figure 85-16 A β_2M amyloid deposition in the femoral head. Postmortem specimen from a long-term hemodialysis patient. Two large lesions *(arrowheads),* partly filled with grayish amyloid and partly cystic, are noted in the femoral head. Also note the marked thickening of the synovial capsule from amyloid deposition *(arrow).*

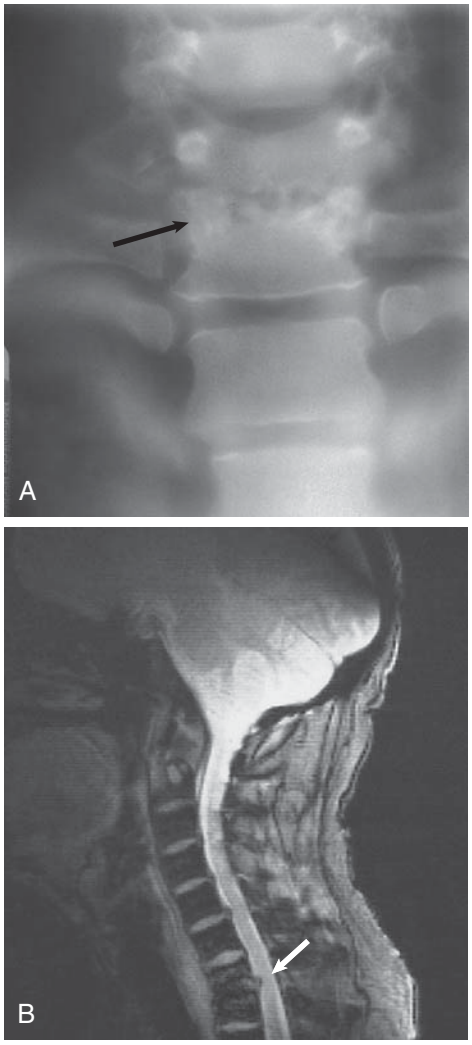

Figure 85-17 $A\beta_2M$ amyloidosis–associated spondyloarthropathy. **A,** Destruction of an intervertebral disk *(arrow)* in the neck vertebrae of a long-term hemodialysis patient. **B,** Magnetic resonance image of the same patient as in **A.** Note destruction of the intervertebral space and protrusion of material into the spinal canal *(arrow).*

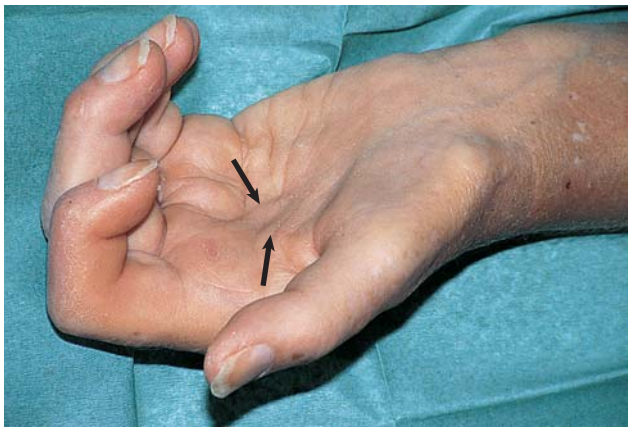

Figure 85-18 Hand involvement in $A\beta_2M$ amyloidosis. Hand of a long-term hemodialysis patient showing maximal extension. Note the prominence of shrunken flexor tendons *(arrows).* This is also known as the "guitar string" sign.

from amyloid deposits along the flexor tendons of the hands (Fig. 85-18). Patients undergoing dialysis can also have subcutaneous tumorous deposits of $A\beta_2M$ amyloid; however, diffuse infiltration of the subcutaneous fat or skin has not been observed.

Case reports of clinically relevant organ manifestations are usually in patients treated with hemodialysis for more than 15 years and have described heart failure, odynophagia, intestinal perforation of both small and large bowel, gastrointestinal bleeding and pseudo-obstruction, gastric dilation, paralytic ileus, persistent diarrhea, macroglossia or functional tongue disturbances (abnormal taste, mobility, articulation), ureteral stenosis, and renal calculi.[54,56]

Diagnosis

Plasma levels of β_2M do not distinguish between patients with the amyloidosis and those without. Ultrasound can detect synovial $A\beta_2M$ amyloidosis as thickening of the joint capsules of the hip and knee, biceps tendons, and rotator cuffs as well as the presence of echogenic structures between muscle groups and joint effusions.[54,56] On radiologic examination, affected joints may present with single or multiple juxta-articular, "cystic" (i.e., amyloid-filled) bone radiolucencies (Fig. 85-19; see also Fig. 85-16). Such bone defects are prone to pathologic fractures. Diagnostic criteria for $A\beta_2M$ amyloid–induced cystic bone radiolucencies have been published.[58] They include (1) diameter of lesions more than 5 mm in wrists and more than 10 mm in shoulders and hips, (2) normal joint space adjacent to the bone defect, (3) exclusion of small subchondral cysts in the immediate weight-bearing area of the joint and of defects of the "synovial inclusion" type, (4) increase of defect diameter of more than 30% per year, and (5) presence of defects in at least two joints. Scintigraphy, using either radiolabeled serum amyloid P component or β_2-microglobulin,[59] offers more specific detection of amyloid deposits but is not widely available. The definitive diagnosis of $A\beta_2M$ amyloidosis relies on histology. Fat aspiration and rectal biopsy are not helpful in $A\beta_2M$ amyloidosis, but diagnostic material can be obtained from synovial membranes, synovial fluid, or bone lesions.[54]

Treatment and Prevention

Therapy for established $A\beta_2M$ amyloidosis is symptomatic. NSAIDs and physical and surgical measures, such as carpal tunnel decompression, endoscopic coracoacromial ligament release, and bone stabilization in areas of cystic destruction, are all used.[54] Although some dialysis modalities allow significant removal of β_2-microglobulin, there is at present no convincing evidence that this is of therapeutic value in an established $A\beta_2M$ amyloidosis. Renal transplantation is the preferred treatment because it leads to rapid symptomatic improvement and halts further progress of the disease, but whether this can actually lead to regression of established $A\beta_2M$ amyloid deposits is a subject of controversy.

A number of strategies exist for prevention of the clinical manifestations of $A\beta_2M$ amyloidosis.[54] The risk of carpal tunnel syndrome is reduced by 40% to 50% in patients treated with high-flux hemo(dia)filtration[60] and minimal in patients receiving online hemodiafiltration.[61] A dramatic reduction in the prevalence of carpal tunnel syndrome occurred in patients dialyzed with ultrapure dialysate.[62] In another study, an 80% reduction of amyloid signs in a chronic hemodialysis population appeared to relate to dialysate factors such as microbiologic purity and the use of bicarbonate buffer.[63] Finally, in uncontrolled studies a β_2-microglobulin adsorption column was reported to decrease $A\beta_2M$ amyloid–associated symptoms, but the effect on bone lesions was not significant.[64]

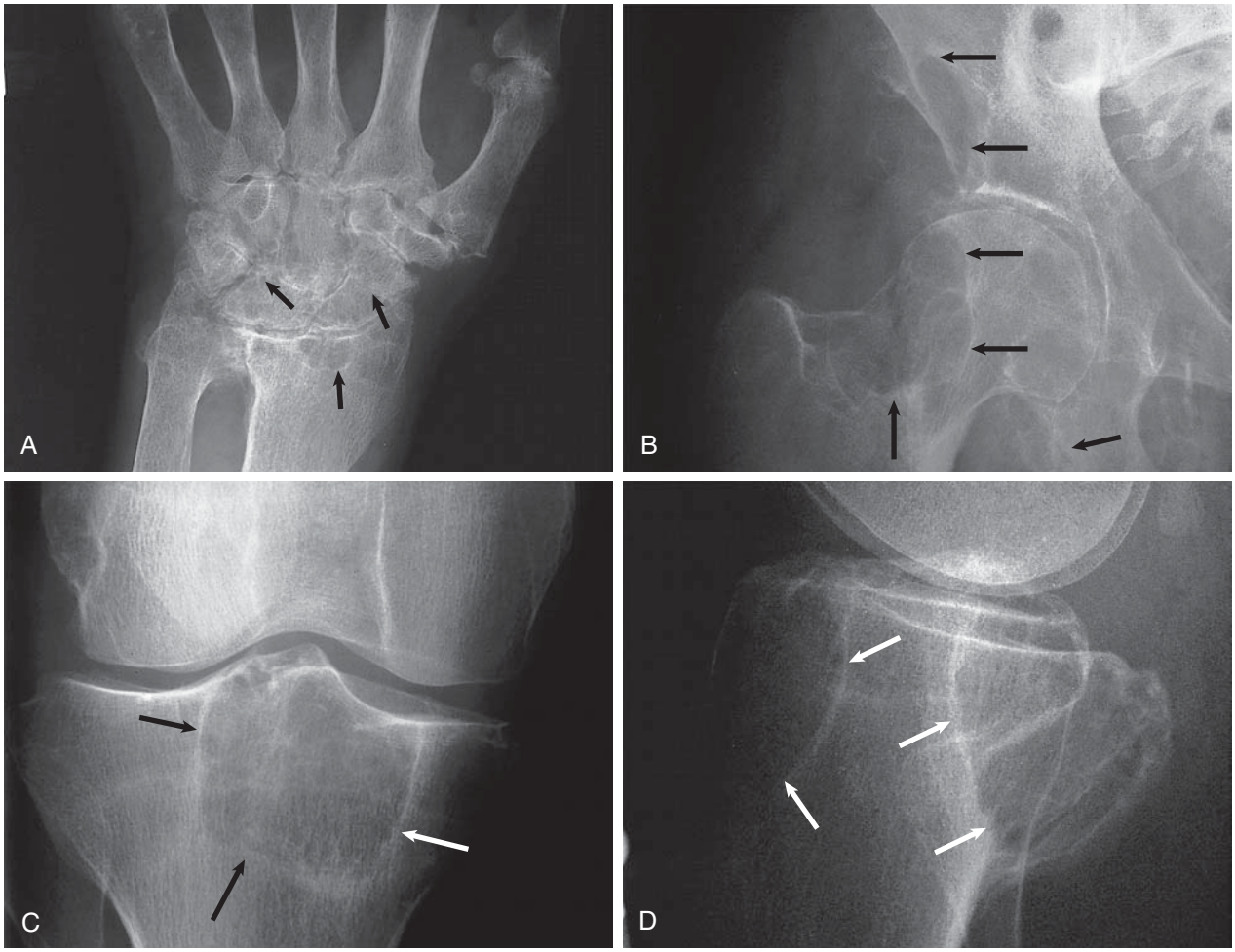

Figure 85-19 Peripheral bone cystic radiolucencies in $A\beta_2M$ amyloidosis. Radiographic findings in a long-term hemodialysis patient. **A,** Multiple cystic lesions *(arrows)* are present in the hand bones. **B,** Large cysts *(arrows)* in the neck of the femur and adjacent pelvic bones. **C** and **D,** Anterior and lateral views of the head of the tibia with two very large, cystic lesions *(arrows)* resulting in posterior bulging of the tibial plateau.

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CHAPTER 86

Neurologic Complications of Chronic Kidney Disease

Julian L. Seifter and Martin A. Samuels

Disorders of the nervous system are associated with renal disease in patients with systemic disorders (e.g., hypertensive encephalopathy, thrombotic microangiopathies, atheroembolic and atherosclerotic disease, vasculitides), and fluid and electrolyte abnormalities. Neurologic complications accompany acute kidney injury in the intensive care setting and in outpatients with chronic kidney disease (CKD). Furthermore, patients with CKD are at increased risk of toxin- and pharmacologic agent–induced neurotoxicity. This chapter focuses on the direct neurologic consequences of CKD.

UREMIC ENCEPHALOPATHY

The syndrome of uremic encephalopathy (UE) involves a spectrum of brain abnormalities that may clinically range from nearly imperceptible changes to coma.

Pathogenesis

The brain in CKD has decreased metabolic activity and oxygen consumption.[1,2] As long as the underlying renal disease has not affected cerebral hemodynamics and responsiveness to carbon dioxide, these functions appear intact, but subtle disturbances have been detected after dialysis.

Many theories support the role of uremic toxins that accumulate in CKD. The balance of excitatory and inhibitory neurotransmitters may be disrupted by organic substances,[3] in particular guanidino compounds, which are increased in the cerebrospinal fluid.[4,5] These compounds antagonize γ-aminobutyric acid $GABA_A$ receptors and at the same time have agonistic effects on *N*-methyl-D-aspartate glutamate receptors, leading to enhanced cortical excitability. Asymmetric dimethylarginine,[6] which is increased in CKD, inhibits endothelial nitric oxide synthase, and levels correlate with cerebrovascular complications in uremia. Disturbances in monoamine metabolism include a depletion of norepinephrine and suppression of central dopamine, which has been linked to the impairment of motor activity in uremic rats. Myo-inositol, carnitine, indoxyl sulfate, polyamine content as well as disrupted solute transport and permeability, have been implicated in the neuronal dysfunction of uremia. Metabolites of drugs, including cimetidine and acyclovir, increased in uremia because of inhibition of organic anion transporter 3 (OAT3) and may result in neurotoxic syndromes.[7] Levels of opiates and in particular metabolites of meperidine increase in plasma because of decreased excretion through renal cation secretory transport, with subsequent neurotoxicity.

Secondary hyperparathyroidism may also play a role in UE[8,9] because brain calcium is increased in CKD and calcium transporters within neurons are parathyroid hormone sensitive. Increased cellular calcium may play a role in neuroexcitation.

Appetite regulation is abnormal in uremia (see Chapter 87). A high rate of tryptophan entry across the blood-brain barrier may increase the synthesis of serotonin, a major appetite inhibitor.[10] High levels of cholecystokinin, a powerful anorectic, and low levels of neuropeptide Y, an appetite stimulant, have been observed. Cachexia may result from anorexia, acidosis, and inflammation. Inflammatory cytokines such as leptin, tumor necrosis factor α, and interleukin-1 may signal anorexigenic neuropeptides such as pro-opiomelanocortin and α-melanocyte–stimulating hormone in the arcuate nucleus of the hypothalamus.

Clinical Manifestations

Whereas 20% of patients with acute kidney injury in an intensive care unit setting developed neurologic impairment,[11] the syndrome in CKD is more subtle, not correlating closely to the level of azotemia.[12] Cross-sectional studies in hemodialysis (HD) patients found cognitive impairment in 30%, with about 10% exhibiting severe impairment. Neurocognitive deficits may have special implications for CKD in early childhood, adversely affecting development of the brain.[13]

Uremic encephalopathy can manifest as complex mental changes or motor disturbances (Table 86-1). The full-blown syndrome is a risk factor for morbidity and mortality.[1,2] Mental findings include emotional changes, depression, disturbing and disabling cognitive and memory deficits, and, in the most severe form, a generalized disorder characterized by delirium, psychosis, seizures, coma, and ultimately death. Such advanced UE is more likely to occur in patients in whom a decision has been made not to initiate renal replacement therapy (see also Chapter 90). Severe motor symptoms or signs are rare. Depression, anxiety, and even suicide are important underdiagnosed and undertreated aspects of uremia and may be related to metabolic or poor nutritional state and fear of dialysis or death. Other known causes of depression should always be sought.

Stable UE manifests with fine action tremor, asterixis, and hyperreflexia. Asterixis is characterized by intermittent loss of muscle tone in antigravity muscles. It is distinguished from tremor by the fact that it is not an oscillation but rather an intermittent loss of tone. Myoclonus is also seen in patients with UE. It is similar in timing to asterixis (10 to 100 milliseconds) but is caused by activation of antigravity muscles. For this reason, some consider asterixis to be a form of negative myoclonus. The distinction between asterixis and myoclonus is less important than once thought because both or either may be present in many metabolic encephalopathies and some structural brain diseases as well. Asterixis and myoclonus may be elicited with the hands outstretched but may be more sensitively assessed by looking at the protruded tongue or the index finger raised with the hand resting on a firm surface. Asterixis and myoclonus may be seen in patients with renal impairment who have received various drugs

Clinical Manifestations of Uremic Encephalopathy	
Early Encephalopathy	**Late Encephalopathy**
Mental Changes	
Mood swings Impaired concentration, loss of recent memory Insomnia, fatigue, apathy	Altered cognition and perception Illusions, visual hallucinations, agitation, delirium Stupor, coma
Motor Changes	
Hyperreflexia Tremor, asterixis Dysarthria, altered gait, clumsiness, unsteadiness	Myoclonus, tetany Hemiparesis Convulsions

Table 86-1 Clinical manifestations of uremic encephalopathy.

(e.g., metoclopramide, phenothiazines, antiepileptic drugs including gabapentin, and opioids, especially meperidine). Metabolic acidosis may also produce an indistinguishable encephalopathy, as can aluminum toxicity. Therefore, before UE is considered a clinical feature of advanced uremia requiring renal replacement therapy, a careful search for other causes should be initiated.

Advanced UE is usually characterized by a reduced level of consciousness, anorexia, asterixis, myoclonus, and upper motor neuron signs that result in disturbances of gait and speech.

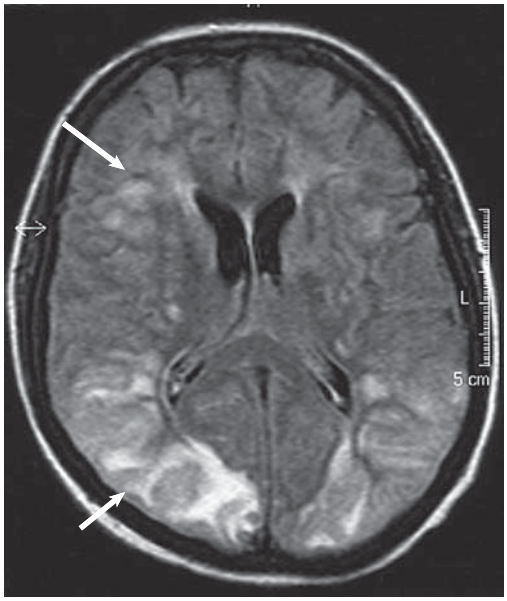

Figure 86-1 Magnetic resonance imaging (MRI) findings in uremic encephalopathy. Axial T2-weighted MRI (fluid-attenuated inversion recovery) scan from a 40-year-old woman. The extensive hyperintense lesion involves the cortical and subcortical areas of both occipital lobes and, in a more focal distribution, the basal ganglia and the frontal white matter *(arrows)*. The volume of the affected brain parenchyma is increased. Reversibility of the MRI changes was noted 2 weeks later after the initiation of regular dialysis. *(Courtesy A. Thron, Aachen, Germany.)*

Diagnosis and Differential Diagnosis

The diagnosis of UE is based on clinical findings and their improvement after adequate therapy (see next section). Lumbar puncture, electroencephalography, and imaging procedures largely serve to exclude other causes in patients in whom the clinical diagnosis is doubtful. In UE the cerebrospinal fluid is often abnormal, sometimes demonstrating a modest pleocytosis (usually <25 cells/mm^3) and increased protein (usually <100 mg/dl). The electroencephalogram is usually abnormal but nonspecific. Generalized slowing with an excess of delta and theta waves is found.[14] Brain imaging usually shows cerebral atrophy and enlargement of the ventricles (Fig. 86-1).

The differential diagnosis of UE is shown in Table 86-2. Seizure activity may be secondary to UE, hypertensive encephalopathy, cerebral embolism, cerebral venous thrombosis, or electrolyte and acid-base abnormalities. Tetany can develop when treatment involves alkalinization of an acidemic patient with renal disease and hypocalcemia.

Treatment

Most nephrologists consider advanced cognitive or memory impairment an indication for initiation of renal replacement therapy. Most of the manifestations of central nervous system involvement are reversible with dialysis within days or weeks, but mild signs of UE may persist. In dialyzed patients with persistent or recurrent symptoms, increasing the delivered dialysis dose may improve clinical findings. Successful renal transplantation usually results in resolution of the UE syndrome within days.

Correction of anemia with recombinant erythropoietin in the dialysis patient to a target hemoglobin level (see Chapter 83) may be associated with improved cognitive function and decreased slowing on the electroencephalogram.[15] Too rapid overcorrection of anemia may be associated with seizures. Similarly, parathyroid hormone suppression with vitamin D analogues and a calcimimetic is important, given the potential role of parathyroid hormone as a neurotoxin (see Chapter 85). Treatment of psychosis in kidney disease must take into account the pharmacokinetics of the specific agent. For example, risperidone may be useful, but dose reduction is necessary because of a prolonged half-life with CKD.

PERIPHERAL NEUROPATHY

Patients with CKD are susceptible to both polyneuropathies and mononeuropathies. The pathophysiologic process of polyneuropathy involves axonal degeneration in a length-dependent fashion. Primary demyelinating neuropathies are rare in the context of CKD except when the renal disease is the result of an illness that also causes demyelination (e.g., multiple myeloma). Mononeuropathies in CKD may be caused by nerve entrapment with compression of metabolically weakened nerves, particularly in wheelchair-bound or bed-bound patients. Mononeuritis multiplex should raise the question of vasculitic neuropathy, especially when systemic vasculitis (e.g., antineutrophil cytoplasmic antibody [ANCA]–positive small-vessel vasculitis or polyarteritis nodosa) is causing the CKD. Functional sparing of small-diameter axons in uremia is suggested by relatively intact thermal thresholds (hot and cold thermal threshold testing is a surrogate for pain threshold). The modestly slowed nerve conduction velocities in the polyneuropathies of uremia may be related to the reversible inhibition of the sodium-potassium adenosine triphosphatase by a uremic toxin. According to the middle molecule hypothesis, accumulated toxins in the range of 300 to 12,000 d, including peptide hormones and polyamines, may lead to progression of neuropathy in HD patients.[4,8,9] Lower limb motor axons in uremic patients are depolarized before but not after dialysis, consistent with a role of hyperkalemia in the development of altered nerve excitability.[16] Elevated magnesium levels will also slow nerve

Differential Diagnosis of Uremic Encephalopathy

Differential Diagnosis	Comment
Hypertensive encephalopathy	
Systemic inflammatory response syndrome (SIRS)	Observed in septic patients
Systemic vasculitis	Vasculitis or lupus with cerebral involvement
Drug-induced neurotoxicity	
Analgesics	Meperidine, codeine, morphine, gabapentin
Antibiotics	High-dose penicillins (may cause seizures), acyclovir, ethambutol (optic nerve damage), erythromycin and aminoglycosides (may cause ototoxicity), nitrofurantoin and isoniazid (peripheral neuropathy)
Psychotropics	Lithium, haloperidol, clonazepam, diazepam, chlorpromazine
Immunosuppressants	Cyclosporine, tacrolimus
Chemotherapeutics	Cisplatinum, ifosfamide
Others	High doses of loop diuretics (ototoxic), ephedrine, methyldopa, aluminum metoclopramide (myoclonus, dystonia)
Cerebral atheroembolic disease	Follows recent aortic or cardiac angiography; associated with peripheral manifestations, including lower extremity cyanosis, livedo reticularis, and eosinophilia
Subdural hematoma	
Posterior leukoencephalopathy	Observed particularly following renal transplantation as a result of reversible, abnormal permeability of the blood-brain barrier Often manifests with headache followed by mental depression, visual loss, and seizures in the context of volume expansion, acute hypertension, and often treatment with corticosteroids or calcineurin inhibitors Lesions in the parietal, temporal, and occipital lobes may be seen on imaging studies

Table 86-2 Differential diagnosis of uremic encephalopathy.

conduction velocity. *In vitro,* extracellular acidosis contributes to decreased sodium conductance in large sensory neurons. Very slow nerve conduction velocities (i.e., less than half normal) suggest a demyelinating neuropathy, a finding that should lead the physician to seek a specific cause (e.g., a paraprotein).

Polyneuropathies occur in about two thirds of uremic patients and may progress rapidly in advanced CKD.[1,16,17] Characteristic symptoms and signs are sensory loss, pain, paresthesias, and insensitivity to temperature, particularly cold. These findings can advance to include motor findings, such as footdrop. Phrenic neuropathy may cause dyspnea because of oor diaphragmatic movement, whereas hiccups are more likely a result of the central nervous system effects of uremia. The distal lower extremities are usually affected first because axonal polyneuropathies are length dependent. Decrease in vibratory sensation and position sense and Romberg sign (i.e., greater instability of stance with eyes closed than with eyes open) are common signs. Muscle stretch reflexes are reduced or absent. In the diabetic dialysis patient who has progressive neuropathy, it is important to establish adequacy of the dialysis as well as glucose control. Uremic polyneuropathy is aggravated by malnutrition, inadequately controlled hypertension, and a number of comorbid conditions, including diabetes mellitus, alcohol abuse, atherosclerotic vascular disease, and medications (e.g., nitrofurantoin, isoniazid, hydralazine).

The diagnosis of uremic polyneuropathy can usually be made from clinical findings. Nerve conduction velocity is modestly reduced, and needle electromyography shows evidence of chronic denervation and sometimes reinnervation. If electromyography and nerve conduction tests are performed, they should not be done in an extremity bearing an arteriovenous fistula because the surgery may cause local nerve injury, which can complicate the interpretation of the clinical neurophysiologic studies.[16]

Lead polyneuropathy should be considered, particularly when there is a known exposure history. Lead accumulates in the dialysis patient but could also be the cause of CKD. A lower motor neuron syndrome caused by lead toxicity may be mistaken for amyotrophic lateral sclerosis. A bone lead scan using K-line x-ray fluorescence spectroscopy of the tibia is a promising new noninvasive test that may become useful. Serum lead values and red cell protoporphyrin levels may be normal if exposure is remote. There may be associated depression, the so-called "saturnine temperament," so named because the ancients believed that Saturn was made of lead and was associated with a melancholy disposition. Gout, hypertension, renal glycosuria, and microcytic anemia also may be caused by lead toxicity.

Other conditions in the differential diagnosis of mixed polyneuropathy include other heavy metals (such as arsenic and mercury), nutritional deficiencies (such as pyridoxine, thiamine, and niacin), human immunodeficiency virus–related neuropathy, amyloid, vasculitis, sarcoid, lupus, and a paraneoplastic syndrome.

Progressive polyneuropathy may be an indication for initiation of dialysis or for renal transplantation. Symptoms usually will not deteriorate further or may even show a slow improvement thereafter. If polyneuropathic symptoms worsen in a dialysis patient, the dialysis dose should be increased. Physical therapy is an important component of the management. Patients experiencing neuropathic pain may be treated with tricyclic antidepressants (e.g., amitriptyline, 10 to 25 mg, increasing to 75 to 150 mg at bedtime) or antiepileptic drugs (e.g., carbamazepine, 200 to 400 mg initially, increasing to 1200 mg maximally; phenytoin, 100 to 200 mg initially, maximally 600 mg).[1,2] Gabapentin is an antiepileptic drug that is sometimes used to treat neuropathy but may result in oversedation and myoclonus in CKD because of marked prolongation of the drugs half-life. When it is used, it should be monitored closely at reduced doses. Deficiencies of cobalamin (vitamin B_{12}), folate, and pyridoxine may be reflected in an elevated serum homocysteine level. Thiamine deficiency, often associated with malnutrition, can also aggravate neuropathy, but whether replacement of any of these vitamins is effective in preventing or curing polyneuropathy in uremic patients is not well established. Thiamine deficiency is the cause of Wernicke encephalopathy in dialysis or malnourished patients. This syndrome is suspected when the triad of mental change (often amnesia), ataxia, and oculomotor disturbances (most often abducens palsies with gaze-evoked nystagmus) is seen in any patient whose diet is deficient in B vitamins. When amnesia is combined with a polyneuropathy, the term *Korsakoff psychosis* applies. In malnourished patients, the cause of Korsakoff psychosis is usually multiple subclinical attacks of Wernicke encephalopathy, hence the term *Wernicke-Korsakoff disease.*

Specific mononeuropathic syndromes include ulnar nerve entrapment, associated with uremic tumoral calcinosis and subsequent ischemia, and carpal tunnel syndrome, for example, caused by

β_2-microglobulin–derived amyloidosis (see Chapter 85) or by an arteriovenous fistula.[1,17] These syndromes may be treated with anti-inflammatory agents, anticonvulsants, and surgical decompression. It is important to ensure adequacy of dialytic treatment.

Pruritus in the uremic patient may be severe and is not primarily a skin disorder (see also Chapter 88). Rather, it may represent a form of sensory neuropathy. This symptom usually improves with renal replacement therapies. Antihistamines, with their sedating effect, are not always effective. Gabapentin and carbamazepine block the afferent pathway in uremic neuropathic itch. Gabapentin and pregabalin inhibit calcitonin gene–related peptide from primary afferent neurons by inhibiting GABA and opioid receptor antagonists (naloxone and naltrexone) and may antagonize transmission of itch. Antidepressants have also been successful, possibly by interfering with reuptake of serotonin and norepinephrine to reduce pruritus perception.[18]

AUTONOMIC NEUROPATHY

Autonomic neuropathy is also very common in patients with advanced CKD, probably because diabetes is a common cause of CKD. Hyperglycemia may be more difficult to control in CKD because glucose filtration is decreased. Amyloidosis, a less common cause of CKD, also is associated with autonomic neuropathy. A typical manifestation is orthostatic hypotension, which is most severe in patients with diabetes mellitus or amyloidosis as a cause of CKD. Some patients have evidence of peripheral neuropathy and may manifest hyporeninemic hypoaldosteronism with hyperkalemia and renal tubular acidosis. The low blood pressure may preclude antiproteinuric treatment with angiotensin antagonists in the predialysis patient and may complicate fluid removal during dialysis. Patients on peritoneal dialysis may be particularly affected. CKD patients were thought to have decreased baroreceptor function, but normal baroreceptor responses to graded decrements in mean arterial blood pressure have been described.[19] Instead, CKD patients have sympathetic hyperactivity, which contributes to hypertension, more rapid progression to renal failure in the predialysis patient, and greater cardiovascular risk. Accordingly, α- and β-adrenergic blockade has been advocated in CKD.[19] Autonomic neuropathy is caused by axonal disease and thus is length dependent. For that reason, the longest autonomic nerve, the vagus, is usually the first affected, resulting in the loss of the normal sinus arrhythmia, significant reductions of day-night blood pressure variation, and possibly sudden cardiac death related to the loss of the balance between the sympathetic and parasympathetic limbs of the autonomic nervous system. Gastrointestinal complaints include gastroparesis, particularly problematic for the diabetic patient. In the predialysis patient, nausea and early satiety associated with gastroparesis may be confused with uremia. Several medical regimens have been used for the uremic patient with gastroparesis; they include erythromycin, which can activate the gastric motilin receptor. Levodopa-carbidopa, as a dopamine agonist, may be effective, as may metoclopramide, 10 mg before sleep, or domperidone 10 to 20 mg. Nocturnal diarrhea is another consequence of vagal neuropathy. Erectile dysfunction and incontinence (urinary more commonly than fecal) may also be related to autonomic neuropathy.

CRANIAL NEUROPATHIES

Cranial nerve involvement is most often vestibulocochlear. Hearing loss needs to be distinguished from drug-induced ototoxicity or the neurosensory deafness of hereditary nephropathy.[1,2] Bilateral vestibular failure leads to inability to stand or to walk normally without vertigo or nystagmus. It is often related to the use of aminoglycoside antibiotics in the patient with CKD, unless the dose is properly adjusted. *N*-acetylcysteine given with aminoglycosides may reduce the risk of cochlear toxicity. Sulfa-based loop diuretics, often used at high doses in patients with CKD, may cause vestibular or cochlear damage. Decreased olfactory function, especially a reduced ability to discriminate among and to identify odors, and dysgeusia are commonly seen in patients with CKD.

SLEEP DISORDERS

Many HD and peritoneal dialysis patients exhibit obstructive sleep apnea that is independent of obesity.[20] The associated sleep deprivation contributes to fatigue and cognitive impairment and increases the risk of cardiovascular complications.[20] Both obstructive and central sleep apnea are seen in patients with CKD. Obstructive sleep apnea is a condition in which blockage of the upper airway can interfere with nocturnal breathing. Nighttime oxygen and continuous positive airway pressure (CPAP) may help. Treatment of obstructive sleep apnea, with use of CPAP in a fashion similar to the treatment of nonuremic individuals, is effective. Nocturnal HD has been reported to significantly reduce the occurrence of sleep apnea.[20] Central sleep apnea, often accompanied by heart failure, causes prolonged apneic episodes and also may respond to oxygen. Initiation of dialysis may be helpful.

Daytime sleepiness is common and underdiagnosed in patients with CKD and contributes not only to worsened hypertension and increased cardiovascular risk but also to social dysfunction. Whether obstructive sleep apnea and its associated excessive daytime sleepiness is an independent risk factor for the progression of renal failure is not yet settled. It is assessed by a multiple sleep latency test, that is, the duration of time from "lights out" to the onset of sleep. If it is less than 5 minutes, it is consistent with sleep deprivation. There was also a reduced proportion of rapid eye movement sleep. An increased arousal frequency is related to periodic limb movements during sleep and the presence of sleep apnea.

Sleep-wake complaints are common in patients on dialysis, with an incidence of up to 80%. Contributors include peripheral neuropathy, pain, and pruritus.

RESTLESS LEGS SYNDROME (EKBOM SYNDROME)

Restless legs syndrome (RLS), described by K. A. Ekbom in 1944,[21] is frequent in CKD, particularly in women. It may result from a decrease in dopaminergic modulation of intracortical excitability, with reduced supraspinal inhibition and increased spinal cord excitability. RLS is characterized by unpleasant "creeping" sensations in the extremities and a compulsive need to move the limbs, usually the legs.[22-24] The movement is worsened by periods of rest or inactivity and is relieved by walking or stretching. Symptoms are worse at night and may lead to insomnia and consequent daytime sleepiness and reduced quality of life. Nocturnal muscle cramps are also common in CKD and should be distinguished from RLS. The Ekbom syndrome consists of restless legs plus other obsessive-compulsive–like disorders including various pica behaviors, such as pagophagia (ice eating), geophagia (clay eating), and amylophagia (starch eating).

Periodic limb movement disorder is characterized by episodes of involuntary repetitive extension of the big toe and dorsiflexion of the

ankle as well as flexion of the knee and hip.[23,24] This disorder is more likely to occur in those with RLS.

Iron deficiency or iron transport into the central nervous system plays a central role in RLS. Iron is a cofactor for the enzyme tyrosine hydroxylase, the rate-limiting step in the biosynthesis of dopamine, possibly explaining the link between iron deficiency and dopamine deficiency in RLS. Overt iron deficiency is easily diagnosed and should be treated.[23,24] In patients with normal red blood cell indices and serum iron and total iron-binding capacity, serum ferritin should be tested. Transferrin saturation ratio may be an even more sensitive indicator of iron deficiency. If these are both normal, a spinal fluid ferritin analysis may reveal a subtle central nervous system iron deficiency syndrome. RLS often persists after initiation of dialysis but may improve after transplantation and has been linked to abnormalities in calcium and phosphorus metabolism as well as to anemia. Iron replacement should be initiated if there is any indication of iron deficiency. Oral replacement is the safest method. Intravenous iron may be required (see Chapter 83). Dopaminergic treatment is often helpful, usually starting with the dopamine receptor agonists pramipexole and ropinirole. Levodopa combined with decarboxylase inhibitors (e.g., carbidopa-levodopa) may be used as well as gabapentin, opioids, and benzodiazepines.[22-24] Care should be taken with gabapentin because of toxicity with accumulation, the symptoms of which are sedation, cognitive slowing, and various movement disorders including tremor, ataxia, and asterixis (see previous discussion). Older dopamine receptor agonists, such as bromocriptine and pergolide, are rarely used now for RLS.

NEUROLOGIC SYNDROMES ASSOCIATED WITH RENAL REPLACEMENT THERAPY

Renal replacement therapy is associated with an increased incidence of subdural hematoma and intracranial hemorrhage, presumably connected to hypertension and anticoagulation with HD as well as Wernicke encephalopathy (see earlier discussion).[1,2] A syndrome of muscle weakness has been attributed to L-carnitine depletion from dialysis, leading to decreased mitochondrial fatty acid usage.

Dialysis disequilibrium syndrome is a rare complication of rapid metabolic changes occurring with HD, usually affecting patients in whom HD is being initiated (see also Chapter 95).[25] It is most common in patients with severe uremia of long duration and with severe hypertension. Characterized by acute onset of headache, nausea, vomiting, disorientation, a confusional state, and seizures, it is a diagnosis of exclusion. It usually results from acute changes in osmolality during HD, in which the rapid decrease in urea in the extracellular fluid favors water movement into brain cells, resulting in cerebral edema. Alternatively, other intracellular osmolytes within brain cells may draw water from the extracellular fluid. The syndrome normally reverses spontaneously after a period of regular HD. If no improvement is seen after a month of HD, one should investigate for other possible causes of the clinical syndrome by imaging the brain, obtaining an electroencephalogram, and examining the spinal fluid. Dialysis disequilibrium syndrome may be prevented by decreasing HD length to 2 to 3 hours, dialyzing daily, and reducing HD efficacy during the first sessions.

Dialysis encephalopathy (formerly called *dialysis dementia*) is probably a multifactorial syndrome occurring in sporadic-endemic and epidemic types. In particular, in the epidemic type, aluminum-based phosphate binders and exposure to a dialysate containing more than 20 μg of aluminum per liter are considered to be major causes.[26,27] Aluminum transferred to the nervous system by transferrin results in a characteristic clinical condition with prominent stuttering that usually worsens toward the end of a dialysis session and encephalopathy, initially responding well to intravenous benzodiazepines but then becoming unresponsive, leading to a severe encephalopathy and death. With the almost universal preparation of dialysate water by reverse osmosis and the marked reduction in aluminum-containing phosphate binder use, aluminum-induced encephalopathy has virtually disappeared. If it is present, aluminum toxicity is treated with deferoxamine (see Chapter 85). Renal transplantation is an effective treatment for dialysis dementia.

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CHAPTER 87

Gastroenterology and Nutrition in Chronic Kidney Disease

Gemma Bircher and Graham Woodrow

GASTROINTESTINAL PROBLEMS IN CHRONIC KIDNEY DISEASE

Gastrointestinal (GI) symptoms and disease are common in patients with chronic kidney disease (CKD), including those receiving renal replacement therapy (Table 87-1). Anorexia, nausea, and vomiting can arise from uremic toxicity. They may indicate the need to start dialysis or may be a manifestation of inadequate dialysis clearances. GI disturbances contribute to the development of malnutrition and wasting. These common complications of advanced CKD carry an adverse prognosis for survival. Some GI conditions are a result of uremia or the effects of renal replacement therapy. Other GI symptoms are manifestations of conditions also responsible for the renal disease. Medications may result in a range of GI complications in patients with CKD.

GASTROINTESTINAL DISEASE IN CHRONIC KIDNEY DISEASE

Oral Disease in Chronic Kidney Disease

Glossitis can result from deficiency of iron, vitamin B_{12}, other B vitamins, or folic acid. Halitosis is a feature of uremia, and reduced taste sensation or abnormal or unpleasant taste can impair dietary intake. Dental disease may prevent adequate nutrition. Gingival hyperplasia is a frequent complication of treatment with calcium channel blockers or cyclosporine. Oral candidiasis occurs in patients receiving immunosuppressive drugs including corticosteroids, in those undergoing antibiotic therapy, in patients with diabetes, and in older malnourished individuals. If extensive, particularly with esophageal involvement, it may lead to dysphagia (Fig. 87-1).

Gastroesophageal Reflux Disease and Esophagitis

Gastroesophageal reflux disease is a common complaint that is defined by symptoms of heartburn or mucosal changes arising from reflux of caustic gastric contents into the esophagus. It occurs more frequently in patients with CKD because of GI dysmotility or delayed gastric emptying and may be more prevalent with peritoneal dialysis (PD) because of increased intra-abdominal pressure.[1] It is more common in patients with scleroderma because of reduced esophageal peristalsis. Esophagitis also results from the irritant effects of drugs, including slow-release potassium preparations, tetracyclines, iron preparations, aspirin, nonsteroidal anti-inflammatory drugs, and bisphosphonates. The diagnosis is made from the patient's symptoms. Typical features appear on endoscopy but may be absent in symptomatic patients. Other investigations include 24-hour ambulatory esophageal pH monitoring and demonstration of reflux on barium swallow examination. It is important to consider ischemic cardiac disease in CKD as an alternative cause of atypical symptoms. Management includes weight loss in obese patients; avoidance of bedtime snacks, fatty foods, cigarettes, and alcohol; and raising the head of the patient's bed. Proton pump inhibitors are the most effective medical treatment, and maintenance therapy may be required. Other drugs include histamine H_2 receptor antagonists and antacid preparations. Sucralfate should be avoided in patients with CKD because of the risk of aluminum accumulation.

Peptic Ulcer Disease, Gastritis, and Duodenitis

In the early days of dialysis, peptic ulceration and GI hemorrhage were major complications of renal failure. However, with effective drug therapies and improvement in dialysis therapy, peptic ulcer disease is not more common in CKD than in the general population, although it remains an important cause of GI hemorrhage. Peptic ulcers in patients with CKD are more often multiple than in the general population and situated in a postbulbar position.[2] Hemorrhage occurs more often, but pain is less frequent.[2]

Gastritis and duodenitis are common in patients with CKD and abdominal symptoms. Hypergastrinemia occurs with CKD but is not important in causation of gastritis, duodenitis, or peptic ulcers. Despite high urea concentrations in patients with CKD, incidence of *Helicobacter pylori* infection is not increased.[3] Increased susceptibility of gastric and duodenal mucosa to damage in CKD may be an underlying mechanism. The presence of *H. pylori* infection in PD has been suggested as a possible cause of anorexia, inflammation, and malnutrition.[4]

Dyspepsia without other warning features (weight loss, vomiting, hemorrhage) may be managed by testing for *H. pylori* with a breath test or stool antigen test (which are valid in CKD) and an empirical course of acid-suppressing therapy. Persistent symptoms of new onset in patients older than 55 years warrant upper GI endoscopy to exclude malignant disease. The frequent coexistence of other symptoms in CKD, such as nausea, vomiting, and weight loss, may lead to a lower threshold for performance of endoscopy. Management includes use of proton pump inhibitors and histamine H_2 receptor antagonists. There is a risk of excess calcium and magnesium absorption with some antacids in CKD, and aluminum- or bismuth-containing preparations should be avoided.

Delayed Gastric Emptying and Gastroparesis

Gastric emptying is impaired in uremia (possibly to a greater degree in PD)[5,6] and is affected by some conditions leading to renal disease, particularly diabetes and amyloidosis. This results in reduced

Important Causes of Common Gastrointestinal Symptoms in Patients with Chronic Kidney Disease

Clinical Feature	Important Causes in CKD
Anorexia	Uremic toxicity Inadequate dialysis clearances Delayed gastric emptying
Nausea and vomiting	Uremic toxicity Delayed gastric emptying Gastritis, duodenitis Peptic ulcer disease Drugs
Constipation	Drugs, including opioid analgesia GI pseudo-obstruction Diverticular disease
Diarrhea	Diabetic enteropathy Dialysis-related amyloidosis Diverticular disease *Clostridium difficile* infection
GI hemorrhage	Gastritis, duodenitis Esophagitis Peptic ulcer disease Angiodysplasia Intestinal ischemia Dialysis-related amyloidosis Vasculitis
Acute abdominal pain	Gastritis, duodenitis Complications of peptic ulcer disease Acute pancreatitis Intestinal ischemia Diverticulitis GI pseudo-obstruction Colonic perforation from fecal impaction Complications of peritoneal dialysis (peritonitis, dialysis catheter malposition, dialysate infusion pain) Complications of autosomal dominant polycystic kidney disease Retroperitoneal hemorrhage

Table 87-1 Important causes of common gastrointestinal (GI) symptoms in patients with chronic kidney disease (CKD).

appetite, early satiety, nausea, vomiting, and malnutrition. Mechanisms in uremia may include autonomic neuropathy and retained GI peptides. The diagnosis is confirmed by scintigraphic measurement of gastric emptying. It may be suspected when endoscopy demonstrates residual gastric contents despite fasting. Endoscopy is important to exclude gastric outlet obstruction. Reversible causes should be addressed, including optimization of diabetic control, correction of electrolyte abnormalities, and discontinuation of drugs that impair gastric emptying (e.g., those with anticholinergic and opioid effects). Dietary measures, with frequent smaller low-fat meals and avoidance of nondigestible solids, are often disappointing. Antiemetic agents are also often ineffective. The mainstay of treatment is prokinetic drug therapy, including metoclopramide, domperidone, and erythromycin. Prokinetic drugs improve nutritional state in patients with delayed gastric emptying.[7] Nutritional support through feeding nasoenteric or jejunostomy tubes may be required.

Large Bowel Disorders

Diverticular disease has an incidence in CKD similar to that in the general population, except in patients with autosomal dominant polycystic kidney disease (ADPKD), in whom it is increased.[8] It presents as acute diverticulitis or colonic perforation and is associated with PD peritonitis caused by enteric organisms. There is a greater risk of bleeding in CKD (because of uremic bleeding tendency) and perforation with high-dose corticosteroids (e.g., after renal transplantation).

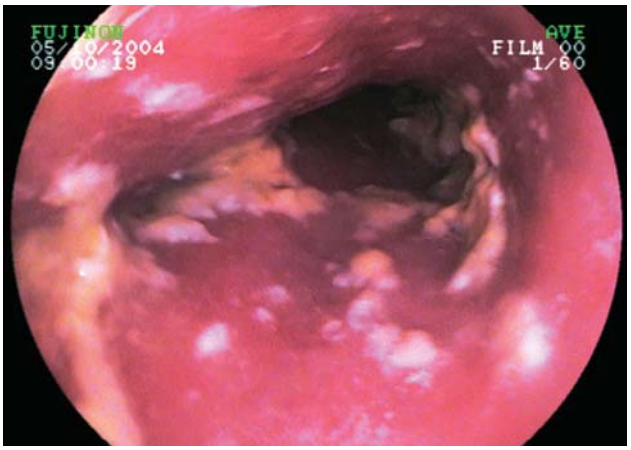

Figure 87-1 Endoscopic appearance of esophageal candidiasis. *(Courtesy Dr. B. Rembacken, Leeds, United Kingdom.)*

Constipation is common in CKD. Predisposing factors include drugs, dietary restrictions, low oral fluid intake, and electrolyte abnormalities, including hypercalcemia. In PD, constipation results in impaired dialysate drainage and catheter malposition. Severe constipation is a risk factor for large bowel perforation. Management includes stool-softening agents, stimulant laxatives, and fiber preparations. Drugs predisposing to constipation include calcium-based phosphate binders, sevelamer, oral iron, opioid analgesics, and calcium resonium.

Colonic perforation may occur in CKD from a number of causes. These include diverticulitis, fecal impaction, and dialysis-related amyloidosis. This condition has a higher mortality in CKD patients.

Gastrointestinal Pseudo-obstruction

Pseudo-obstruction presents with acute or more chronic clinical features of abdominal pain, vomiting, constipation, or diarrhea. It arises from disordered gut motility and is more common in dysmotility states, such as diabetes, amyloidosis, and scleroderma. Drugs that reduce bowel motility and electrolyte disturbance such as hypokalemia predispose to pseudo-obstruction, and it may be acutely precipitated by surgery, constipation, and retroperitoneal hemorrhage. Investigations include plain abdominal radiography, computed tomographic scanning, and bowel contrast studies. Management includes nutritional support (which may require parenteral feeding) and prokinetic agents. Nasogastric tube insertion and aspiration may be required for symptomatic control. Complications include intestinal perforation[9] and bacterial overgrowth.

Vascular Disease of the Gastrointestinal Tract

Intestinal ischemia is an important cause of an acute abdomen in older CKD patients. A proportion of cases result from nonocclusive mesenteric ischemia, in which there is no critical vascular occlusion.[10] It may be precipitated by excess fluid removal by hemodialysis (HD). Predisposing factors include hypotension, cardiac failure, hypoxia, increased plasma viscosity, and constipation (which increases intraluminal pressure, impairing vascular perfusion).

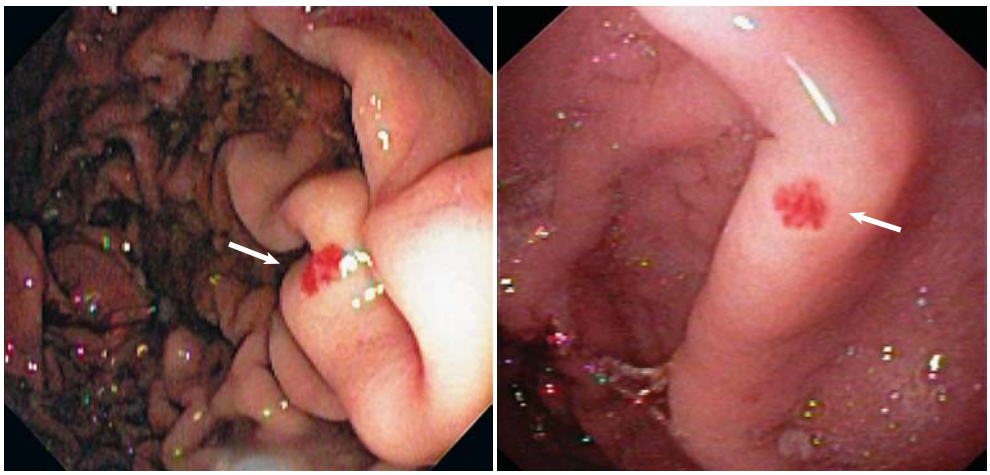

Figure 87-2 Two examples of gastric angiodysplasia *(arrows)* in a dialysis patient. *(Courtesy Drs. R. Winograd and C. Trautwein, Aachen, Germany.)*

Presentation is with abdominal pain, diarrhea, or lower GI bleeding. Abdominal signs such as peritonism can be misleadingly modest at presentation, but there is often peripheral neutrophil leukocytosis and progressive lactic acidosis. Milder cases may settle with hemodynamic resuscitation. Patients with more severe cases with features of peritonism and intestinal infarction require laparotomy and have a high mortality.

GASTROINTESTINAL HEMORRHAGE

Gastrointestinal hemorrhage is an important complication of CKD, with increased incidence compared with the general population. Causes include a greater incidence of lesions such as gastritis and duodenitis,[11] angiodysplasia, and, more rarely, dialysis-related amyloidosis and systemic vasculitis (Fig. 87-2). Uremic hemostatic defects and anticoagulation during HD are also important. Upper GI endoscopy is the major diagnostic investigation in upper GI bleeding and also allows therapeutic procedures to stop bleeding. Flexible sigmoidoscopy and colonoscopy are performed for lower GI bleeding. Investigations in which the cause remains unclear include angiography, small bowel enteroscopy or capsule study, and radiolabeled red cell scanning.

Resuscitation requires careful monitoring in patients with CKD. Adequate fluid replacement to maintain renal perfusion in patients not on dialysis or with residual renal function in patients on dialysis, but avoiding fluid overload, is crucial. Monitoring of serum potassium with avoidance of hyperkalemia complicating blood transfusion is also important. Correction of coagulation defects in patients with CKD includes optimization of dialysis clearance, correction of anemia, and use of DDAVP or cryoprecipitate. Drugs that increase bleeding risk should be discontinued when possible. HD, when it is required, should be performed without heparin for anticoagulation. Specific treatment is directed at the cause of hemorrhage. Bleeding from angiodysplasia in HD may improve on transfer to PD.[12] The presence of CKD increases the risk of mortality in GI hemorrhage.[10]

Clostridium difficile Infection

Clostridium difficile is a major cause of nosocomial diarrheal illness. Clinical manifestations vary from mild diarrheal illness to severe pseudomembranous colitis (Fig. 87-3). Patients with CKD are at risk of more frequent or severe infection and have a higher resulting mortality.[13] Reasons include the older age of CKD patients, frequent use of acid-suppressing drugs, and antibiotics. Diagnosis is made by identifying *C. difficile* toxin in diarrheal stools. In severe cases, there are radiologic appearances of acute colitis with mucosal edema, but these are not specific for *C. difficile.* A pseudomembrane may be visualized on sigmoidoscopy, but diarrhea can occur in its absence. The precipitating antibiotic should be stopped if possible. Oral metronidazole is first-line antibiotic therapy; oral vancomycin is used if there is intolerance of or failure to respond to metronidazole. Fidaxomicin is a newer, expensive agent that may be used for recurrent infection, and intravenous immunoglobulin has been used for refractory cases.[14] Fluid and electrolyte replacement are important, and drugs that reduce diarrhea or impair gut motility must be avoided because they may precipitate toxic megacolon. Colectomy may be required in life-threatening disease. *C. difficile* infection is a major problem in the hospital setting, including renal units. Preventive measures, including hand washing, cleanliness of physical

Figure 87-3 Computed tomographic appearance of *Clostridium difficile* colitis in a hemodialysis patient, demonstrating pancolitis with markedly edematous haustra *(arrows)* after treatment with broad-spectrum antibiotics. *(Courtesy Dr. M. Weston, Leeds, United Kingdom.)*

Gastrointestinal-Renal Syndromes: Conditions Typically Resulting in Both Renal and Gastrointestinal Disease		
Disorder	**Renal Involvement**	**GI Involvement**
Diabetes	Proteinuria, CKD	Gastroparesis, diabetic enteropathy, constipation
Systemic vasculitis	Proliferative glomerulonephritis, CKD	Intestinal ischemia, GI hemorrhage, bowel perforation, hepatobiliary involvement, acute pancreatitis
Systemic amyloidosis	Nephrotic syndrome, CKD	Diarrhea, malabsorption, splenic rupture
Autosomal dominant polycystic kidney disease	CKD, cyst hemorrhage, and infection	Abdominal pain (from renal or hepatic cysts), diverticular disease, hernia
Inflammatory bowel disease	AA amyloidosis, drug-induced interstitial nephritis, IgA nephropathy, oxalate renal calculi (with terminal ileal Crohn disease)	Abdominal pain, diarrhea, GI hemorrhage, malabsorption
Scleroderma	CKD, acute scleroderma renal crisis	Dysphagia, constipation, malabsorption, and bacterial overgrowth
Fabry disease	Hematuria, proteinuria CKD	Abdominal pain, episodes of diarrhea, or constipation
Celiac disease	IgA nephropathy	Malabsorption, iron-deficiency anemia
IgG4-related tubulointerstitial nephritis	Tubulointerstitial nephritis	Autoimmune pancreatitis

Table 87-2 Gastrointestinal (GI)-renal syndromes: conditions typically resulting in both renal and GI disease. *CKD,* Chronic kidney disease.

environment, and isolation of affected inpatients with barrier nursing, are essential. Antibiotic policies should minimize use of broad-spectrum antibiotics, which induce *C. difficile* infection.

Acute Pancreatitis

There is some evidence suggesting that acute pancreatitis is more common in CKD, and the incidence may be greater in PD than in other CKD patients.[15] Most cases are secondary to biliary tract disease or alcohol use or are idiopathic. Rarer causes, in CKD patients, are hypercalcemia, vasculitis, and drugs including corticosteroids, azathioprine, angiotensin-converting enzyme (ACE) inhibitors, and diuretics. Serum amylase is the usual diagnostic measure, although concentrations are normally elevated up to threefold in renal failure and are lowered in PD patients receiving icodextrin dialysate (because of competitive inhibition of icodextrin and metabolites with the amylase assay). Serum lipase is an alternative diagnostic marker (although it is also elevated in uremia). Amylase and lipase concentrations may be measured in dialysate in PD patients with suspected pancreatitis. Radiology, including ultrasound, computed tomography, and magnetic resonance imaging, is useful to confirm the diagnosis and to detect underlying biliary disease and complications such as pancreatic necrosis and pseudocyst formation. In PD patients with acute pancreatitis, dialysate may become cloudy with increased leukocytes, hemorrhagic, or dark brown (cola colored).

Acute Abdomen

Some causes of acute abdominal pain occur more commonly in or are specific to CKD patients. A high index of suspicion for ischemic bowel is important because of the frequency of vascular disease in CKD. Pain may result from complications of autosomal polycystic kidney disease. Retroperitoneal hemorrhage can arise from anticoagulation, including during HD. In PD, abdominal pain arises from peritonitis, acidity of the fluid (causing dialysate infusion pain), catheter malposition, constipation, and encapsulating peritoneal sclerosis. Other surgical conditions need to be distinguished from dialysis-specific causes. Although air uncommonly enters the peritoneal cavity during PD, in the setting of acute abdominal symptoms the finding of free gas on radiologic imaging of the abdomen suggests visceral perforation.

GASTROINTESTINAL-RENAL SYNDROMES

A number of conditions result in both renal and GI manifestations (Table 87-2).

Diabetes

Diabetes is commonly complicated by disordered gut motility. Gastroparesis needs to be distinguished from uremic upper GI symptoms. Diarrhea caused by diabetic enteropathy is also common, classically is nocturnal, and usually is neurogenic in origin. Treatment is usually by antimotility agents. Bacterial overgrowth is uncommon and is diagnosed by the hydrogen breath test. GI symptoms may be exacerbated by drug treatments for diabetes, including metformin and α-glucosidase inhibitors. Gastroparesis results in difficulties with glycemic control, fluid and electrolyte imbalance, drug malabsorption, and malnutrition. The speed of colonic transport is decreased in diabetes, which may result in constipation.

Systemic Vasculitis

Gastrointestinal manifestations of vasculitis include intestinal ischemia or infarction, hemorrhage, and perforation with peritonitis. Abnormal liver function test results arise from hepatitis, and cholecystitis and pancreatitis have been described. Serositis with abdominal pain is a feature of systemic lupus erythematosus. Abdominal pain, vomiting, and GI hemorrhage are typical of Henoch-Schönlein purpura.

Systemic Amyloidosis

Primary AL amyloidosis may result in both renal and GI involvement. Conversely, inflammatory bowel disease is an important cause of secondary AA amyloidosis, which may result in renal

involvement. Thus, in a patient with renal amyloidosis who has GI symptoms, it is important to characterize the type of amyloid and the underlying cause of GI disturbance.

Autosomal Dominant Polycystic Kidney Disease

Abdominal hernias are more common in ADPKD[16] and are a particular problem in PD patients. Colonic diverticular disease occurs more frequently. The enlarged kidneys can result in abdominal pain, hemorrhage, abdominal fullness, and anorexia. Hepatic cysts and occasionally massive hepatomegaly may cause chronic abdominal pain and fullness. Common bile duct dilation, of uncertain significance, occurs more frequently in ADPKD.

Inflammatory Bowel Disease

Inflammatory bowel disease may be complicated by AA amyloidosis and IgA nephropathy. Drug therapy, such as aminosalicylates, can lead to renal disease, including chronic interstitial nephritis. Terminal ileal disease in Crohn disease can lead to hyperoxaluria and oxalate calculi.

Celiac Disease

Celiac disease is a relatively common condition and occurs with increased frequency in association with other autoimmune conditions, such as diabetes mellitus. There is also a reported association with IgA nephropathy.[17]

DRUGS AND GASTROINTESTINAL DISEASE IN CHRONIC KIDNEY DISEASE

Drugs commonly used in CKD can lead to GI problems (Table 87-3). Phosphate-binding drugs commonly result in abdominal symptoms. Nausea and vomiting are important complications of cinacalcet. Other drugs important in CKD that may cause GI problems include statins, ACE inhibitors, iron supplements, sodium bicarbonate, bisphosphonates, and metformin. Acid-suppressing drugs including proton pump inhibitors and H_2 receptor blockers are commonly prescribed in CKD. They are often inappropriately continued for long periods[18] and have their own associated side effects. They increase the risk of *C. difficile* infection. Proton pump inhibitors can result in symptoms including nausea, vomiting, abdominal pain, diarrhea, and constipation. By reducing gastric acidity they may also reduce the effectiveness of calcium carbonate prescribed as a phosphate binder (because it is only soluble in an acid environment).

SPECIFIC GASTROINTESTINAL COMPLICATIONS OF RENAL REPLACEMENT THERAPY

Idiopathic Dialysis-Related Ascites

Idiopathic ascites occurs in HD patients and may be caused by suboptimal dialysis clearances. Diagnosis is by exclusion of other causes of ascites. Aspirated fluid usually has an elevated protein content. Management includes fluid and sodium intake restriction and ultrafiltration by dialysis. Small-solute clearance must be optimized, and paracentesis may be required for symptom control. The condition may resolve after renal transplantation, and switching to PD can be tried.

Gastrointestinal Side Effects of Drugs Commonly Used in Patients with Chronic Kidney Disease

Drug	GI Side Effects
Calcium-based phosphate binders	Constipation, abdominal discomfort
Sevelamer	Constipation, dyspepsia, bowel obstruction (very rare)
Lanthanum carbonate	Dyspepsia, nausea, diarrhea
Cinacalcet	Anorexia, nausea, vomiting
Statins	Abdominal discomfort, diarrhea, constipation
ACE inhibitors	Nausea, constipation, diarrhea, acute pancreatitis
Iron supplements	Nausea, epigastric pain, constipation, diarrhea
Bisphosphonates	Esophagitis, esophageal ulcers and strictures
Polystyrene sulfonate (calcium resonium, Kayexalate)	Severe constipation, colonic necrosis
Calcium channel blockers	Constipation, intestinal pseudo-obstruction
Metformin	Anorexia, nausea, vomiting, diarrhea
Proton pump inhibitors	Nausea, vomiting, abdominal pain, constipation, diarrhea
Mycophenolate mofetil	Diarrhea, abdominal pain, vomiting
Azathioprine	Dyspepsia, acute pancreatitis, hepatitis

Table 87-3 Gastrointestinal (GI) side effects of drugs commonly used in patients with chronic kidney disease (CKD). *ACE,* Angiotensin-converting enzyme.

Peritoneal Dialysis–Related Gastrointestinal Conditions

A number of complications relating to PD may affect the abdomen, including infectious peritonitis, pain on dialysate infusion and drainage, and encapsulating peritoneal sclerosis (see Chapter 97). Hemoperitoneum in PD is typically related to the menstrual cycle, occurring during menstruation or ovulation, or may be self-limited, probably resulting from minor peritoneal membrane trauma from the PD catheter (Fig. 87-4). Rarely, underlying pathologic causes are present, including encapsulating peritoneal sclerosis, malignant disease, pancreatitis, hepatobiliary disease, and hemorrhage from polycystic kidneys.

Dialysis-Related Amyloidosis

Amyloidosis caused by deposition of β_2-microglobulin in very rare patients on very long-term dialysis can result in GI manifestations. These include GI hemorrhage, diarrhea, pseudo-obstruction, ischemia, and perforation (see Chapter 85).

Transplantation and Gastrointestinal Disturbance

A variety of GI problems occur after renal transplantation (see Chapters 104 and 105). Gastritis or duodenitis results from corticosteroid therapy, and peptic ulcers occur most commonly in the initial year after transplantation.[19] Mycophenolate mofetil commonly leads to

Figure 87-4 Hemoperitoneum. Blood-stained peritoneal dialysate from a peritoneal dialysis patient who has developed acute pancreatitis.

diarrhea, abdominal pain, or vomiting. Infectious complications of the GI tract include oral and esophageal candidiasis, cytomegalovirus disease, and diarrhea from *C. difficile* infection. Post-transplantation lymphoproliferative disease may also involve the GI tract.

NUTRITION IN CHRONIC KIDNEY DISEASE

Nutrition plays an important role in the management of hypertension, obesity, hyperlipidemia, and diabetes, all of which affect CKD progression. As the glomerular filtration rate (GFR) deteriorates, retention of nitrogenous metabolites, decreased ability to regulate levels of electrolytes and water, and certain vitamin deficiencies can be affected by dietary changes. In addition, protein-energy depletion predicts a poor outcome.

Malnutrition: Protein-Energy Wasting

In kidney disease there are often conditions that lead to wasting that are not related to reduced intake alone. Many terms exist to indicate wasting in CKD, including *uremic malnutrition, protein-energy malnutrition,* and *malnutrition–inflammation complex syndrome.* Because *malnutrition* refers to an intake that is inadequate for the needs of the individual, it can be misleading to use this blanket term when reduced intake is not necessarily the sole cause of wasting. Nutrition intervention alone in these cases may not successfully reverse the loss of skeletal muscle and fat mass. Accepted definitions are useful to help clinicians recognize problems and develop appropriate treatment strategies as well as to focus research; in 2008 the International Society of Renal Nutrition and Metabolism recommended that the term *protein-energy wasting* be used for loss of body protein and fuel reserves.[20]

The prevalence of protein-energy wasting in dialysis patients ranges from 10% to 70%, depending on the choice of nutritional marker and the population studied.[21,22] There is also diminished nutritional status before initiation of dialysis, which strongly predicts mortality on dialysis. Paradoxically, several investigators have found a significant inverse relationship between mortality risk and body size in HD populations, a phenomenon termed *reverse epidemiology* (see Chapter 82).

Several factors related to the uremic state may contribute to the high incidence of protein-energy wasting:

Assessment of Nutritional Status

Area	Assessments
Physical examination	
Assessment of dietary intake	Diet history, food diaries, appetite assessment questionnaires
Anthropometric measurements	Body weight, height, body mass index Percentage weight change Skinfold thickness Midarm muscle circumference
Body composition	Neutron activation Near-infrared reactance Bioelectrical impedance Dual-energy x-ray absorptiometry (DXA) Total body potassium
Biochemical determinations	Serum electrolytes Serum proteins PNA, PCR Serum cholesterol Creatinine index
Nutritional scoring systems	Subjective global assessment
Immunologic assays	Blood lymphocytes Delayed cutaneous hypersensitivity tests
Functional tests	Grip strength

Table 87-4 Assessment of nutritional status. Methods used to assess nutritional status are shown. *PCR,* Protein catabolic rate (mathematically identical to PNA); *PNA,* protein equivalent of total nitrogen appearance. The creatinine index is measured as the sum of creatinine removed from the body (measured from the creatinine removed in dialysate, ultrafiltrate, and/or urine), any increase in the body creatinine pool, and the creatinine degradation rate. See also http://www.kidney.org/professionals/kdoqi/pdf/KDOQI2000NutritionGL.pdf.

- Inadequate protein and calorie intake. Nutrient intake parallels the decrease in GFR and is largely driven by CKD-associated anorexia.[23] This anorexia is caused by impaired taste acuity and diminished olfactory function, medications, autonomic gastroparesis, psychological and socioeconomic factors, and inadequate dialysis. Elevated serum leptin, a long-term regulator of appetite, has also been linked to the anorexia seen in CKD.[24]
- Nutritional losses occur during treatment. Eight to 12 g of amino acids is lost per HD treatment, and 5 to 10 g of protein is lost daily during PD, depending on the peritoneal membrane transport type. This may be significantly higher during episodes of PD peritonitis.
- Metabolic acidosis and periods of acute or chronic illnesses may induce protein catabolism. This is mediated in large part through the ubiquitin-proteasome pathway of protein degradation.[25]
- Protein catabolic effects that can further compromise patients early after transplantation include large doses of corticosteroids, the stress response to surgery, and delayed graft function.
- Inflammatory state of uremia (see also Chapter 82).[26]
- Endocrine disorders, such as insulin resistance, increased parathyroid hormone concentrations (which may promote amino acid catabolism and gluconeogenesis), and vitamin D deficiency (which can contribute to proximal myopathy), may have an adverse effect on nutritional status.

Assessment of Nutritional Status

The measurement of nutritional status does not lend itself to one simple test, and a panel of measures is required for optimal screening of nutritional status. Table 87-4 summarizes some of the methods used for assessment of nutritional status.

Estimation of Intake

Diet history, recall, and food diaries are the mainstays for estimation of dietary intake. In addition, a gradual decrease in blood urea nitrogen and reduced phosphate and potassium levels may indicate a decrease in protein intake in dialysis-dependent patients, and low serum cholesterol level may indicate a poor calorie intake.

The excretion of the protein end product urea is easily measured and is often used to estimate adequacy of dialysis. The protein equivalent of total nitrogen appearance (PNA) can be estimated on HD from interdialytic changes in urea nitrogen concentration in serum and the urea nitrogen content of urine and dialysate. nPNA is the term for PNA related to body weight. On the basis of the assumption that nitrogen excretion equals nitrogen intake in steady state, nPNA has been used to approximate dietary protein intake in the short term. Results, however, need to be interpreted with caution (urea kinetic modeling and adequacy of dialysis are further discussed in Chapters 94 and 96. Equations for estimation of nPNA have been recommended by the Kidney Disease Outcomes Quality Initiative (KDOQI).[27]

Body Composition

A range of techniques are available that can distinguish body compartments on the basis of physical characteristics, which can provide information about nutritional state (body lean tissue and fat content) and hydration.

Skinfold thickness can be used to assess body fat, and muscle mass can be assessed by measurement of mid–upper arm muscle circumference (MAMC; Fig. 87-5). The midpoint of the upper dominant arm is used, as this is the arm less likely to have an arteriovenous fistula.

$$\text{MAMC (cm)} = \text{Midarm circumference (cm)} - \left[3.14 \times \text{Triceps skinfold (cm)}\right]$$

Figure 87-5 Routine measurement of skinfold thickness. The dominant arm, which does not have an arteriovenous fistula or graft, is used in patients with renal failure.

The measurement is taken after dialysis for patients on HD. Although these anthropometric measurements are inexpensive and relatively easy to learn and quick to carry out, they are limited by intervariability and intravariability. Nevertheless, serial measures over time can be useful to track changes in the same patient when they are used in conjunction with other nutritional indices.

Subjective global assessment (SGA) is a reliable nutritional assessment tool for patients on dialysis.[28] A series of questions about recent changes in nutrient intake is used with simple observations of the patient's body weight and muscle mass to determine subjectively the nutritional status of the individual; patients are classified as well nourished; mildly malnourished or with suspected malnutrition; or severely malnourished. Figures 87-6 and 87-7 show muscle wasting in a patient on HD classified by SGA as severely malnourished. SGA is by definition subjective and has been criticized for being insufficiently sensitive to define the degree of malnutrition. Other scoring

Figure 87-6 A severely malnourished hemodialysis patient. There is marked wasting of the quadriceps and calf muscles. In addition, note skin lesions from scratching due to uremic pruritus.

Figure 87-7 A severely malnourished hemodialysis patient. Muscle wasting around clavicle and shoulder.

systems that use components of the conventional SGA are presently being evaluated.

Visceral Protein

Fluid status, impaired liver function, age, and acute inflammatory conditions can all affect albumin levels. However, despite its relatively long half-life (20 days), albumin still remains an important measure of nutritional status and health of the patient. Clinically, it may be possible to observe the growth of white nails when there has been a transient period of hypoalbuminemia (Fig. 87-8). Other serum protein markers of nutritional status are also difficult to interpret because of the influence of factors other than nutrition. Serum transferrin is linked to body iron stores and may be altered with changes in iron status. Prealbumin levels can be increased by CKD because of impaired metabolism in the kidney. Levels of prealbumin also decline rapidly during episodes of acute inflammation.

With the low specificity and sensitivity of many of the anthropometric and biochemical markers, it becomes clear that integration of a range of measurements along with evaluation of the subjective well-being of the patient is needed to assess nutritional status (Table 87-5).

Figure 87-8 White nails in hypoalbuminemia. The white band grew during a transient period of hypoalbuminemia caused by nephrotic syndrome.

Nutritional Guidelines

Guidelines are useful, but it is important that dietary restrictions not be unnecessarily imposed and that advice be tailored to the individual and altered as circumstances dictate. Table 87-6 summarizes the nutritional recommendations for CKD.

Hyperlipidemia

Although disturbances in lipid metabolism are commonly seen in CKD, there is a paucity of data on the effect of diet therapy in this group. A diet low in fat, particularly saturated fat, with an increased intake of soluble fiber may be helpful in reducing cholesterol level,

Some Indices of Malnutrition

Assessment	Indices
Biochemical parameters	Serum albumin below the normal range Serum prealbumin <300 mg/l (30 mg/dl) (for maintenance dialysis patients only, because levels may vary according to GFR level for CKD 2-5) Low serum creatinine, phosphate, potassium, urea in patients on dialysis Serum cholesterol <150 mg/dl (3.8 mmol/l) Low creatinine index Low PNA, PCR
Anthropometric parameters	Continuous decline in weight, skinfold thickness, midarm muscle circumference Body mass index <20 kg/m^2 Body weight <90% of ideal Abnormal muscle strength

Table 87-5 Some indices of malnutrition. *GFR,* Glomerular filtration rate; *PCR,* protein catabolic rate; *PNA,* protein equivalent of total nitrogen appearance.

Nutritional Recommendations in Chronic Kidney Disease

Daily Intake	Predialysis CKD	Hemodialysis	Peritoneal Dialysis
Protein (g/kg ideal BW) (see KDOQI[27] for estimation of adjusted edema-free body weight)	0.6-1.0 Level depends on the view of the nephrologist 1.0 for nephrotic syndrome.	1.1-1.2[27,31] This is a broad recommendation; protein intake would be individualized according to the patient's nutritional status, serum phosphate levels, and dialysis adequacy.	1.0-1.3[27,38]
Energy (kcal/kg BW)	35[27] (younger than 60 yr) 30-35[27] (older than 60 yr)	35[27] (younger than 60 yr) 30-35[27] (older than 60 yr)	35[27] including dialysate calories (younger than 60 yr) 30-35[27] including dialysate calories (older than 60 yr)
Sodium (mmol)	<100 (more if salt wasting)	<100	<100
Potassium	Reduce if hyperkalemic	Reduce if hyperkalemic	Reduce if hyperkalemic; potassium restriction is generally not required.
	If hyperkalemic, advice will take the form of decreasing certain foods (e.g., some fruits and vegetables) and giving information about cooking methods.		
Phosphorous	Reduce; level dependent on protein intake Advice will take the form of reducing certain foods (e.g., dairy, offal, some shellfish), processed foods with high content of added phosphates, and giving information about the timing of binders with high phosphorus meals and snacks.		
Calcium	In CKD stages 3-5, total intake of elemental calcium (including dietary calcium) should not exceed 2000 mg/day.	Total intake of elemental calcium (including dietary calcium) should not exceed 2000 mg/day.	Total intake of elemental calcium (including dietary calcium) should not exceed 2000 mg/day.

Table 87-6 Nutritional recommendations in chronic kidney disease (CKD). Recommendations are for typical patients but should always be individualized on the basis of clinical, biochemical, and anthropometric indices. *BW,* Body weight; *KDOQI,* Kidney Disease Outcomes Quality Initiative.

although the role of cholesterol lowering in CKD patients is controversial (see Chapter 82). Losing weight if overweight and consuming a diet lower in sugar may improve hypertriglyceridemia, but a balance needs to be struck between healthy eating concepts and nutritional adequacy. Additional fiber, within the confines of the diet, has the benefit of helping to regulate bowel function, particularly important in PD patients.

Hypertension

The role of diet in the prevention and treatment of hypertension is discussed fully in Chapter 35.

Vitamins, Minerals, and Trace Elements

Vitamin, mineral, and trace element abnormalities in CKD relate to dietary restriction, dialysate losses, and the necessity of intact kidney function for normal metabolism of certain vitamins. However, the dietary requirements for patients with CKD are not clear-cut.

Protein and potassium restrictions can lead to inadequate intakes of pyridoxine, vitamin B_{12}, folic acid, vitamin C, iron, and zinc. The use of recombinant human erythropoietin may increase the requirement for iron and folic acid (see Chapter 83).

Increased serum homocysteine is a known risk factor for cardiovascular morbidity in CKD (see Chapter 82). However, lowering of serum homocysteine concentration with folic acid, vitamin B_{12}, and pyridoxine supplements has been shown to have no effect on mortality or risk of cardiovascular events in patients with end-stage renal disease (ESRD).[29] A recent systematic review and meta-analysis also showed that the effects of folic acid–based homocysteine lowering did not reduce cardiovascular events in people with kidney disease.[30]

A variety of multivitamin preparations are available that contain a recommended vitamin profile for dialysis patients. The preparations vary slightly, but the following is one example: vitamin C, 60 mg; biotin, 300 µg; calcium pantothenate, 10 mg; cyanocobalamin, 6 µg; folic acid, 800 µg; niacinamide, 20 mg; pyridoxine, 10 mg; riboflavin, 1.7 mg; and thiamine, 1.5 mg. In the absence of firm guidance, it is prudent to have a low threshold for commencing such a vitamin preparation. The European Best Practice Guidelines (EBPGs) on nutrition give opinion-based recommendations for intakes of vitamins, minerals, and some trace elements in patients on HD.[31]

Although there is evidence for vitamin C having a role in improving anemia management in ESRD, high-dose vitamin C supplements, popular in the general population, should not be taken, because there is a risk that this may lead to tissue oxalate deposition in response to increased serum oxalates not being cleared by the failing kidneys.

A review summarizing the current literature on fat-soluble vitamins in advanced CKD has recently been published.[32] There is universal agreement that supplementation with vitamin A is generally not recommended (unless a patient is receiving total parenteral nutrition) because deficiencies are rare, dialysis losses are minimal, and accumulation leading to toxicity can occur. Vitamin E is known to have antioxidant properties. Deficiency and toxicity are reportedly rare, and status in dialysis patients is inconsistent. More guidance is needed around potential benefits of vitamin E supplementation in CKD, although the EBPGs do recommend that vitamin E can be supplemented in HD patients for secondary prevention of cardiovascular events (based on results from the Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease [SPACE] study) and prevention of recurrent muscle cramps.[31]

Vitamin K functions as a cofactor for the enzyme gamma-glutamyl carboxylase and may have a role in inhibiting vascular calcification (see Chapter 85). There is evidence to suggest that most dialysis-dependent patients have subclinical vitamin K deficiency, and there is no known toxicity. However, research is ongoing in this area to determine if supplementation of vitamin K, and at what level, may have a beneficial role in preventing vascular calcification and reducing mortality in patients with advanced CKD.

Guidelines for vitamin D type and dose as well as phosphorus and calcium intake in CKD have been provided by KDOQI and recently updated by the KDIGO (Kidney Disease: Improving Global Outcomes) organization (see also Chapter 85).

Recommendations for mineral intakes are shown in Table 87-6.

Monitoring and Treatment

Monitoring of patients with CKD involves a combination of nutritional assessment, noting relevant biochemistry (potassium, phosphate, lipids), and observation of fluid status. The challenge comes in giving advice that carefully balances control of electrolytes while not compromising nutritional status. When anorexia is present, strategies to treat this should be considered, and nutrient intake maximized by use of one or more of the methods discussed in the following sections.

Enteral Supplementation

If food fortification advice is insufficient, supplements, in the form of high-protein, high-calorie drinks, powders, and puddings, should be administered. Enteral tube feeding is also an option if nutrient intake cannot be increased sufficiently by use of oral supplements. Renal-specific tube feeds and supplements are available that have lower fluid and electrolyte contents. A systematic review suggested that enteral multinutrient support increases serum albumin concentration and improves total dietary intake in patients receiving maintenance dialysis.[33] In addition, maintenance hemodialysis patients with albumin levels of 3.5 g/dl or lower received intradialytic oral nutritional supplements in a recent large retrospective matched-cohort study. Despite limitations, the results indicated a significantly better survival in the supplemented group versus similarly matched patient controls.[34]

Supplementation of Dialysate Fluids

Intradialytic parenteral nutrition (IDPN) has been used to provide intensive parenteral nutrient therapy with use of concentrated hypertonic solutions three times weekly during HD treatments without the need for establishing a central venous line. The nutrients, usually a mixture of amino acids, glucose, and lipid, are infused into the venous blood line, and only about 10% of infused amino acids are lost into the dialysate. In 2010 a systematic review of the evidence for use of this treatment was published and concluded that the evidence from clinical studies is insufficient to demonstrate either a net benefit or a net harm associated with providing IDPN to malnourished HD patients. The authors recommended that further clinical research is needed in this area.[35]

Intraperitoneal amino acids (IPAAs) can be used in PD. A 1.1% amino acid solution is substituted for glucose in PD fluid, and about 80% of the amino acids are absorbed in a 4-hour period.[36] The long-term effects of IPAAs on nutritional status and clinical outcomes are not known, and the solution is often used primarily to reduce glucose exposure.

Kidney Disease Outcomes Quality Initiative has suggested that IPAAs (for PD) or IDPN (for HD) should be considered for patients who have evidence of protein or energy malnutrition and inadequate protein or energy intake and who are unable to tolerate adequate oral supplements or tube feeding.[27] However, the American Society for Parenteral and Enteral Nutrition (ASPEN) presently recommends that IDPN not be used as a nutritional supplement in malnourished

hemodialysis patients, because studies so far do not offer strong support for IDPN.[37] Clearly, larger randomized controlled trials in malnourished patients are needed to determine the clinical benefit of this treatment.

Appetite Stimulants

Megestrol acetate, a progesterone derivative, moderately improved appetite in HD patients in small studies. However, as megestrol acetate is not without its side effects, larger trials are required before recommendations can be made for CKD patients. More studies are also required for ghrelin, an orexigenic hormone, and melanocortin-receptor antagonists.

Metabolic Acidosis

Although some trials have shown no detrimental effect of mild metabolic acidosis, many others have reported that normalization of the predialysis serum bicarbonate concentration is beneficial for protein nutritional status and bone metabolism. Medical management of metabolic acidosis is discussed further in Chapter 12. Current guidelines recommend the correction of acidosis in dialysis-dependent patients.[31,38]

Exercise

There is a large body of research in the area of exercise training for adults with chronic kidney disease showing significantly beneficial effects on physical fitness, cardiovascular parameters, well-being, and nutritional markers.[39] The future is likely to hold more guidance in this area for clinical practice.

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CHAPTER 88

Dermatologic Manifestations of Chronic Kidney Disease

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Cutaneous disorders are common in patients with end-stage renal disease (ESRD), with the most prevalent disorder being hyperpigmentation. Many of these cutaneous disorders are caused by the underlying renal disease, whereas others relate to the severity and duration of uremia.

Skin lesions associated with cutaneous aging have a high incidence in ESRD patients, including wrinkling, senile purpura, actinic keratoses, and diffuse hair loss. The prevalence of skin cancers does not appear to be increased unless the patient has received or is receiving immunosuppression.

Improved treatments in dialysis patients have resulted in changes in the frequency and types of skin disorders observed in conjunction with ESRD. Dermatologic conditions such as uremic frost, erythema papulatum uremicum, uremic roseola, and uremic erysipeloid now rarely occur. Pigmentary alterations, xerosis, ichthyosis, half-and-half nails, acquired perforating dermatosis, bullous dermatoses, pruritus, and calcific uremic arteriolopathy (CUA) are prevalent (Fig. 88-1), whereas nephrogenic systemic fibrosis is a rare and waning entity, now that the causative agent has been identified.[1,2] The last four skin disorders are the focus of this chapter because they are associated with significant morbidity or mortality and represent an ongoing diagnostic or therapeutic challenge.

UREMIC PRURITUS

Clinical Manifestations

Uremic pruritus (UP) is a frequent symptom of ESRD with a reported prevalence ranging from 22% to 48%. Although its incidence in adult dialysis patients has declined as a result of improved dialysis efficacy and the introduction of so-called "biocompatible dialysis membranes," pruritus remains a frustrating problem for patients, causing serious discomfort and skin damage, often in association with disturbance of day and night rhythm, sleeping disorders, depression, anxiety, and diminished quality of life.[3,4] The intensity and spatial distribution of UP vary significantly among patients and over time throughout the course of renal disease. Excoriations, induced by uncontrollable scratching with or without superimposed infection, are frequently encountered in severely affected patients and rarely lead to prurigo nodularis, that is, a treatment-resistant lichenified or excoriated papulonodular chronic skin eruption (Fig. 88-2). The most frequently involved body areas are the back, limbs, chest, and face; 20% to 50% of patients report generalized pruritus.[5]

Pathogenesis

Many uremic factors are thought to contribute to UP. Parathyroid hormone (PTH) and divalent ions (calcium, phosphate, and magnesium) have been implicated because itching is a frequent symptom accompanying severe secondary hyperparathyroidism and elevated calcium-phosphate product. However, the lack of consistent correlations between serum and skin levels of PTH, calcium, phosphorus, and magnesium with the severity of UP indicates that other factors contribute to its development. Histamine released by mast cells has been implicated in UP. The number of dermal mast cells is increased in uremic patients, and higher tryptase and histamine plasma concentrations are reported in severe cases. Histamine release is triggered by substance P, a neurotransmitter involved in itch sensation. The role of elevated serotonin (5-hydroxytryptamine [5-HT_3]) levels in dialysis patients with UP is debated; clinical trials using a selective inhibitor of 5-HT_3 have yielded conflicting results (see later discussion). Xerosis is a common skin problem in dialysis patients (60% to 90%) that predisposes to UP. Skin dryness is caused by primary dermal changes associated with uremia, such as atrophy of sweat glands with impaired sweat secretion, disturbed stratum corneum hydration, sebaceous gland atrophy, and abnormal arborization of free cutaneous nerve fiber endings.

There are two major hypotheses of the mechanisms of UP. The opioid hypothesis proposes that UP is caused by overexpression of opioid μ receptors in dermal cells and lymphocytes. Consistent with this hypothesis, activation of the κ opioid system using a κ-receptor agonist was efficient in reducing pruritus in a mouse model. In contrast, the immune hypothesis considers UP an inflammatory systemic disease rather than a local skin disorder. Studies examining the beneficial effects of ultraviolet B (UVB) exposure on pruritus showed that UVB attenuates the development of Th1-type lymphocytes in favor of the Th2 type. Indeed, the number of CXCR3-expressing and interferon-γ–secreting $CD4^+$ cells (indicating Th1 differentiation) is significantly increased in the circulation of dialysis patients with pruritus compared with those without. Levels of serum markers of inflammation, such as C-reactive protein, interleukin-2, and interleukin-6, are also higher in patients with UP.

Treatment

Common causes of UP in chronic kidney disease (CKD) and dialysis patients, such as primary skin disorders (e.g., urticaria, psoriasis, atopic and contact dermatitis), liver disease (e.g., hepatitis), and endocrine diseases (e.g., hypothyroidism, diabetes mellitus) should be ruled out and adequately treated. The treatment approach to UP is shown in Figure 88-3.

Optimizing Dialysis and Mineral Metabolism Therapy

Optimizing dialysis biocompatibility and efficacy and improving the nutritional status may result in a reduced prevalence and severity of UP. Adequate control of calcium and phosphorus serum concentrations by short-term use of dialysate with low calcium and magnesium concentrations ameliorated pruritus symptoms in only a few small studies and may lead to worsening of renal osteodystrophy in

Figure 88-1 Cutaneous disorders in patients with end-stage renal disease. A, A spectrum of pigmentary alterations occurs in dialysis patients, brownish hyperpigmentation in sun-exposed areas being the most prevalent. **B,** Xerosis, a dry or roughened skin texture, is seen in up to 75% of dialysis patients. **C,** Half-and-half nails (also termed red and white nails) occur in as many as 40% of patients on dialysis. The nails exhibit a whitish or normal proximal portion and an abnormal brown distal portion. **D,** Acquired perforating dermatosis affects approximately 10% of the dialysis population. The lesion is usually asymptomatic and consists of grouped dome-shaped papules and nodules, 1 to 10 mm in diameter. The trunk and the extremities are most commonly involved.

cases of prolonged use. Parathyroidectomy is not advocated for relief of UP because no consistent beneficial effects have been demonstrated.

Skin Emollients

Emollients continue to be the primary treatment given by nephrologists, although the literature is mixed on the overall efficacy of this approach. The use of simple emollients without perfumes or other additives is preferred. Continuous bath oil therapy containing polidocanol, a mixture of monoether compounds of lauryl alcohol and macrogol, seems to be of value for some patients. Sericin, a biopolymer protein from the silkworm *(Bombyx mori)* contains 32% serine, the main amino acid of the natural moisture factor in human skin, and suppresses the release of proinflammatory cytokines. Sericin was shown to effectively reduce UP score in a randomized, double-blind, placebo-controlled 6-week study in 50 dialysis patients.[6]

Antihistaminic Drugs

Classic antihistamines have limited efficacy and do not differ in efficacy compared with emollients; newer, second-generation

antihistamines (e.g., desloratadine) might have some effect in UP. Ketotifen (2 to 4 mg/day), a putative mast cell stabilizer, was beneficial in one small study.

Phototherapy

Ultraviolet light, especially UVB (wavelength, 280 to 315 nm), is effective for treatment of UP and is well tolerated except for occasional sunburn. The duration of the antipruritic effect of thrice-weekly total body UVB therapy (total, 8 to 10 sessions) is variable, but it may last for several months. Potential carcinogenic effects of UV radiation require serious consideration, and its prolonged use is contraindicated in patients with a fair complexion (skin phototypes I and II).

5-Hydroxytryptamine Antagonist

Ondansetron, a selective 5-HT_3 antagonist, was used successfully in a small study in peritoneal dialysis patients. However, a subsequent larger randomized, placebo-controlled study failed to show superiority over placebo in HD patients.

Figure 88-2 Prurigo nodularis. *(Courtesy I. Macdougall, London, United Kingdom.)*

Opioid Receptor Agonists

A κ-opiate receptor agonist, nalfurafine, given intravenously after HD, was tested in two randomized, double-blind, placebo-controlled trials comprising 144 patients. Itching intensity, excoriations, and sleep disturbances were significantly reduced in patients receiving the active compound without an excess of drug-related side effects compared with placebo.[7] Oral daily doses of 2.5 to 5 mg nalfurafine were equally effective in reducing UP scores compared with placebo during a 2-week treatment period in 337 dialysis patients.[8] A subsequent 1-year study (n = 211) confirmed the sustained beneficial effect of 5 mg nalfurafine on UP, with the most frequently reported adverse events being insomnia (19%), constipation (7%), and increased blood prolactin concentrations.[9]

Gabapentin

Gabapentin, an anticonvulsant drug, administered after dialysis (300 mg) was effective in reducing pruritus. A reduced dose is required if it is given chronically to patients with ESRD, because it has a narrow therapeutic window, and it can accumulate and cause neurotoxic side effects.[10] UP score was significantly reduced in two controlled studies after 4 weeks of gabapentin therapy at a dose of 100 to 300 mg administered thrice weekly after dialysis. Gabapentin was well tolerated; no patients stopped therapy because of side effects, which were limited to dizziness, somnolence, fatigue, and nausea. Similar effects were demonstrated in a smaller study using pregabalin.

Immunomodulators and Immunosuppressive Agents

A 7-day course of thalidomide reduced the intensity of UP by up to 80% in a placebo-controlled crossover study of 29 HD patients. Because of its strong teratogenic properties, thalidomide should probably be reserved for therapy-resistant severe UP in individuals

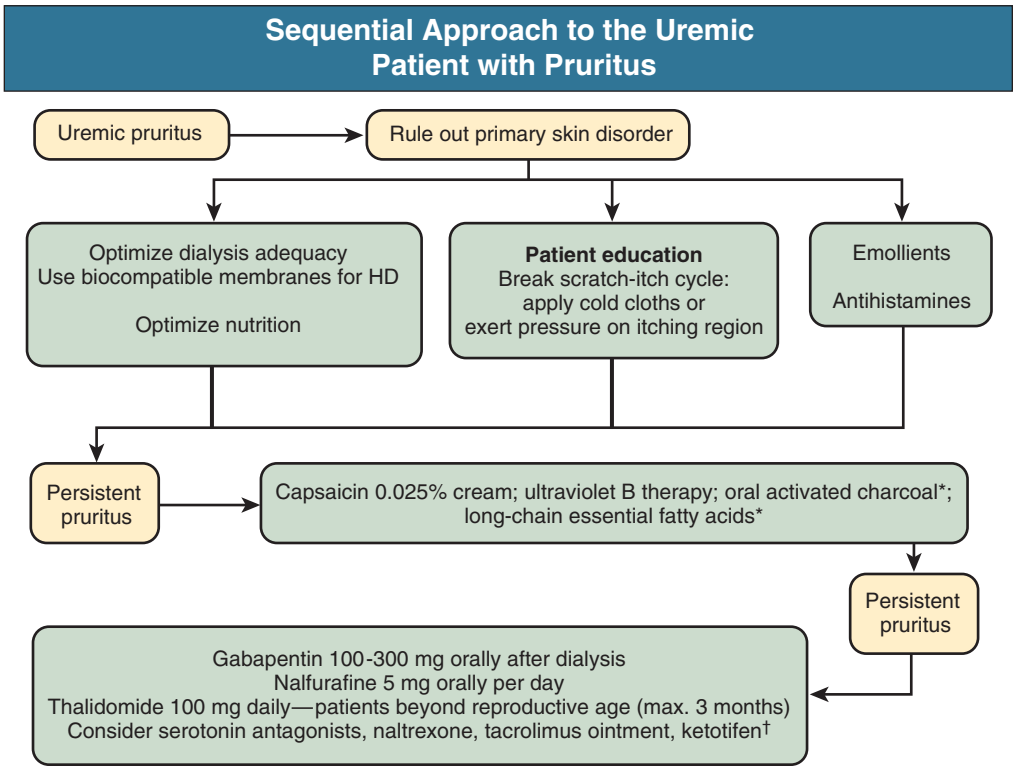

Figure 88-3 Sequential approach to the uremic patient with pruritus. *See text for details. †Therapeutic benefit in studies has been described variably; see text for details. *HD,* Hemodialysis.

outside the reproductive-age category. Adverse effects of thalidomide, such as peripheral neuropathy and cardiovascular side effects, limit its continuous longer use. A prospective, single-center study of 25 chronic dialysis patients with UP demonstrated that 6 weeks of treatment with tacrolimus ointment (0.1%) significantly reduced the severity of UP. Tacrolimus was well tolerated in this trial and caused no detectable systemic exposure or side effects.[11] However, a subsequent, smaller vehicle-controlled trial showed equal relief of UP with vehicle and tacrolimus. The risks of long-term topical use of these agents are currently unknown, and their prolonged use is not recommended until more data are available.

Long-Chain Essential Fatty Acids

Oral administration of γ-linoleic acid (GLA)–rich primrose oil resulted in significant improvement of UP in chronic dialysis patients. Supplementation of GLA-rich primrose oil is thought to augment synthesis of anti-inflammatory eicosanoids. Similar effects could be obtained through use of fish oil, olive oil, and safflower oil.

Capsaicin

Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide) is a natural alkaloid found in the pepper plant that depletes the cutaneous type C sensory nerve endings of substance P. Two clinical studies showed that application of a 0.025% capsaicin cream significantly alleviated UP in dialysis patients, who exhibited no side effects.

Oral Activated Charcoal

Pruritus symptoms completely disappeared or were significantly reduced in chronic dialysis patients treated with activated charcoal (6 g/day) for 8 weeks. In two different clinical studies, comparable results were obtained with this inexpensive and well tolerated compound, rendering it a valuable alternative for patients with UP.

Miscellaneous

Various other types of therapies have been examined in the treatment of pruritus but are, despite the effectiveness of some, not considered first choice in chronic HD patients because of undesirable side effects, cumbersome use, or incompatibility with renal replacement therapy (sauna, cholestyramine, nicergoline). Other therapies that have not reduced UP in a controlled setting and are therefore not advocated include acupuncture, low-protein diet, intravenous lidocaine, sertraline, and mexiletine.

BULLOUS DERMATOSES

Bullous dermatoses are reported in up to 16% of patients on maintenance dialysis. This skin disease entity mainly comprises pseudoporphyrias (e.g., secondary to nonporphyrinogenic drugs and chemicals) and other photodermatoses, whereas true porphyrias (e.g., porphyria cutanea tarda [PCT], variegate porphyria) remain a rare entity.[9] Pseudoporphyrias, true porphyrias and photodermatoses are clinically and histologically similar and are characterized by a blistering photosensitive skin rash. The dorsal hands and the face are the most affected areas (Fig. 88-4).

Porphyria cutanea tarda is caused by abnormalities in the porphyrin-heme biosynthetic pathway leading to an accumulation of highly carboxylated uroporphyrins in the plasma and skin. Phenotypic expression of the disease also requires one or more of a number of external contributory factors, including alcohol, estrogens, iron overload, and infection with hepatitis B and C. It is important to distinguish PCT from other porphyrias in which patients are at risk for development of potentially fatal neurologic attacks if they are exposed to porphyrinogenic drugs and other precipitants. Therapeutic options include avoidance of environmental triggers, HD with high-flux membranes, repeated small-volume phlebotomies, and iron chelators.

Figure 88-4 Porphyria cutanea tarda. Tense bullae, erosions, and crusts of the dorsal hands. *(From reference 12.)*

The term *pseudoporphyria* was originally used for patients with normal plasma porphyrins who exhibited PCT-like skin lesions secondary to drugs and chemicals. However, some dialysis patients also develop similar skin lesions that spontaneously heal and leave a hypopigmented area; this entity is known as *dialysis porphyria;* a proportion of these patients have raised plasma porphyrins but without the disturbances in porphyrin metabolism classically found in the porphyrias. In rare patients, an offending medication can be identified. However, in most dialysis patients, protection from sun exposure appears to be the only preventive measure.

CALCIFIC UREMIC ARTERIOLOPATHY (CALCIPHYLAXIS)

Definition

Calcific uremic arteriolopathy, or calciphylaxis, is a devastating and life-threatening ischemic vasculopathy confined primarily to patients with CKD. There are also reports of this disease in nonuremic patients. The ischemia may be so severe that frank infarction of downstream tissue develops. The most common and most noticeable damage is in the skin and subcutaneous tissues.[12,13] CUA should be distinguished from benign nodular calcification (calcinosis cutis), which can develop in patients with very high serum calcium-phosphate product (Fig. 88-5).

Pathogenesis

The pathogenesis of CUA involves abnormalities in mineral metabolism in uremia that predispose to vascular and soft tissue calcification,[14] but no single abnormality is sufficient to predict the development of this disorder. Elevated levels of PTH and therapy with vitamin D analogues have been associated with an increased risk of CUA, although the evidence is not always striking. A perturbation of the calcium and phosphate homeostasis most probably underlies the positive association. However, in acute CUA serum calcium and phosphate levels can be low. Insufficient activation or expression of inhibitors of calcification should also be considered in the pathogenesis. Inhibitors of vascular calcification include matrix GLA protein (MGP), osteoprotegerin, pyrophosphate, and fetuin-A.

Figure 88-5 Benign nodular calcification (calcinosis cutis). Firm subcutaneous nodule adjacent to the elbow.

MGP requires vitamin K–mediated γ-carboxylation for its functional activity. As a consequence, coumarin anticoagulants and vitamin K deficiency may antagonize MGP function and stimulate vascular calcification. Levels of both osteoprotegerin and fetuin-A decline with inflammation. Finally, several lines of evidence indicate that a hypercoagulable state secondary to an absolute or functional protein C or protein S deficiency may be involved in the pathogenesis of CUA.[11]

Epidemiology and Risk Factors

Although hard epidemiologic data are lacking, the incidence of CUA may be increasing. This might in part result from increased physician awareness and the high-risk profile of contemporary dialysis patients. The estimated incidence ranges from 1 to 4 per 100 patient-years.

Female gender, Caucasian race, obesity, diabetes, use of coumarin anticoagulants, and dialysis vintage are established risk factors. In a recent case control study, the incidence of CUA was shown to be 10-fold higher in dialysis patients treated with warfarin or coumarins. Probable risk factors include low serum albumin concentrations, the use of calcium salts and vitamin D analogues, and exposure to high doses of iron salts. There is no correlation between the severity of any of these factors and the development of CUA.[11]

Clinical Manifestations

Calcific uremic arteriolopathy is typically characterized by areas of zoster-like tenderness and ischemic necrosis of the dermis, subcutaneous fat, and, less often, muscle. These ischemic changes lead to livedo reticularis or violaceous, painful, plaque-like subcutaneous nodules on the trunk, buttocks, or proximal extremity—that is, in areas of greatest adiposity (proximal CUA; Fig. 88-6, *A*). The early purpuric plaques and nodules progress to ischemic or necrotic ulcers with eschars that often become infected. Proximal CUA is frequently precipitated by a specific event, such as local skin trauma or a hypotensive episode. CUA can also affect the hands, fingers, and lower extremities, thereby mimicking atherosclerotic peripheral vascular disease (distal CUA; Fig. 88-6, *B*). Peripheral pulses are preserved distal to the area of necrosis. Myopathy, hypotension, fever, dementia, and infarction of the central nervous system, bowel, or myocardium have been described in association with cutaneous necrosis. This condition is termed *systemic CUA*.[11,12]

Pathology

The histologic features of CUA are suggestive but not pathognomonic. Specimens from incisional biopsies of early lesions show subtle histologic changes. Late lesions characteristically show epidermal ulceration, dermal necrosis, and mural calcification with intimal hyperplasia of small and medium-sized blood vessels in the dermis and subcutaneous tissue (Fig. 88-7).

Diagnosis and Differential Diagnosis

Many clinicians base the diagnosis of CUA on physical examination findings only. Although ulceration is an obvious presentation of CUA, increasing awareness of the condition should allow diagnosis at an earlier, nonulcerative stage when a distinct subcutaneous tenderness can be felt below the early skin lesions.[12] Biopsies are discouraged by most but not all experts because of potential ulceration in the region of the incision and the risk of sample error. Other potentially useful diagnostic procedures include measurements of transcutaneous oxygen saturation, bone scintigraphy (Fig. 88-8), and xeroradiography.[12]

The following conditions should be considered in the differential diagnosis: herpes zoster, systemic vasculitis, peripheral vascular disease, pyoderma gangrenosum, atheroemboli, cryoglobulinemia, warfarin-induced skin necrosis, and systemic oxalosis. A skin biopsy should performed when clinical circumstances do not suggest CUA or when detailed clinical and laboratory examinations, including the assessment of coagulation and immunologic parameters, point to an alternative diagnosis.

Natural History

Despite intensive combined treatments, the prognosis of patients with CUA remains poor; the overall 1-year survival is 45% and the 5-year survival is 35%, with a relative risk of death of 8.5 compared with other dialysis patients. Patients with ulcerative or proximal CUA have the worst prognosis. Infection accounts for up to 60% of the mortality.[12]

Prevention and Treatment

Preventive approaches include attention to calcium, phosphorus, PTH homeostasis, and nutritional state. Specific therapeutic regimens have been limited to uncontrolled case series (Box 88-1). A reasonable plan of intervention should include an aggressive program of wound care and prevention of superinfection, adequate pain control, and correction of underlying abnormalities in serum calcium and phosphorus concentrations. This includes cessation of vitamin D supplementation, intensification of the dialysis regimen, and use of a low-calcium dialysate and non–calcium-containing phosphate binders (e.g., sevelamer, lanthanum carbonate). Furthermore, local tissue trauma, including subcutaneous injections, should be avoided. Parathyroidectomy is effective in the control of CUA in some series but not in others and should be reserved for patients with severe hyperparathyroidism.[11] In such patients, calcimimetic agents may be a suitable noninvasive alternative. Vitamin K supplementation is advised in patients with warfarin- or coumarin-associated CUA. Novel and promising therapies include sodium thiosulfate and bisphosphonates. Sodium thiosulfate has recently been licensed as an orphan drug for CUA by the European Medicines Agency. It enhances the solubility of calcium deposits[12] because exchange of calcium for sodium results in extremely soluble calcium thiosulfate. Besides being a chelator of calcium, sodium thiosulfate is also a potent antioxidant. Sodium thiosulfate is given intravenously at the

Figure 88-6 Proximal (A), and distal (B, C) calcific uremic arteriolopathy.

end of every HD session (12.5 to 25 g during 30 to 60 minutes). Apart from nausea and vomiting, the therapy is well tolerated. The major side effect of sodium thiosulfate infusion is the development of metabolic acidosis. The optimal duration of treatment and potential effects of long-term treatment on bone are unknown.

NEPHROGENIC SYSTEMIC FIBROSIS

Definition

Nephrogenic systemic fibrosis (NSF), formerly known as nephrogenic fibrosing dermopathy, is a scleroderma-like fibrosing disorder that develops in the setting of renal failure. The fibrotic process affects the dermis, subcutaneous tissues, fascia, and other organs, including striated muscles, heart, and lungs.[17]

Pathogenesis

Gadolinium-based contrast (GBC) agents have recently been identified as the cause of NSF; exposure to gadolinium before the onset of disease was confirmed in more than 95% of reported cases. Free gadolinium ions are highly toxic to tissues. The toxic effects of gadolinium are circumvented by sequestration of the metal by chelates, large organic molecules that form a stable complex with gadolinium and make the ion biochemically inert and nontoxic. Under normal circumstances, GBC agents are eliminated by the kidney through glomerular filtration. Evidence points toward aberrant activation of circulating fibrocytes as a central event in the genesis of NSF. Other investigators have suspected that the strongly profibrotic mediator transforming growth factor β may be involved in the pathogenesis of NSF.

Epidemiology

Nephrogenic systemic fibrosis is a rare disorder. Since the identification of the first patients with NSF in 1997, the NSF registry has confirmed more than 215 patients from medical centers worldwide. NSF equally affects men and women. The risk for development of NSF after GBC agent exposure is related to the degree of renal failure and stability of the chelate. The incidence of NSF in patients with

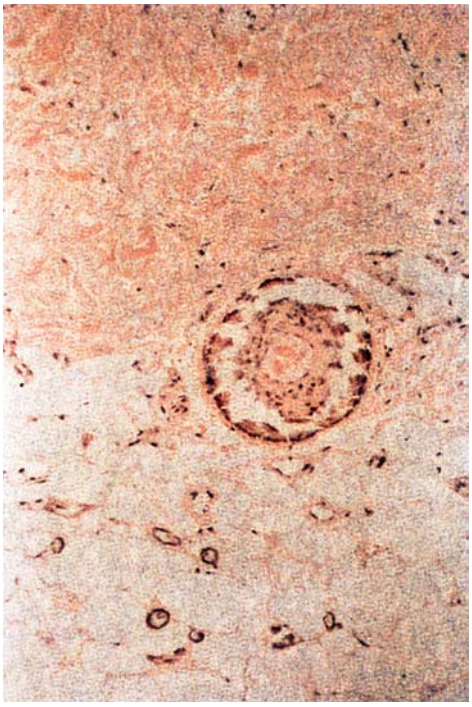

Figure 88-7 Histopathologic features of calcific uremic arteriolopathy. Medial calcification and intimal hyperplasia of an arteriole at the dermal-subcutaneous junction. Note calcification of interlobular capillaries in the subcutaneous tissue. Van Kossa staining. *(From reference 12.)*

Figure 88-8 Bone scintigraphic abnormalities in calcific uremic arteriolopathy. Calf calcification in a patient with gross ulcerations in both legs from the popliteal fossae to the ankles. *(From reference 15.)*

severe renal dysfunction (glomerular filtration rate below 30) varies from 0.19% to 4%. Gadodiamide (marketed as Omniscan in the United States), the linear nonionic chelate–based formulation, maintains the highest risk on the basis of epidemiologic data and animal studies. Gadopentetate, the linear ionic chelate–based product, probably has a medium risk, less than linear nonionic chelates but more than macrocyclic chelates. Other factors reported to be associated with NSF (without definitive proof) include coagulation abnormalities and deep venous thrombosis, recent surgery (particularly vascular surgery), hyperphosphatemia, and the use of high doses of recombinant erythropoietin. Angiotensin-converting enzyme (ACE) inhibitors might protect against NSF. It may be expected that the ban of the linear gadolinium chelates gadodiamide, gadoversetamide, and gadopentetate in individuals with renal dysfunction (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2) will result in the progressive disappearance of NSF in the near future.

Treatment Options in Patients with Calcific Uremic Arteriolopathy (CUA)

1. **Reduction of procalcifying factors**
   - Intensified (e.g., daily, hemodialysis; switch from peritoneal dialysis to hemodialysis; low-calcium dialysate)
   - Avoidance of vitamin D and calcium supplements; administration of calcium-free phosphate binders; bisphosphonate administration (caution if adynamic bone disease is suspected)
   - Parathyroidectomy (in case of hyperparathyroidism) or administration of cinacalcet
2. **Improving the status of calcification inhibitors**
   - Halt vitamin K antagonists (warfarin)
   - Aggressive treatment of infections or other proinflammatory stimuli to increase fetuin-A levels (a negative acute-phase protein)
   - Experimental:
     - *Administration of high-dose vitamin K_2?*
     - *Administration of fetuin-A (e.g., by fresh frozen plasma or plasma exchange?)*
3. **Prevention or reversal of calcium-phosphate precipitation**
   - Administration of sodium thiosulfate
4. **Supportive measures**
   - Avoidance of additional local tissue trauma by atraumatic wound care with gentle debridement of necrotic tissue and avoidance of subcutaneous injections
   - Anticoagulation (heparin and low-molecular-weight heparins)
   - Adequate pain management
   - Adequate infection control

Box 88-1 Treatment options in patients with CUA (calciphylaxis). Theoretical options based on pathophysiologic considerations, which have not been tested in clinical practice, are printed in italics. *(Modified from reference 16.)*

Clinical Manifestations and Natural History

The lesions of NSF are typically symmetric and develop on limbs and trunk. A common location is between the ankles and midthighs and between the wrists and mid-upper arms bilaterally. On occasion, swelling of the hands and feet, sometimes associated with bullae, is noted. The primary lesions are skin-colored to erythematous papules that coalesce into erythematous to brawny plaques with a *peau d'orange* appearance (Fig. 88-9, *A*). These plaques have been described as having an ameboid advancing edge. Nodules are sometimes also described. Involved skin becomes markedly thickened and woody in texture. Joint contractures may develop rapidly, with patients becoming wheelchair dependent within days to weeks of onset (Fig. 88-9, *B*). Patients often complain of pruritus, causalgia, and sharp pains in the affected areas.[13] Although NSF has not been reported as a cause

Figure 88-9 Nephrogenic systemic fibrosis. A, *Peau d'orange* appearance. **B,** Swelling of the hands, accompanied by palmar erythema, blisters, and contracture of the fingers.

of death, the impairment of mobility seen in this disorder has led to fractures that ultimately resulted in a protracted hospital course and death.

Pathology

The histopathologic changes in affected skin include marked proliferation of spindle cells, the presence of numerous dendritic cells, and accumulation of mucinous material and thick collagen bundles (Fig. 88-10). Most dermal spindle cells in NSF have the immunophenotype of a circulating fibrocyte, a recently characterized circulating cell that expresses markers of both connective tissue cells and circulating leukocytes. Metastatic calcification and NSF may be found in the same lesion.

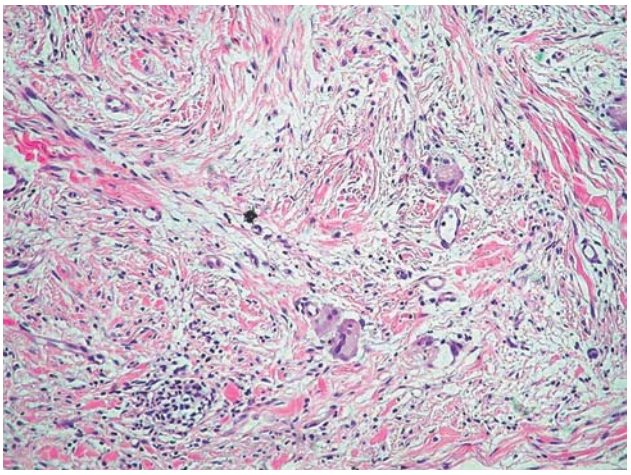

Figure 88-10 Histopathologic features of nephrogenic systemic fibrosis. Haphazardly arranged dermal collagen bundles with surrounding clefts and a strikingly increased number of similarly arranged spindled and plump fibroblast-like cells.

Diagnosis and Differential Diagnosis

The gold standard of diagnosis is histopathologic examination of skin biopsy specimens from an involved site. Skin lesions can also be visualized by [^{18}F]-fluorodeoxyglucose whole-body positron emission tomography. NSF resembles other fibrosing skin disorders including scleromyxedema, scleroderma, eosinophilic fasciitis, eosinophilia-myalgia syndrome, and Spanish toxic oil syndrome. The specific distribution of cutaneous involvement, the occurrence in the setting of renal failure, the history of recent exposure to linear GBC agents, and the unique histopathologic features distinguish NSF from the other fibrotic disorders.

Treatment and Prevention

There is no consistently effective therapy for NSF. There is variable evidence for the efficacy of plasma exchange. Other therapeutic modalities that have been used (or are under investigation) include imatinib, oral and topical corticosteroids, selective histamine blockade, calcipotriene ointment, cyclophosphamide, cyclosporine, thalidomide, interferon alfa, photopheresis, and PUVA (psoralen ultraviolet A) therapy. Intense physiotherapy is advised in every patient to prevent or to reverse limb disability related to contractures of the joints. At present, prevention of NSF seems more important than any of the currently available interventions, and widespread clinical awareness of this condition is required. Avoidance of linear GBC agents in high-risk patients (acute kidney injury [AKI] and patients with CKD with an estimated glomerular filtration rate <30 ml/min/1.73 m^2) is the best measure to prevent this catastrophic complication. If GBC agent exposure is required, use of the smallest dosage of a macrolytic chelate is strongly advised. HD (three sessions within 72 hours) should be considered after GBC agent exposure in patients who are already on this modality.

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CHAPTER 89

Acquired Cystic Kidney Disease and Malignant Neoplasms

Anja S. Mühlfeld and Frank Eitner

DEFINITION

Acquired cystic kidney disease (ACKD) was first recognized in 1847 by John Simon in patients with chronic Bright disease. He described the development of cystic renal changes with cysts ranging from "mustard seed to as large as cocoa nuts" and also noted that they "run a slow and insidious progress during life, and often leave in the dead body no such obvious traces as would strike the superficial observer." ACKD was "rediscovered" by Dunnill and colleagues[1] in 1977 in kidneys from dialysis patients.

Acquired cystic kidney disease consists of chronic kidney disease of any cause and must be differentiated from other types of cystic kidney disease (see Chapters 46 and 47). It is usually defined as more than three to five macroscopic cysts in each kidney of a patient who does not have a hereditary cause of cystic disease. ACKD is associated with renal neoplasms with such high frequency that some authors consider ACKD preneoplastic.[2]

PATHOGENESIS

Most cysts are lined by a single layer of epithelium composed of flat nondescript cells, cells with abundant cytoplasm and hyaline droplets, or small cuboidal cells resembling those from distal tubules or collecting ducts.[2] Some authors have argued that the presence of a brush border on the luminal membrane suggests that the cysts arise primarily from proliferation of proximal tubular epithelial cells. Although the mechanisms of tubule transformation into cysts are not entirely clear, tubular epithelial cell hyperplasia is currently viewed as a central early event in ACKD pathogenesis (Fig. 89-1).[3] Various factors have been implicated in the development of tubular hyperplasia, including plasticizer, ischemia, and uremic metabolites. However, the most important factor appears to be slow, progressive parenchymal loss, which could explain why the development or progression of ACKD does not appear to be influenced by the type of underlying renal disease or the choice of dialysis modality. The loss of intact nephrons is a strong stimulus for compensatory growth of the remaining, still intact nephrons, which is achieved by initial hypertrophy and later by hyperplasia. In these hyperplastic tubules, a cyst will develop if transepithelial fluid secretion continues, and if it is a result of anatomic distortion or obstruction, the distal outflow is impaired.

With the continuing presence of mitogenic stimuli, the epithelial layer of the cyst becomes multilayered and atypical cells form intracystic papillary structures or mural adenomas. Activation of protooncogenes, chromosomal abnormalities, and additional factors such as genetic background, environmental chemicals, and sex hormones thereafter probably account for the transition of the proliferative process into malignant growth (see Fig. 89-1).[3]

EPIDEMIOLOGY

Among patients starting maintenance dialysis treatment, prevalences of ACKD ranging from 5% to 20% have been described. ACKD can occur in some patients even before dialysis is initiated. In both chronic hemodialysis and peritoneal dialysis patients, prevalence then increases at a similar rate and reaches 80% to 100% after 10 years of treatment (Fig. 89-2).[4-7] Children are also prone to the development of ACKD. Several but not all studies have reported an increased frequency or faster progression in men than in women. The rate of progression appears to slow after 10 to 15 years of dialysis.

The frequency of ACKD as well as of renal tumors in dialysis patients may be underestimated on the basis of imaging methods alone. Renal cysts are detectable by ultrasound with a minimum size of 0.5 cm. Data obtained from 260 native nephrectomy specimens at the time of transplantation with a median dialysis duration of 1.0 year identified ACKD in 33%, renal adenomas in 14%, and renal cell carcinomas (RCCs) in 4% of the specimens.[8]

CLINICAL MANIFESTATIONS

Acquired cystic kidney disease can manifest as unilateral or bilateral cysts, which are mostly cortical and variable in size and number. Rarely, severe ACKD can become macroscopically indistinguishable from adult polycystic kidney disease (PKD). In contrast to hereditary cystic diseases, the cysts of ACKD are strictly confined to the kidneys. The disease is usually asymptomatic and discovered accidentally during abdominal imaging procedures. Alternatively, it may manifest with potential complications or consequences of ACKD:

- Cystic hemorrhage with or without hematuria; bleeding may occur with cyst rupture with subsequent perinephric hemorrhage or retroperitoneal hemorrhage, which may in rare patients be severe enough to lead to hypovolemic shock.
- Calcifications in or around cysts and, in rare patients, stone formation (calcium-containing stones or β_2-microglobulin stones).
- Cyst infection, abscess formation, or sepsis.
- Erythrocytosis in advanced cases, similar to the erythrocytosis observed in PKD.
- Malignant transformation.[9]

Acquired Cystic Kidney Disease–Associated Renal Cell Carcinoma

Malignant transformation, the most feared complication of ACKD, accounts for about 80% of the renal cell neoplasms observed in uremic patients. In an unselected series of chronic dialysis or transplant patients, the cumulative incidence of RCC complicating ACKD

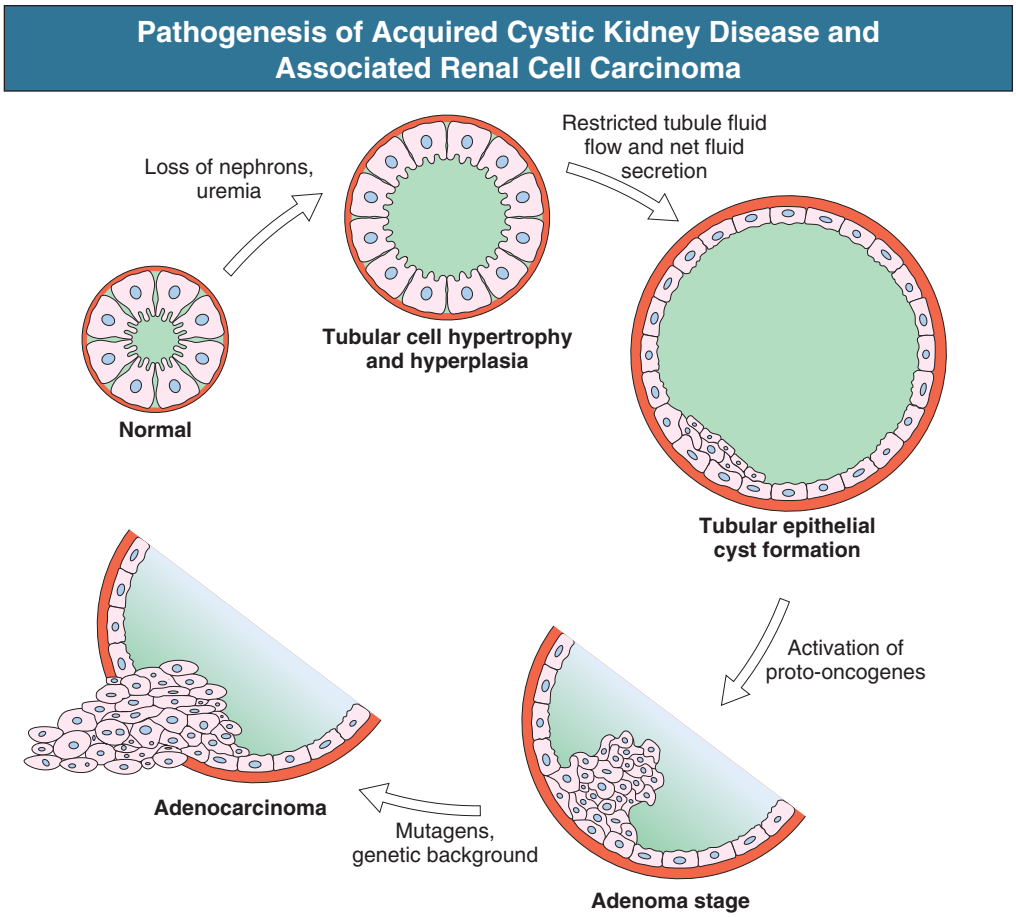

Figure 89-1 Pathogenesis of acquired cystic kidney disease (ACKD) and associated renal cell carcinoma. Diagram of events leading to the development of ACKD and subsequent malignant transformation. *(Modified from reference 3.)*

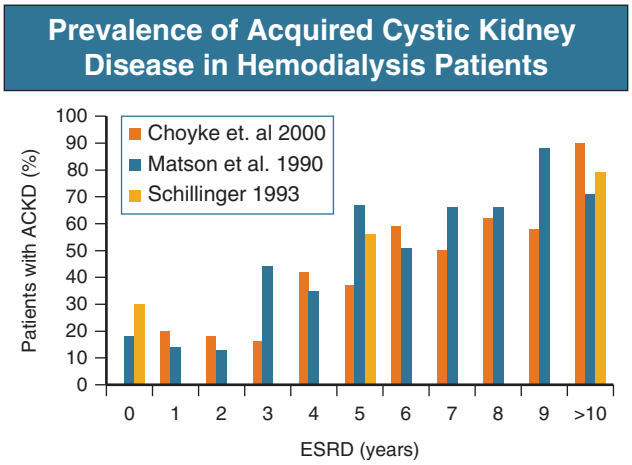

Figure 89-2 Prevalence of acquired cystic kidney disease (ACKD) in hemodialysis patients. Summary of reported ACKD prevalences in chronic hemodialysis patients in relation to the length of hemodialysis treatment. Results of three separate studies are shown. *ESRD,* End-stage renal disease. *(Data from references 5 to 7.)*

is probably below 1%, although rates up to 7% have been reported in some small studies. These data indicate an up to 40-fold increased risk for RCC in ACKD patients compared with RCC in the general population. Risk factors include male gender (male-female ratio, 7:1), African American ethnicity, long duration of dialysis, and severe ACKD with marked organ enlargement. It is unknown whether the risk of malignant transformation differs between hemodialysis and peritoneal dialysis patients.

About 85% of ACKD-associated RCCs are asymptomatic at the time of diagnosis. The remaining cases mostly manifest with bleeding, usually gross hematuria, from the tumor. In cases in which nephrectomy had to be performed in dialysis patients for intractable hematuria, RCCs not visualized before surgery were diagnosed in about one third of the patients.

Compared with sporadic RCCs, ACKD-associated RCCs are characterized by younger age of the patient, male predominance, more frequent multicentric and bilateral manifestation, and less frequent metastases.[2]

PATHOLOGY

Cystic changes in ACKD are typically bilateral but may vary between kidneys. Most ACKD kidneys are smaller than normal. An increase in size above normal can be observed in patients with cyst hematoma formation or malignant transformation. The cysts are usually restricted to the renal cortex. The size of the cysts ranges from microscopic to about 2 cm; about 60% of the cysts are smaller than 0.2 cm.[2] Preneoplastic changes can be detected in ACKD kidneys, including atypical cyst-lining cells forming multiple cell layers and intracystic nodular formations.

Up to 25% of kidneys with ACKD harbor tumors, about one third of which are carcinomas. RCCs arising from ACKD are multicentric in about 50% of cases and bilateral in about 10%. There is a unique

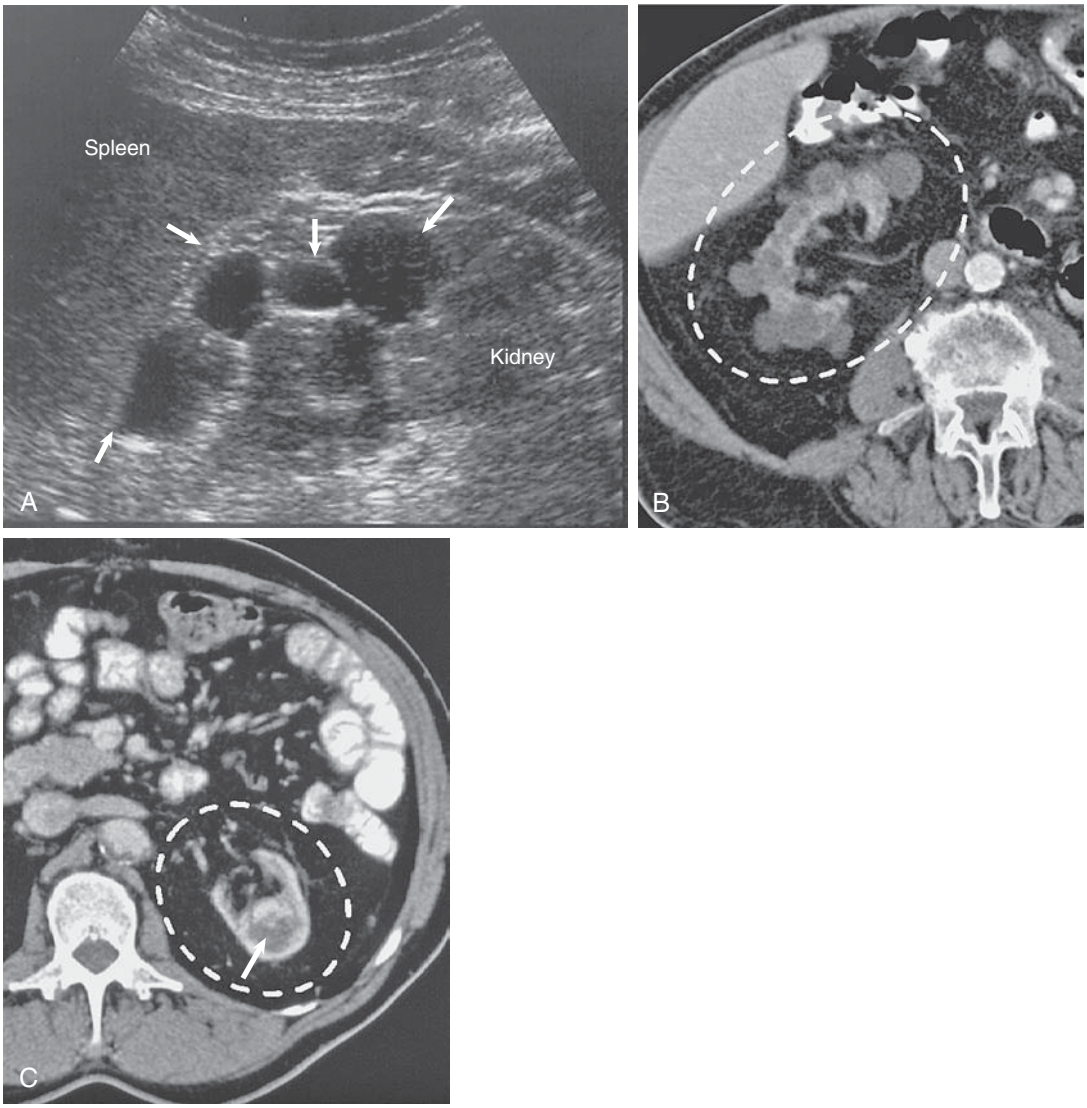

Figure 89-3 Imaging studies in acquired cystic kidney disease (ACKD). A, Ultrasound image of the left native kidney of a patient after 16 years of chronic hemodialysis (HD). Multiple cysts are present in the renal cortex *(arrows).* **B,** Computed tomography (CT) image of a patient after 5 years of chronic HD demonstrating multiple cysts within the right kidney *(dashed circle).* **C,** Contrast-enhanced CT image of a renal transplant patient who developed a renal cell carcinoma *(arrow)* originating from the left native kidney with ACKD *(dashed circle).*

histologic pattern in tumors arising in kidneys with ACKD, termed *ACKD-associated carcinoma.* They are characterized by a typical microcystic architecture, eosinophilic cytoplasm with Fuhrman grade 3 nuclei, and a frequent association with intratumoral oxalate crystals. In addition, these tumors commonly exhibit papillary architecture and clear cytoplasm.[10]

In patients with end stage renal disease without ACKD, the most common histologic type is clear cell carcinoma (44%) and the second most common is ACKD-associated carcinoma (23%).[9] Clear cell carcinoma seems to be the most frequent type in patients with a dialysis duration of less than 10 years, whereas ACKD-associated carcinoma is the predominant tumor type in patients with dialysis duration of more than 10 years.[11,12]

Renal cell carcinomas in renal transplant patients tend to be smaller and to exhibit a lower T stage and a lower grade at diagnosis compared with patients with end-stage renal disease. Tumors are more often multifocal and bilateral, and the papillary subtype occurs more often.[13,14] Because of the earlier stage at detection, the prognosis of RCC after renal transplantation generally is more favorable.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnostic approach to ACKD usually involves ultrasound, which is a sensitive means of detecting ACKD or large RCCs (Fig. 89-3).[4,5] However, the differentiation between simple cysts and renal carcinomas can be difficult given the echogenicity of end-stage kidney parenchyma and the complexity of cysts in ACKD. Computed tomography (CT) scanning, in particular with early contrast enhancement, is superior to ultrasound in detecting small malignant lesions (see Fig. 89-3).[4,5,15] A classification of renal cysts based on their appearance in CT scans, introduced by Bosniak, is now widely accepted and is also applied to ultrasound and magnetic resonance imaging (MRI; Table 89-1).[17] Criteria that favor the diagnosis of RCC as opposed to a simple cyst include thickened and irregular walls, the presence of septa or renal tissue within the lesions, contrast enhancement, multilocularity, and large size (>4 cm). Given the risk for the development of nephrogenic fibrosis, gadolinium-enhanced MRI cannot currently be recommended for dialysis patients and renal transplant patients with a glomerular filtration rate (GFR)

Renal Cyst Classification System		
Category	**Synonymous**	**Description**
I	Benign simple cyst	Hairline-thin cyst wall; no septa; no calcifications; no solid components; no contrast enhancement
II	Benign cyst	Minimal regular thickening of the cyst wall; few, hairline-thin septa; smooth, hairline-thin calcifications in wall or septa; no contrast enhancement
IIF	Moderately complex cyst	Minimal regular thickening of the cyst wall; multiple, minimal smooth thickening septa; thick, nodular calcifications in wall or septa; no contrast enhancement
III	Indeterminate cystic mass	Irregular thickening of cyst wall; multiple, measurably thick, irregular septa; thick, nodular, irregular calcifications in wall or septa; contrast enhancement present
IV	Clearly malignant cystic mass	Gross irregular thickening of cyst wall; irregular gross thickening of septa; thick, nodular irregular calcifications in wall or septa; contrast enhancement present in tissue and cysts

Table 89-1 Renal cyst classification system. *(Modified from reference 16.)*

below 60 ml/min. The diagnostic value of MRI without contrast enhancement in this setting is not well defined. A small study has evaluated contrast-enhanced ultrasound for the assessment of complex cysts in renal transplant recipients and compared this method with standard ultrasound. The authors found a benefit of contrast-enhanced ultrasound, especially in correctly characterizing Bosniak I and II cysts.[18]

Because of the risk of malignant transformation, screening for ACKD on a regular basis, as well as regular follow-up imaging in patients with established ACKD, has been advocated. A proposal for ACKD and tumor screening is outlined in Figure 89-4. However, the cost of screening must be weighed against the risk-benefit ratio of nephrectomy in dialysis patients. A decision analysis[19] concluded that screening for ACKD (by either ultrasound or CT scanning) in young patients with a life expectancy of 25 years offers as much as a 1.6-year gain in life expectancy. This is similar to the gain obtained in young healthy people who stop smoking. In contrast, in ACKD patients older than 60 years, no significant gain in life expectancy is achieved by regular screening.[20] In a different analysis of 797 dialysis patients who had developed RCCs (90% identified by screening, 10% by clinical symptoms), screening provided a mean survival benefit of 3.3 years after adjustment for age and dialysis vintage.[20] Screening during transplant evaluation by ultrasound followed by CT in the case of suspicious lesions is recommended on the basis of recent data showing a prevalence of renal cancer in up to 4% of the patients and concerns about the role of immunosuppression in accelerating tumor growth.[21]

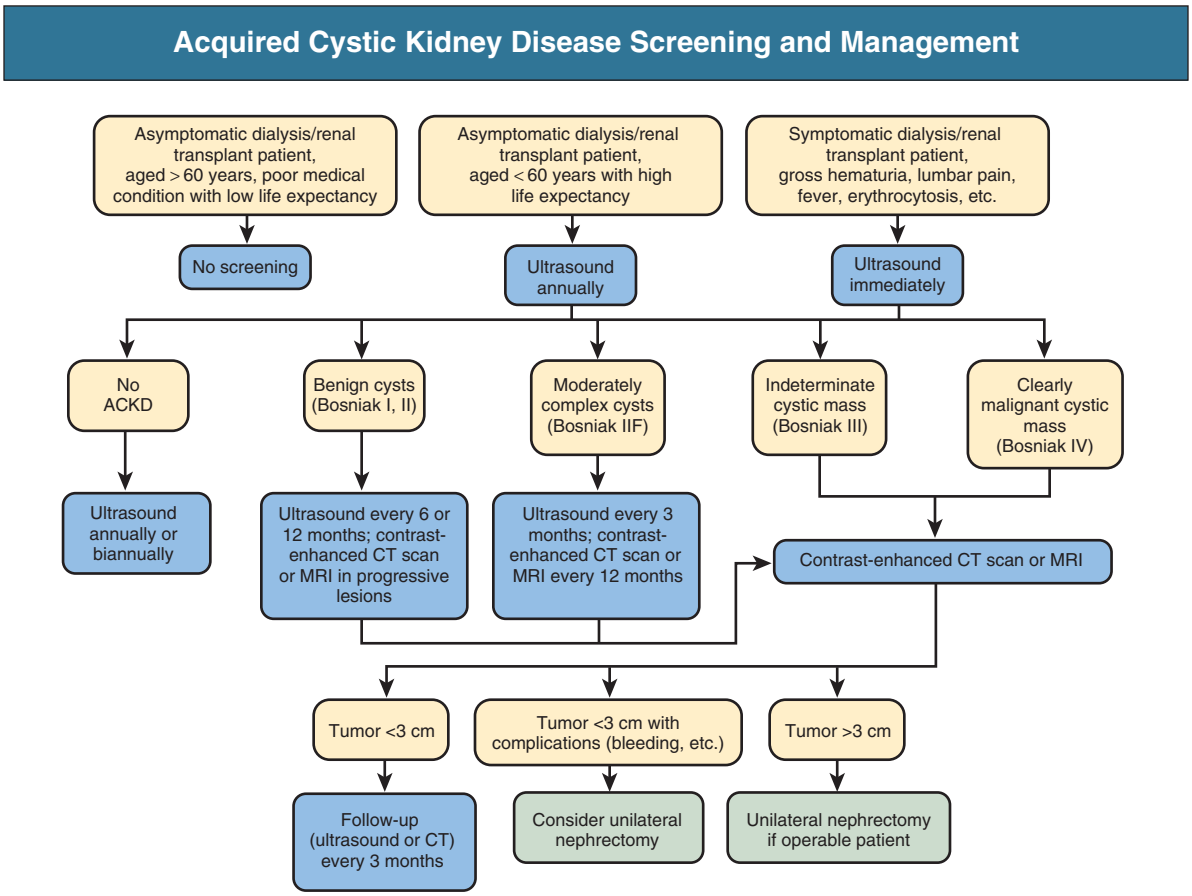

Figure 89-4 Proposed approach to acquired cystic kidney disease (ACKD) screening and management of suspected renal cell carcinoma. *CT,* Computed tomography; *MRI,* magnetic resonance imaging. *(Modified from references 9, 19, and 24.)*

NATURAL HISTORY

Cystic dilations of renal tubules may develop microscopically once the creatinine clearance falls below 70 ml/min.[22] As discussed earlier, ACKD thereafter progresses and reaches a prevalence of nearly 100% after more than 10 years of dialysis (see Fig. 89-2). A CT study demonstrated a constant increase in kidney volume that seems to reach a plateau after about 20 years of hemodialysis, and at least partial regression may occur after ultra-long-term hemodialysis.[23] In malignant transformation, tumor growth rates are highly variable. The incidence of metastases at diagnosis (15% to 30% of patients) and 5-year survival rates (35%) are comparable to those observed in RCC in the general population. Death is usually associated with widespread metastases and accounts for about 2% of the deaths in renal transplant patients.

After renal transplantation, the course of ACKD is variable. It is not established whether renal transplantation affects the natural history of RCC complicating ACKD, although immunosuppression has been suggested as a risk factor for RCC in transplant patients with ACKD.[9] A prospective, single-center ultrasound screening of the native kidneys in 561 renal transplant recipients identified ACKD in 23%.[24] The mean duration of dialysis was 4 to 5 years, and the mean time after transplantation was 9 years. In this cohort, ACKD was slightly less frequent than had been reported in dialysis patients, possibly indicating that renal transplantation might inhibit the development of ACKD.[24] The prevalence of RCCs among all 561 patients was 4.8%. However, among the patients with ACKD, RCCs were detected in almost 20%, whereas among the patients without ACKD, RCCs were detected in only 0.5%.[24]

TREATMENT

Treatment of ACKD is warranted only when complications such as hemorrhage, cyst infection, or malignant transformation develop. Whereas the first two complications may be handled conservatively and only rarely require surgery, malignant transformation should raise the question of nephrectomy. Given the perioperative morbidity and mortality of nephrectomy, in particular in multimorbid dialysis or transplant patients, it is not surprising that the threshold for surgical intervention in cases of RCC is still controversial.

Most authors agree that tumors larger than 3 cm in diameter justify nephrectomy, because with tumors above this size, RCCs in the general population frequently metastasize (see Fig. 89-4).[7] However, this strategy is based on an extrapolation from otherwise healthy persons, and a more aggressive approach may be required under certain circumstances. This is particularly true because tumor size in ACKD is often difficult to establish by imaging studies (given its frequent multilocular development) and because metastases have been described in ACKD even when renal tumors were not detected by imaging studies.

In the case of tumors of less than 3 cm in diameter with no complications, the slow tumor growth may justify observation with repeated imaging studies (see Fig. 89-4). Patients with high life expectancy or patients listed for transplantation might be considered for nephrectomy also in case of tumors with diameters less than 3 cm. In general, tumor enlargement should be used as an indication for nephrectomy if it is permitted by the patient's status.

A prophylactic contralateral nephrectomy, in the case of unilateral tumors, is not routinely recommended because of the morbidity associated with the procedure, the worsening of anemia, and the loss of residual renal function in those who are not considered transplant candidates. A delay before transplantation is generally not suggested in patients who have had an asymptomatic RCC associated with ACKD in their nephrectomy. In such a setting, a contralateral nephrectomy can be recommended to decrease the potential risk of neoplastic growth and to avoid a delay in transplantation.

Most authors perform screening for renal masses in transplant recipients and perform nephrectomy in case of a suspicious mass or RCC in the native kidneys. However, although immunosuppression is possibly associated with the development of RCC, it does not seem to diminish the likelihood of cure, especially because RCCs in transplant patients, possibly as a result of regular screening for malignancy, tend to be detected at an earlier stage.[25] In addition, nephrectomy in renal transplant recipients can be safely performed without a high risk of surgical complications.[26]

MALIGNANT NEOPLASMS IN DIALYSIS PATIENTS

Even if the risk of malignant transformation of ACKD is disregarded, dialysis patients have a slightly higher cancer risk compared with the general population. Analysis of more than 800,000 dialysis patients in three registries from the United States, Europe, and Australia and New Zealand revealed that most of the increased risk was a result of cancers of the kidney, bladder, and endocrine organs (Fig. 89-5).[27] In addition to the specific risk associated with malignant transformation of ACKD, some of the increased risk is directly related to the underlying renal disease or to the immunosuppression that may have been administered to patients with immune-mediated renal disease. Cyclophosphamide therapy, for example, may predispose to bladder and ureteral cancer that presents after patients have been initiated on dialysis. Renal disease or immunosuppressive therapy may underlie the apparent risk of dialysis patients for development of multiple myeloma (see Fig. 89-5). In addition, patients with analgesic nephropathy or Chinese herb or aristolochic acid nephropathy are

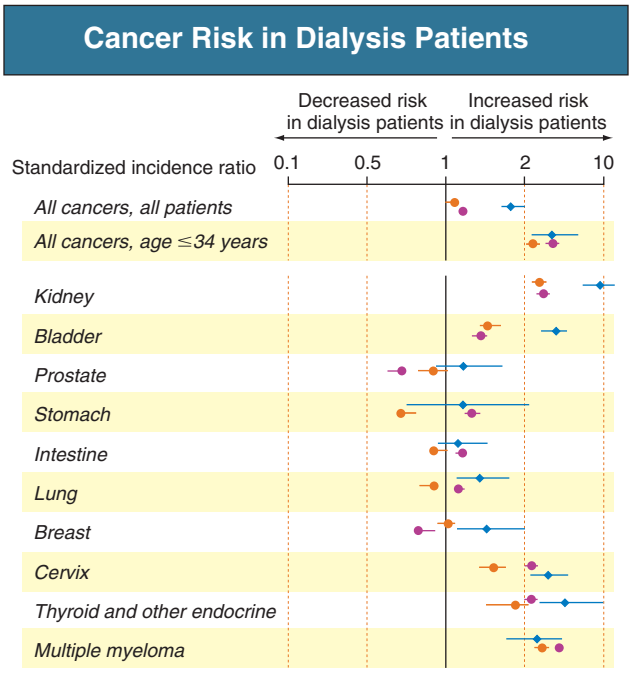

Figure 89-5 Cancer risk in dialysis patients. Relative risk of cancer (plus 95% confidence interval) compared with the general populations in 831,804 dialysis patients from Australia and New Zealand *(blue diamonds),* Europe *(orange circles),* and the United States *(purple circles). (Modified from reference 27.)*

at high risk for development of transitional cell carcinoma of the upper urinary tract.[28] Particularly after renal transplantation, these tumors tend to be less differentiated and in an advanced stage, and therefore the patients have a relatively poor outcome. For this reason, patients with analgesic nephropathy and aristolochic acid nephropathy should be screened for the presence of transitional cell carcinoma before transplantation and annually after transplantation. It has been advocated that screening should include cystoscopy, retrograde ureteral catheterization with washings and brushings, and sonography imaging.[29] Other malignant neoplasms that have been observed at increased frequencies in dialysis patients include carcinoma of the cervix and thyroid and other endocrine neoplasias (see Fig. 89-5). In addition, at least in the United States Renal Data System (USRDS) database, dialysis patients have a 1.5- to 2-fold increase in the risk for non-Hodgkin lymphoma, Hodgkin disease, and leukemias.[27] This suggests that female dialysis patients should undergo gynecologic screening including cervical smear in the same intervals as suggested for the general population. Regular thyroid ultrasound is probably also justified, although no formal decision analysis is available to support this recommendation; lymphoma and leukemia screening will be difficult to impose, and clinical vigilance is advocated.

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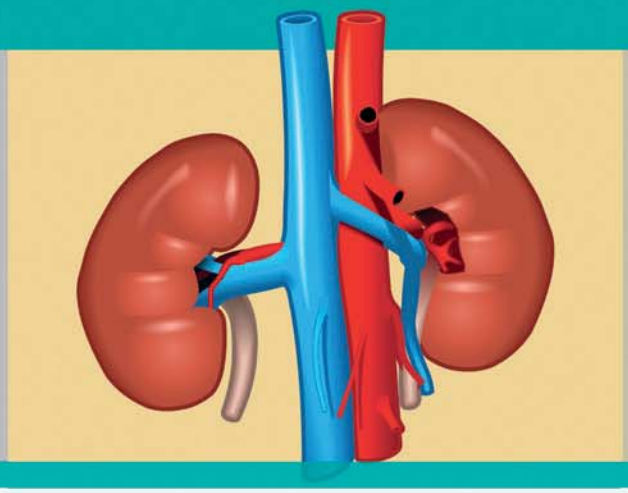

SECTION XVII

Dialytic Therapies

CHAPTER 90

Approach to Renal Replacement Therapy

Hugh C. Rayner and Enyu Imai

TREATMENT OPTIONS FOR RENAL REPLACEMENT THERAPY

The number of patients receiving renal replacement therapy (RRT) each year, measured as a rate per million population, varies enormously among countries (Fig. 90-1). These rates have risen steadily over the last decade, although this has slowed more recently in some countries. The RRT incidence rate is the product of a complex mix of factors: the incidence and prevalence of diseases that may lead to end-stage renal disease (ESRD), most notably diabetes mellitus[1]; the effectiveness of chronic kidney disease (CKD) management to slow progression to ESRD; the level of kidney function at which RRT is commenced; and, last, the availability of resources to provide RRT.

Renal replacement therapy is a major undertaking for any patient. It is costly and time-consuming and once started may continue for many years. Each ESRD treatment option requires preparation, both physical and psychological. All patients likely to reach ESRD, and their families and care givers, need education about their future options in a form that they find accessible. This chapter sets out an approach to these challenging issues.

PREDICTION OF THE START OF DIALYSIS

Preparation for ESRD treatment requires two things: (1) identification of those patients who are at high risk of reaching ESRD and (2) prediction of the likely time when RRT may be needed. Diabetes, heavy proteinuria, declining estimated glomerular filtration rate (eGFR) and previous episodes of acute kidney injury make it more likely that a patient will progress to ESRD. Prediction of ESRD is made easier by a graphic display of eGFRs, derived from creatinine by the Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, or from cystatin C.[2,3] The graph tells the story of a patient's CKD and is much easier to understand than columns of figures (Fig. 90-2). The trajectory of the eGFR accurately reflects changes in the true GFR over time.[4]

MULTIDISCIPLINARY CARE IN ADVANCED CHRONIC KIDNEY DISEASE

Advanced CKD care aims to address a number of issues: preservation of remaining kidney function; prevention or treatment of complications of CKD; involvement of the patient and his or her family and care givers in making an informed choice among peritoneal dialysis (PD), hemodialysis (HD), and conservative kidney management; creation of dialysis access in good time; and, in appropriate patients, preparation for kidney transplantation, ideally before dialysis is started.

Patients need time, often months, to understand and make decisions about dialysis and its implications.[5] The best approach is to transfer patients with declining GFR to a multidisciplinary team at least 12 months before the predicted date of dialysis. Unfortunately, it is often difficult to predict the future trajectory of eGFR.[6] eGFR can remain between 20 and 30 ml/min/1.73 m^2 for many years, particularly in elderly patients, and so discussions about dialysis may be premature and cause unnecessary anxiety. Conversely, intercurrent illness can cause a sudden drop in GFR and precipitate urgent dialysis. Symptoms and complications of CKD become more common and severe as eGFR falls below 20 ml/min/1.73 m^2. Patients with more stable eGFR may be transferred to multidisciplinary care when this threshold is crossed.

Advanced CKD care is best delivered by a multidisciplinary team including a dietician, nurse educator, pharmacist, physical therapist, occupational therapist, social worker, and sometimes a trained peer-support volunteer.[7] Patients receiving this additional care have better biochemical results, are more likely to start dialysis in a planned way with less hospitalization, and may even have improved survival rates once they have started dialysis.[8,9] In addition to being good clinical practice, these programs make good financial sense because the savings in inpatient costs outweigh the costs required to run the clinics.

Lack of access to effective predialysis care is a significant issue in the United States. Forty-two percent of new ESRD patients in 2011 had not seen a nephrologist before beginning therapy, and this is associated with a reduction in use of arteriovenous (AV) fistulas as vascular access.[60] Among these patients, only 10.5% began hemodialysis with a mature fistula compared with 50.2% of those who had received more than 1 year of nephrologist care.

Predialysis Education Programs

Predialysis programs approach the choices in ESRD care through shared decision making. Whereas clinicians are expert in the technical aspects of dialysis and transplantation, the patient knows best about his or her own needs and preferences. Patients with advanced CKD may not gain sufficient knowledge and understanding to make good decisions from conventional office consultations, even when they have been seen on multiple occasions by a nephrologist.[10]

Patient education should follow the principles of adult learning: first, assess the patient's existing level of knowledge and understanding; second, build on this knowledge by the delivery of appropriate information in an appropriate form; and third, establish that the patient has understood and accepted the information given. Education can be delivered both individually and in groups. The clinician is encouraged to send a personal letter to the patient summarizing the issues because this enhances the educational value of consultations. This should be copied to the patient's family doctor to enhance coordination of care. In a group education session, patients may

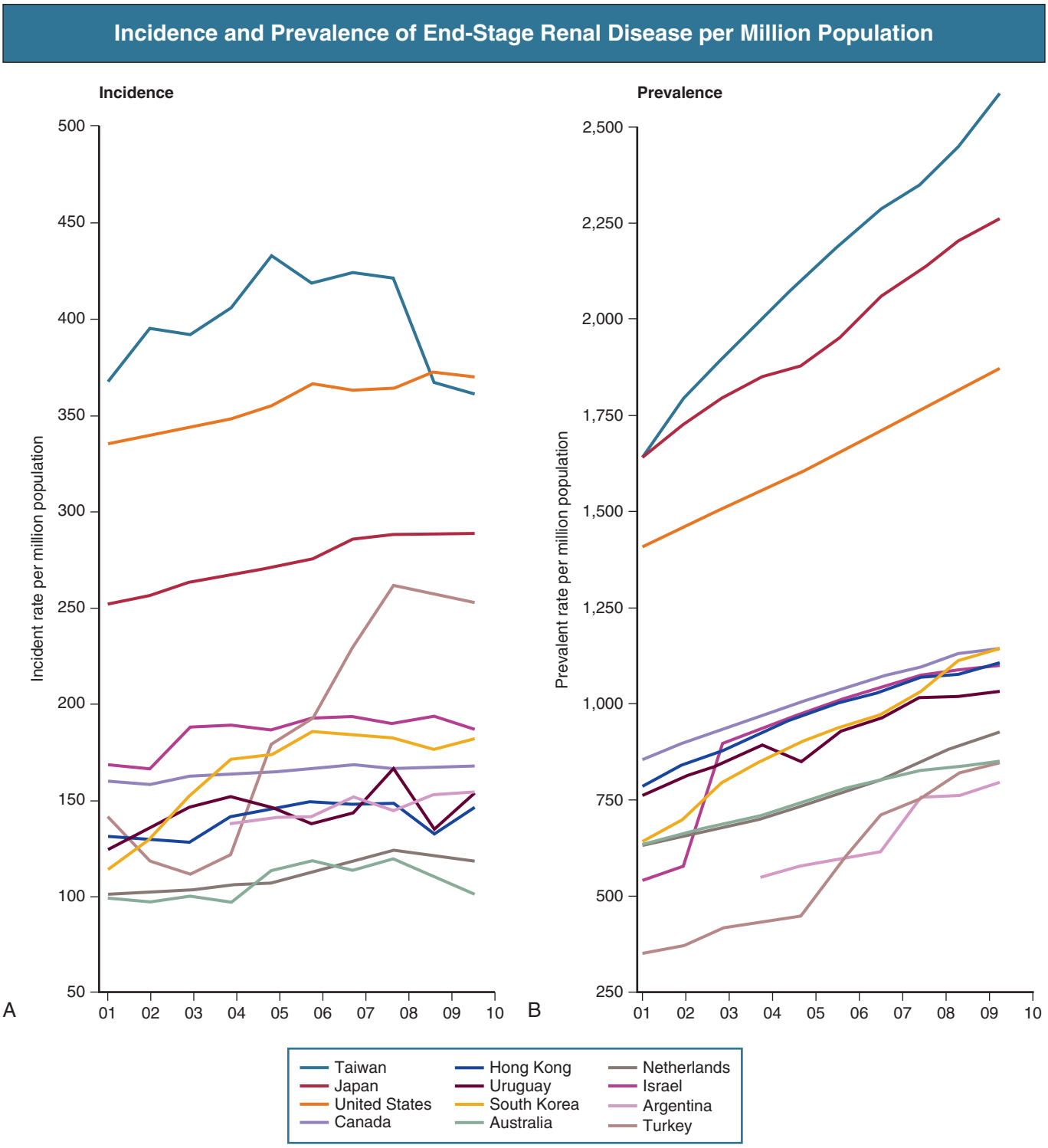

Figure 90-1 Incidence (A) and prevalence (B) of end-stage renal disease per million population. All rates are unadjusted. Data from Argentina (2005 to 2007), Japan, and Taiwan are dialysis only. *The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government. *(From reference 60.)*

learn more from fellow patients within a support group than from the group's facilitator. Furthermore, patient support groups help patients and their relatives appreciate that they are not alone in facing the demands of ESRD.

Representatives of all members of the multidisciplinary team, both medical and nonmedical, should deliver the predialysis program. For example, a controlled trial in California studied the value of social worker input to the predialysis program in reducing unemployment.[11] In the intervention group, patients and their relatives met regularly with a licensed social worker both before and after starting dialysis, to explore strategies for continuing the patient's current employment. Blue-collar workers in the intervention group were 2.8 times more likely to continue working. Patients in work had a better quality of life, greater self-esteem, and a more positive

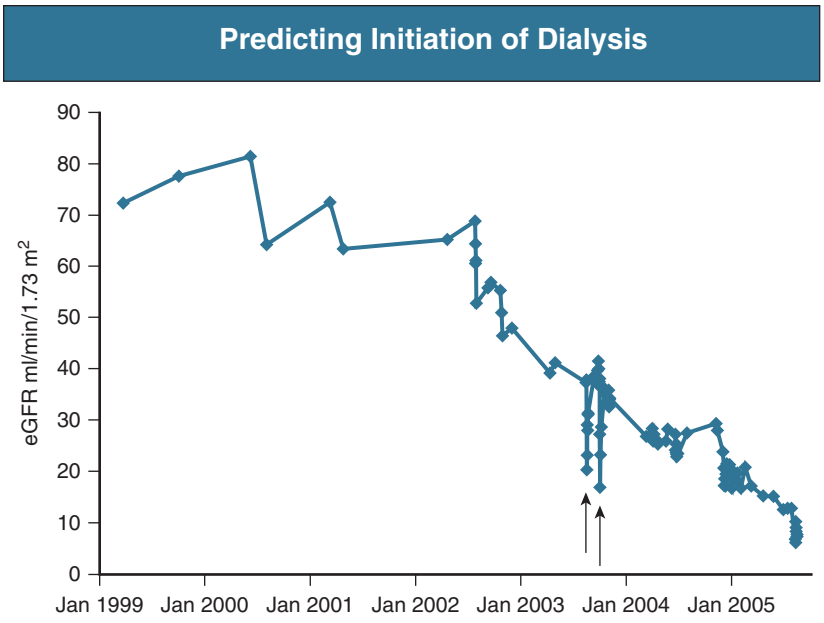

Figure 90-2 Predicting initiation of dialysis. Graph of estimated glomerular filtration rate *(eGFR)* over time for a patient with diabetes and progressive chronic kidney disease. The graph displays sequential eGFR values, telling the story of this patient's CKD. 1996: Diabetes mellitus diagnosed. 2000: Blood pressure 196/108 mm Hg and proteinuria detected. 2002: Acute myocardial infarction. 2005: Dialysis started. The *arrows* indicate episodes of radiocontrast-induced acute kidney injury following a computed tomography scan and a coronary angiogram.

attitude toward work. Because it is difficult for dialysis patients to regain jobs once they are lost, this result is particularly valuable for the long-term rehabilitation of patients.

In addition to engaging in face-to-face sessions, patients should be directed to the wide range of educational materials available. A number of books have been written specifically for dialysis patients. Many national organizations provide web-based patient information and produce printed and audiovisual material—for example, the National Kidney Foundation in the United States (www.kidney.org). Decision aids can help patients think through their options and choose the treatment that best meets their needs and priorities.

Education About Transplantation

For those who are suitable, transplantation offers the best prospect for improved survival and quality of life, especially in younger patients.[12] Even in older patients with greater comorbidity, transplantation can improve survival and be cost-effective.[13]

The options of transplanting kidneys from a deceased or living donor should be discussed, as well as combined kidney and pancreas transplants for people with diabetes. Although outcome data from the local transplanting centers should be made available, published data can be used to inform patients (www.ustransplant.org/annual_reports/current/survival_rates.htm).

The ideal time for the transplant to be performed is before dialysis is ever begun: preemptive transplantation. A U.S. study[14] showed that preemptive transplantation was associated with a 52% reduction in the risk of graft failure during the first year after transplantation, an 82% reduction during the second year, and an 86% reduction during subsequent years, compared with transplantation after dialysis. Increasing duration of dialysis was associated with increasing odds of rejection within 6 months of transplantation, possibly because of immunologic stimulation during long-term dialysis.

WHEN SHOULD DIALYSIS BE STARTED?

The eGFR at the start of dialysis has steadily increased over recent years and varies among countries. Mean eGFR of Japanese patients at the start of dialysis increased from 5.0 ml/min/1.73 m^2 in 1989 to 6.5 ml/min/1.73 m^2 in 2007. In the United Kingdom, the mean eGFR at the start of dialysis increased from 6 ml/min/1.73 m^2 in 1997 to 8.5 ml/min/1.73 m^2 in 2012 (www.renalreg.com, UK Renal Registry 2011 Report). In the United States, 17.7% of patients started dialysis with an eGFR of 10 to 15 ml/min/1.73 m^2 in 2000; by 2011 this had increased to 29%, with a further 16% starting with an eGFR of more than 15 ml/min/1.73 m^2.[60]

Aging of the population of CKD patients may contribute to earlier initiation of dialysis. In Japan the median age at initiation of dialysis increased from 59 to 69 years from 1989 to 2007.[15] A higher-threshold eGFR may be used in diabetics, as they tend to tolerate uremia poorly and are frequently troubled by sodium retention and fluid overload. Other measurements to be considered include a rising serum phosphate, falling serum bicarbonate, and protein-energy malnutrition that persists despite vigorous attempts to optimize dietary intake. A fall in serum albumin is a late sign of reduced protein intake and debility.[7]

Arbitrary guidelines have been established to gain Medicare approval for dialysis reimbursement in the United States. These include eGFR below 15 ml/min/1.73 m^2 for patients older than 18 years and below 20 ml/min/1.73 m^2 (Schwartz formula) for those younger than 18 years. Alternatively, adults should have a serum creatinine level above 8 mg/dl (700 µmol/l; >6 mg/dl [530 µmol/l] in diabetes). Patients may also qualify for Medicare if they do not meet these criteria but have uremic symptoms (nausea, vomiting, pericardial pain, acidosis, or hyperkalemia) or pulmonary edema refractory to diuretics.

Limitations of a Purely Clinical Approach to the Initiation of Dialysis

Waiting for patients to develop uremic symptoms carries the risk that the patient will start dialysis in a malnourished state with an increased risk of mortality. Renal failure itself is a catabolic state, and it is commonly difficult for patients on dialysis to regain lost weight.

Given the chronic nature of renal disease, patients frequently remain unaware of the severity of their illness. Protein intake may fall spontaneously with the result that symptoms of uremia do not develop, but this is at the expense of a loss of lean body mass. Similarly, patients may gradually reduce their activities as their exercise

tolerance declines. It is only when dialysis is started that many patients appreciate how ill they have become.

Lack of awareness can be avoided by carefully questioning the patient for insidious symptoms of uremia. For example, patients should be asked to compare their current eating habits and lifestyle with those 6 to 12 months previously. Close friends and relatives provide a useful third-party view of the patient's well-being.

Limitations of a Purely "Lab Result–Based" Approach in the Initiation of Dialysis

Routine early initiation of dialysis would need to confer significant benefits to justify the added inconvenience to the patient, the additional risk of dialysis-related complications, and the additional cost. Because dialysis treatment has a finite life, either from loss of peritoneal function or failure of vascular access, starting treatment earlier will bring forward the time when further procedures or a change of modality is necessary.

Moreover, there is likely to be resistance from many patients to the suggestion that they should start dialysis when they have no symptoms of uremia. The nephrologist would need complete confidence in the laboratory values as well as in the evidence supporting early commencement of dialysis to persuade a reluctant, asymptomatic patient.

Starting dialysis is the first step in a lifelong commitment to renal replacement therapy. Patients will be asked to comply with a wide variety of inconvenient and sometimes unpleasant treatments. A high level of compliance is required for a successful outcome, and, particularly in the United States, there is concern about the level of noncompliance that is associated with increased mortality.[16] The commitment to dialysis is likely to be greater if the patient feels better after it has started.

A prospective study in The Netherlands provides useful data to help the patient and nephrologist agree when to commence treatment.[17] Patients who started dialysis with less residual renal function (5 ml/min/1.73 m^2 vs. 7 ml/min/1.73 m^2) had a poorer quality of life in the early period after starting dialysis. However, this difference was no longer present by the end of the first 12 months of treatment. This has subsequently been confirmed in a randomized controlled trial that showed no difference in survival or quality of life between patients who started dialysis at an eGFR (MDRD equation) of 9.0 ml/min/1.73 m^2 and those who started 6 months later at an eGFR of 7.2 (Fig. 90-3).[18] Starting dialysis earlier was not associated with better quality of life and incurred higher health care costs.[19] One advantage in the early-start group was that a higher proportion of patients who had chosen PD actually started dialysis with PD (80% vs. 70%, $P = .01$).[20]

CHOICE BETWEEN PERITONEAL DIALYSIS AND HEMODIALYSIS

The majority of patients with ESRD are suitable for treatment with either PD or HD. It is difficult to envisage an ethically acceptable trial in which patients are allocated randomly to PD or HD, and the various possible modifications within each modality make a simple comparative trial impractical. Retrospective and prospective nonrandomized comparative studies have failed to indicate a consistent survival advantage for either modality.[20] There is some evidence that PD may be inferior to HD over the longer term in patients with coronary heart disease and congestive heart failure.[21,22] This contradicts a commonly expressed opinion that PD is gentler for such patients because it avoids rapid fluid shifts and causes less stress on the heart. Change in treatment from PD to HD is associated with an increased risk of hospitalization and mortality.[23] A planned change from PD to HD may not be associated with this increased risk, although this has not been studied systematically in a large population. Patients having PD for longer than 7 years are at an increased risk of encapsulating peritoneal sclerosis.[24] This may prompt a planned change to HD.

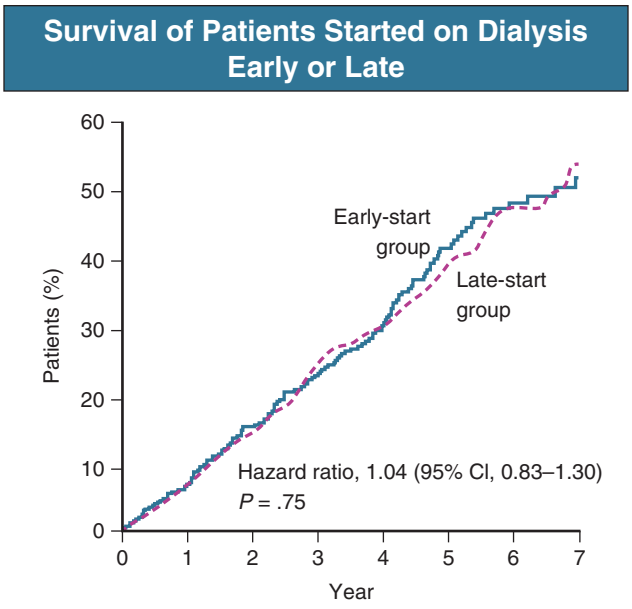

Figure 90-3 Survival of patients started on dialysis early or late. Data from the IDEAL Study. Kaplan-Meier curves showing no difference in time to death after early or late dialysis start. *CI,* Confidence interval. *(From reference 18.)*

Contraindications to Dialysis Modalities

Absolute Contraindications	Relative Contraindications
Peritoneal Dialysis	
Loss of peritoneal function producing inadequate clearance	Recent abdominal aortic graft
Adhesions blocking dialysate flow	Ventriculoperitoneal shunt
Surgically uncorrectable abdominal hernia	Intolerance of intra-abdominal fluid
Abdominal wall stoma	Large muscle mass
Diaphragmatic fluid leak	Morbid obesity
Inability to perform exchanges in absence of suitable assistant	Severe malnutrition
	Skin infection
	Inflammatory bowel disease
Hemodialysis	
No vascular access possible	Difficult vascular access
	Needle phobia
	Advanced cardiac failure
	Coagulopathy

Table 90-1 Contraindications to dialysis modalities. Absolute and relative contraindications to hemodialysis and peritoneal dialysis. *(Adapted from reference 25.)*

Contraindications to Peritoneal Dialysis

There are a few situations in which PD is contraindicated (Table 90-1). Relative contraindications to PD are discussed in the following sections.

Fresh Intra-abdominal Foreign Body

Patients with prosthetic aortic grafts have been successfully treated with PD. HD is usually used initially for up to 16 weeks to allow the

graft to be covered with epithelium and so avoid the risk of graft infection via peritoneal dialysate. However, this risk must be balanced against that of bacterial seeding from the patient's HD access.

Body Size Limitations and Intolerance of Intra-abdominal Fluid Volume

Body size can be a problem at both ends of the spectrum. Small patients may be intolerant of the volume of dialysate needed to achieve adequate dialysis, particularly if they have negligible residual renal function. Alternative methods of fluid exchange such as nocturnal automated PD can be used to overcome this limitation. It may also be difficult to achieve adequate clearances in patients with a body mass index exceeding 35 kg/m^2. Discomfort resulting from increased intra-abdominal volume can be significant in patients with chronic respiratory disease, low-back pain, or large polycystic kidneys. In general, it is hard to predict a patient's tolerance of intra-abdominal fluid, and so these limitations usually appear after a patient has started PD.

Bowel Disease and Other Sources of Infection

The presence of ischemic bowel disease, inflammatory bowel disease, or diverticulitis is likely to increase the incidence of peritonitis as a result of organisms passing through the bowel wall into the peritoneum. Abdominal wall infection may lead to peritonitis via the exit site and catheter tunnel.

Screening for methicillin-resistant *Staphylococcus aureus* (MRSA) before all elective surgical procedures is good practice. Nasal carriage of *S. aureus* increases the risk of subsequent staphylococcal exit site infection and peritonitis, and clearance of nasal *S. aureus* with topical mupirocin cream has been shown to significantly reduce the risk of staphylococcal infection at the exit site.[26]

Severe Malnutrition or Morbid Obesity

Patients should ideally commence PD in an adequate nutritional state. Severe malnutrition may lead to poor wound healing and to leakage from the catheter tunnel. In addition, peritoneal protein losses during dialysis may exacerbate hypoalbuminemia. At the other end of the spectrum, it may prove difficult to satisfactorily place a peritoneal catheter through the abdominal wall in patients with morbid obesity. Thereafter, absorption of glucose from the dialysate, which may average as much as 800 kcal/day, may contribute to further weight gain.

Contraindications to Hemodialysis

Contraindications to HD are few (see Table 90-1). As discussed in Chapter 91, access to the circulation can usually be obtained, even in patients with extensive vascular disease or previous surgery. An aversion to needle puncture of the AV fistula is common in the early stages but can usually be overcome by careful use of local anesthetic and nursing encouragement. Severe coagulopathy may make management of anticoagulation for the extracorporeal circuit difficult.

HOME HEMODIALYSIS

In the last two decades, the use of home HD has declined. For example, in the United Kingdom the percentage of the dialysis population on home HD fell from 35% in 1984 to 3% in 2010. New Zealand, Australia, and Denmark are the only countries with a significant proportion of patients on home HD (Fig. 90-4). There are a number of reasons for the fall in home HD. First, HD usually requires the presence of an assistant throughout the period of dialysis in case

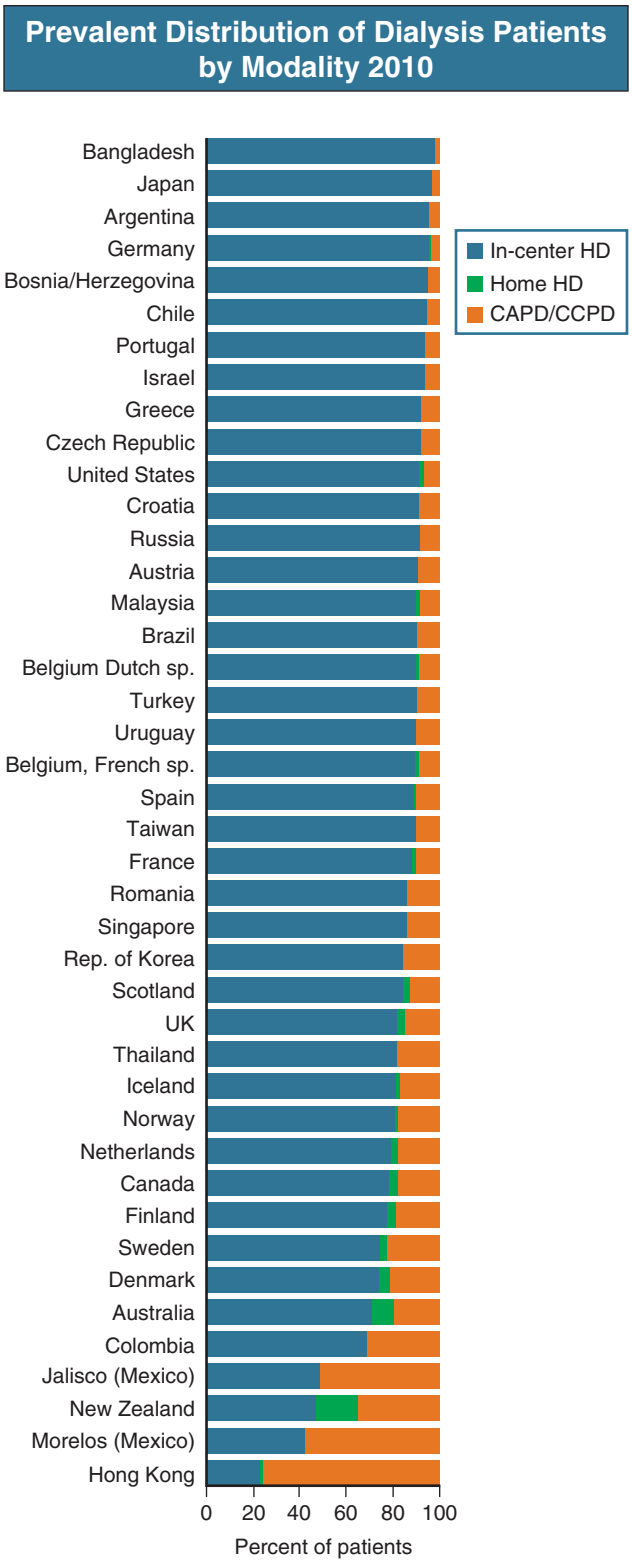

Figure 90-4 Prevalent distribution of dialysis patients by modality, 2010. All data are unadjusted for case mix. Data were supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author and in no way should be seen as an official policy or interpretation of the U.S. Government. *CAPD/CCPD,* Continuous ambulatory peritoneal dialysis or continuous cycling peritoneal dialysis. *(Modified from reference 60.)*

the patient becomes hypotensive or unconscious. Because an increasing proportion of new dialysis patients are elderly, there may be no one available who is able or willing to take on this responsibility. Second, there is the added cost of installing a dialysis machine and its associated water treatment, which is not required for PD. However, the subsequent running costs are less for at-home than for in-center HD. With improvements in dialysis machine technology, home HD may become cheaper and more widespread.

Home HD can provide significant benefits. It removes the inconvenience of traveling to and from the dialysis facility and gives patients the freedom to dialyze at a time that suits them. Although no randomized controlled trial has compared hospital and home HD, comparative studies where correction has been made for differences in comorbidity suggest that patients on home HD have a better outcome in terms of morbidity and mortality.[27] Patients are able to perform more frequent treatments per week, and some dialyze overnight. More frequent dialysis significantly reduces the time taken to recover after each treatment, reduces dietary restrictions and antihypertensive medications, and leads to an improved quality of life.[28]

PATIENT CHOICE OF HEMODIALYSIS OR PERITONEAL DIALYSIS

In the facility of one of the authors in Birmingham, United Kingdom, all patients entering the ESRD program are given "modality-neutral" counseling and allowed to select their preferred mode of treatment.[29] Of patients without a medical contraindication to PD, 45% have selected PD. These relative proportions are similar to those found in a U.S. study of patients' choices after counseling.[30] Independent predictors for choosing HD are increasing age, comorbidity, and male sex. Independent predictors for choosing PD include marriage, counseling before the start of dialysis, and an increasing distance from the base unit.[31] However, although 45% of patients chose PD, not all actually start dialysis on this modality. Patients who require urgent dialysis invariably receive HD rather than PD. Once started on HD, only a small proportion of patients transfer to PD, even if this was their original preference. Patients presenting late for dialysis should still benefit from an education program about their options for long-term treatment.[32]

The major differences in dialysis modality among countries (see Fig. 90-4) suggest that the type of dialysis patients receive is more often determined by physicians and organizational factors rather than by patients. Possible factors affecting these decisions are discussed in the following sections.[33,34]

Reimbursement of Physicians and Funding of Dialysis Facilities

The arrangements by which doctors and dialysis facilities are reimbursed for the cost of providing treatment vary widely around the world. There are also large differences between the levels of payment for HD and PD in many countries. In countries such as the United Kingdom and Canada, where facilities are publicly funded from taxation, the use of more expensive types of dialysis—for example, high-volume hemodiafiltration—is limited. Conversely, in places such as Hong Kong, where dialysis is available only in the private sector, more patients are treated by PD because it is less expensive. In HD facilities, an arrangement whereby payment depends on the number of patients treated creates an incentive to increase patient numbers. If the patient's nephrologist has a financial interest in the HD facility, this may directly influence the decision on which modality of treatment to recommend.

Physician Preference

In a United States Renal Data System (USRDS) survey reported in 1997, only 25% of HD patients remembered having PD discussed with them. In contrast, 68% of patients on PD reported discussions about HD. It is interesting to note that a much greater proportion of patients on HD felt that the choice had been made by the medical team rather than by themselves or by joint decision. Since then, there has been a marked decline in the proportion of dialysis patients treated by continuous ambulatory peritoneal dialysis (CAPD) in the United States, from 14% in 1995 to 7% in 2010. This compares with 35% in New Zealand in 2010.

IMPORTANCE OF DIALYSIS ACCESS

Ideally, every patient would make an informed choice between PD and HD after a period of in-depth counseling and preparation, and dialysis access would be established in advance of starting dialysis. Sadly, dialysis is frequently started in less than ideal circumstances. Late presentation with ESRD is a worldwide phenomenon, indicating that no system of health care has overcome the problems of identifying patients with progressive CKD and bringing them to the attention of nephrologists in a timely manner (Fig. 90-5).

Reports from both Europe and the United States document the excess morbidity and mortality associated with patients presenting late with ESRD and requiring emergency dialysis.[9] Compared with nonemergency patients, their length of hospital stay is significantly greater, and during this time there is a higher incidence of major complications and death. A significant part of the increased mortality is related to the use of a catheter rather than an AV fistula. In the United States, many incident patients have received an AV graft rather than a fistula because grafts can be cannulated more easily and earlier than fistulas (Fig. 90-6).[35]

International data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) show that the risk of death is higher for patients dialyzing in units that use catheters in a high proportion of their patients.[36] The risk is also increased, but to a slightly lesser extent, if AV grafts are commonly used. The detrimental effects of central venous catheters persist even after the catheter has been removed. The survival rate associated with subsequent AV fistulas is significantly worse in patients who have had a previous catheter in place compared with those who started directly on a fistula, even after correction for case mix and comorbidity, possibly because of development of central venous stenosis after removal of the catheter.[35] There is wide variation among countries in the time required for permanent access to be created and used.[35] If a fistula can be created swiftly and used as soon as it is mature, perhaps after only 2 weeks, the need for a catheter may be avoided. Details of HD access surgery are discussed in Chapter 91, and PD catheter placement is discussed in Chapter 96.

DECISION WHETHER TO OFFER RENAL REPLACEMENT THERAPY

Availability of Dialysis Facilities

Renal replacement therapy is unavailable to the majority of the world's population with ESRD.[37] The practice of rationing dialysis has been candidly documented in a report from a South African center[38] in which more than half the patients with ESRD assessed from 1988 to 2003 were not offered dialysis; socioeconomic factors such as age, race, employment, and marital status outweighed medical factors in the decision to begin treatment.

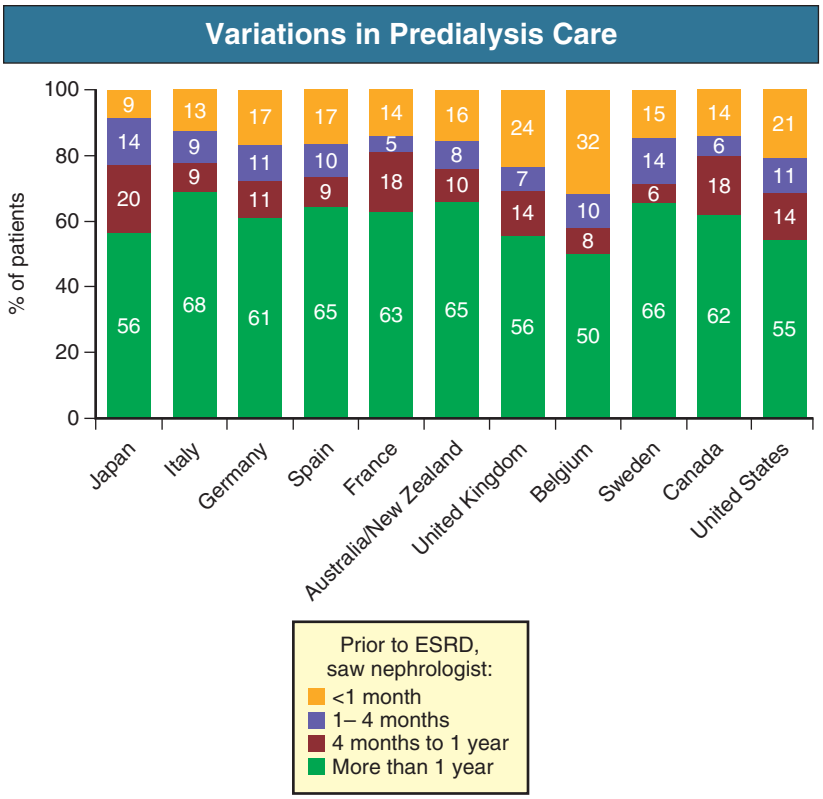

Figure 90-5 Variations in predialysis care. Percentage of patients who saw a nephrologist at different time periods before ESRD. *ESRD,* End-stage renal disease. *(From reference 61.)*

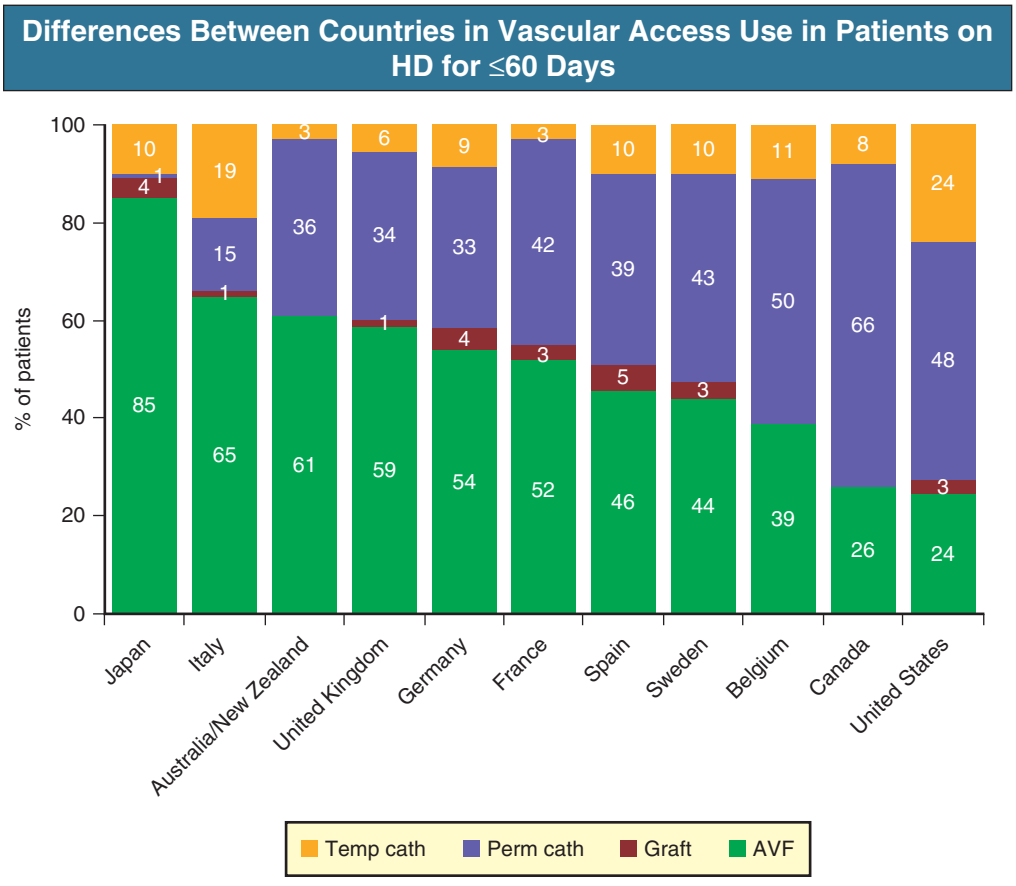

Figure 90-6 Differences by country in vascular access use in patients on hemodialysis (HD) for 60 days or less. Percentage of patients on HD for less than 60 days (mean vintage 32 to 38 days in each country) using an arteriovenous fistula *(AVF),* an arteriovenous graft, or an intravenous catheter, by country. *(From reference 61.)*

Selection of Patients by Physicians and Nephrologists

Incidence rates of RRT have increased over recent decades. Not all of this increase is attributable to more patients developing ESRD. A long-term study from California has shown a steady increase in the likelihood of people going on to receive RRT that could not be explained by an increase in age, diabetes, high blood pressure, proteinuria, or reduced eGFR.[39] This indicates a greater enthusiasm for use of RRT over recent years.

In the developed world, the practice of starting dialysis in patients who are very elderly or dependent on others for their care or who have multiple comorbid conditions varies significantly among countries and among nephrologists within those countries.[40] For example, the percentage of patients who were living in a nursing home or who were unable to eat independently within 90 days of starting dialysis is much higher in the United States (11.6%) and Japan (19.2%) than in France (1.3%), Germany (6.4%), Italy (4.7%), Spain (2.0%), and the United Kingdom (1.5%).

Severe cognitive impairment in a patient would much more strongly influence a nephrologist in the United Kingdom not to start dialysis than in the United States.[40] Furthermore, nephrologists in the United States were much more likely than those in the United Kingdom and Canada to start dialysis in patients with dementia or in a persistent vegetative state, if pressured to do so by family members. In a Japanese study, cognitive impairment was present in 9.9% of chronic dialysis patients.[41] Fear of litigation was particularly influential in persuading nephrologists to offer treatment.

The Renal Physicians Association (RPA) in the United States has issued guidelines for decisions to not initiate or to discontinue dialysis[42] and provides a comprehensive toolkit to support shared decision making (www.renalmd.org./End-Stage-Renal-Disease) (Fig. 90-7). It has also provided a systematic approach to conflict resolution if there is disagreement regarding the benefits of dialysis (Fig. 90-8).

RATIONING VERSUS RATIONAL DIALYSIS TREATMENT

On the grounds that the greatest good should be derived from the limited resources available, it has been argued that patients who are expected to survive for only a few months should not be offered dialysis. This is supported by the view that it is preferable to avoid suffering by not starting dialysis than to withdraw treatment when the patient's condition becomes distressing. Withdrawing dialysis seems more like actively causing death than withholding dialysis, whereby death is allowed to occur naturally.

This utilitarian approach to the allocation of resources goes against instincts to act in the patient's best interest and may be unacceptable to many physicians. Furthermore, it does not take into account the value of even a short extension of life that allows the patient and his or her family to prepare for death. It also makes only a small contribution to minimizing the use of resources because the costs of an HD program are in proportion to the length of time for which the patient continues to receive treatment.

Against this ethical background, are there any objective criteria that can be applied to identify patients who are unsuitable for dialysis? One criterion to be dismissed is age. Although advanced age was used as a simple exclusion criterion in the early days of dialysis, the elderly are now the most rapidly growing section of the dialysis population.

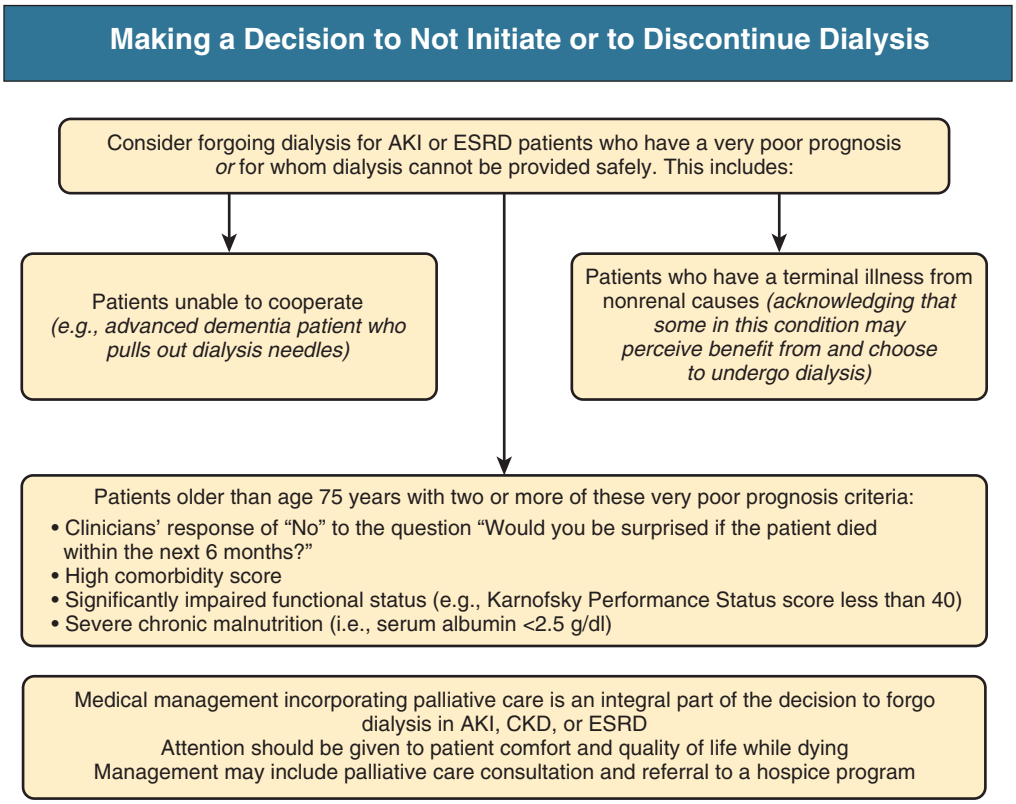

Figure 90-7 Making a decision to not initiate or to discontinue dialysis. *AKI,* Acute kidney injury; *CKD,* chronic kidney disease; *ESRD,* end-stage renal disease. *(Adapted from reference 42.)*

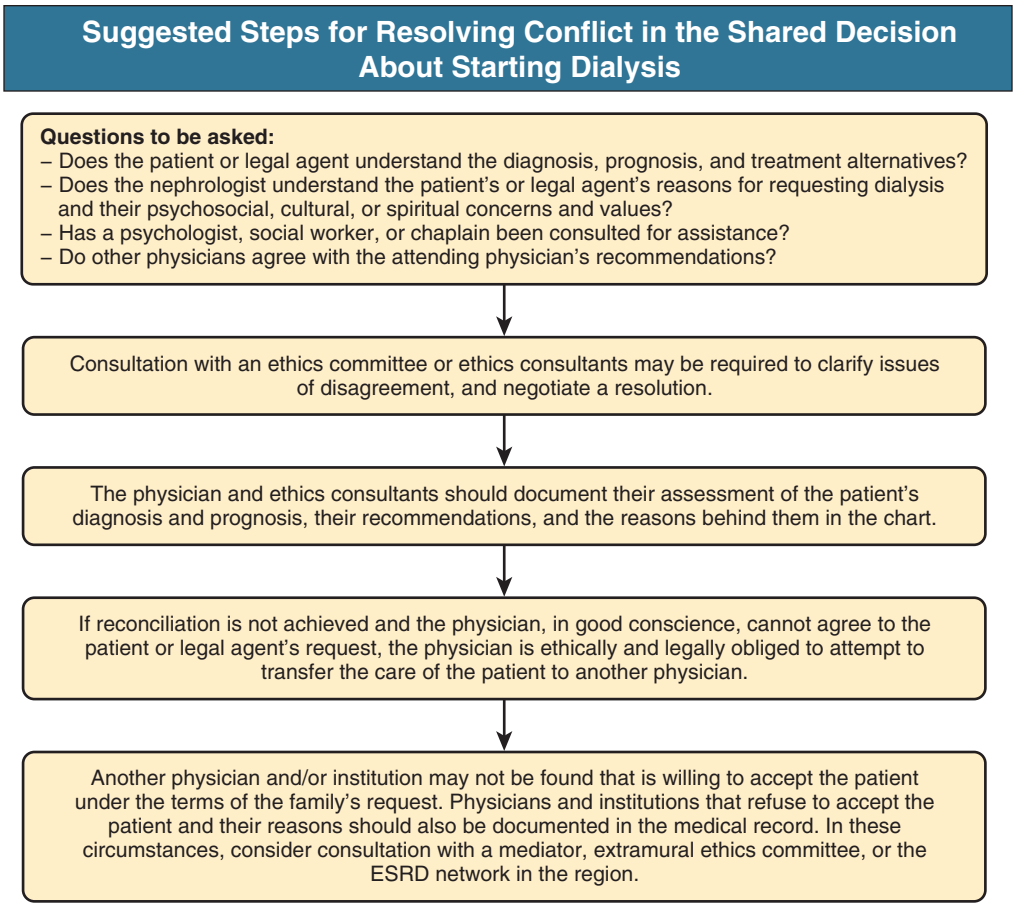

Figure 90-8 Suggested steps for resolving conflict in the shared decision about starting dialysis. *ESRD,* End-stage renal disease. *(Adapted from reference 42.)*

Predictive Factors

Studies have attempted to identify other predictive factors. A Canadian study of patients starting dialysis[43] used a comorbidity scoring system to quantify factors likely to predict early death. The predictive value of this scoring system was compared with the value of an estimate made by the patient's nephrologist of the probability that the patient would die within 6 months. It was not possible to predict early death accurately using either the comorbidity scoring system or the clinician's opinion. Indeed, it was impossible even to identify the small proportion of patients with a very poor prognosis. Clinicians were more accurate than the scoring system in identifying patients with less than a 50% risk of death by 6 months, but they tended to overestimate the risk of death in the worst prognostic groups. For example, 30% of patients whose predicted probability of death was considered to be 80% or higher survived for more than 6 months.

In a U.S. study, HD patients were categorized by risk factors for mortality; however, even patients in the highest risk category still had a 1-year survival of more than 50%.[44] A U.K. study[45] identified a high-risk group using factors associated with poor survival in a statistical model, which included poor functional status at presentation, comorbidity, and underlying disease. Although these patients had a 1-year survival of only 19%, some survived at least 2 years.

ADVISING PATIENTS ABOUT PROGNOSIS ON DIALYSIS

Despite these uncertainties, an individual patient should be given an estimate of his or her likely future on dialysis. The RPA has suggested the following criteria to help identify patients older than 75 years who have a poor prognosis on dialysis[42]:

1. Clinicians' response of "No, I would not be surprised if my patient died in the next 6 months."
2. High comorbidity score.
3. Significantly impaired functional status (e.g., Karnofsky Performance Status score less than 40).
4. Severe chronic malnutrition (i.e., serum albumin less than 2.5 g/dl with the bromcresol green method).

Quality of life is also strongly predictive of mortality, even after statistical correction for these comorbid factors.[46]

For patients whose prognosis is particularly uncertain, or when there is disagreement between the views of the patient and those of the dialysis team, a time-limited trial of dialysis may be offered. This may give the patient and his or her family a better understanding of what life on dialysis entails and may allow time for further discussion among all parties. The duration of the trial should be judged for each individual, and clinical and biochemical parameters such as serum albumin should be reviewed regularly.

Most people would agree that patients who are certain to have an unacceptable quality of life should not be subjected to the discomfort of HD.[47] Patients choosing conservative kidney management are spared the inconvenience and discomfort of travelling to the dialysis unit and surgical procedures. Although their survival may be shorter than if they were to start dialysis (adjusted median survival 13 months shorter for conservative management than for HD), most of this time difference (11 months) would be made up of days having dialysis treatment. The quality of life is better without dialysis, and patients are more likely to die at home.[48,49]

Many of the symptoms and complications of ESRD—anemia, acidosis, pruritus, insomnia, depression, fluid overload, and hypertension—can be treated with medication and a low-protein diet,[50] so a decision not to start dialysis is not the same as a decision to withhold active treatment. Conservative therapy is best delivered by the specialist predialysis multidisciplinary team and should include a dietician, a social worker, and psychological support. The team should have close links with palliative care specialists so that there is a smooth transition from active medical therapy to end-of-life care.[42]

PATIENT WHO DOES NOT WANT DIALYSIS

Nephrologists may be presented with the dilemma of a mentally competent patient whom they would normally treat, but who does not wish to have dialysis. From an ethical viewpoint, a patient's decision not to start dialysis or to discontinue it is justified on the principle of individual autonomy—legally, in the United Kingdom, on the basis of the individual's common-law right to self-determination, and in the United States on the constitutional right of liberty. When the patient is able to express a clear wish, the physician is obliged to respect this, because to treat a patient against his or her will constitutes an assault. The physician nonetheless must ensure that all reversible factors have been addressed, such as unfounded fears about what dialysis will entail or a depressive illness affecting the patient's judgment, and ideally should request a psychiatric evaluation. It is not uncommon for patients to express a strong desire not to have dialysis, particularly if they are relatively asymptomatic, only to change their mind when they become more symptomatic. At this late stage, the basic will to survive comes to the fore. An advance directive written by the patient should never be held as a reason against a change of mind.

DISAGREEMENT ABOUT A DECISION TO DIALYZE

There will inevitably be differences of opinion about the benefits of dialysis to individual patients. Dialysis nurses may disagree with the nephrologist's decision to treat a patient. If the dialysis nurses and doctors are functioning well as a team, they should feel able to express these reservations and have the issue adequately discussed. It is very demoralizing for individual staff and the team as a whole if they feel pressured into giving treatment that they feel is inappropriate.

The nephrologist may remain unwilling to offer dialysis despite the insistence of the patient or, more often, the patient's care providers, the legal agent, or another doctor (see Fig. 90-7). Dialysis must never be given at the insistence of others if it is against the patient's clearly expressed wishes. However, if the patient insists on treatment against the nephrologist's advice, dialysis should usually be given while a resolution is reached. Extensive discussions and explanations of the treatment options and prognosis may be needed to gain a better understanding of the reasons behind the differing views. Helpful advice may be obtained from another physician, particularly the patient's family doctor, who will have a broader understanding of the patient's circumstances. It may be appropriate to involve a psychologist, social worker, or religious counselor. It may be necessary to refer the case to a formal ethics committee, if one exists locally, to clarify the issues of disagreement and enable a resolution. A physician cannot be compelled to offer treatment against his or her professional judgment, but the physician is ethically and legally obliged to attempt to transfer the care of the patient to another physician. Only as a last resort, if no alternative dialysis unit can be found and after adequate advance notice has been given, should dialysis be withdrawn.

MANAGEMENT OF DISRUPTIVE PATIENTS ON DIALYSIS

Most nephrologists have had experience of treating a small number of patients who, for one reason or another, will not comply with the discipline required for maintenance dialysis and who become disruptive to the staff and other patients. This behavior can range from noncompliance with treatment, which harms the patient but is merely inconvenient to the staff, to verbal or even physical aggression toward the staff and other patients in the unit. The impact of this small number of patients can be very great.[51]

The strategy for dealing with such patients must be tailored to the individual. However, useful suggestions for resolving conflict have been provided by the RPA (Box 90-1). They emphasize the

Suggested Steps for Dealing with Disruptive Patients

Identify and document problem behaviors and discuss them with the patient
- Seek to understand the patient's perspective.
- Identify the patient's goals for treatment.
- Share control and responsibility for treatment with the patient.

Educate the patient so that he or she can make informed decisions.

Involve the patient in the treatment as much as possible.

Negotiate a behavioral contract with the patient.
- Consult a psychiatrist, psychologist, or social worker for assistance in patient management or determination of decision-making capacity.
- Be patient and persistent; try not to be adversarial.
- Allow the patient to express concerns, but do not tolerate verbal abuse or threats to staff or patients.
- Contact law enforcement officials if physical abuse is threatened or occurs.
- If satisfactory resolution has not occurred with the above strategies, contact the local ESRD Network to discuss the situation and ensure due process.
- As a last resort, consider transferring the patient to another facility or discharging the patient.

Consult with legal counsel before proceeding with plans for discharge, and do not discharge without advance notice and a full explanation of future treatment options.

Box 90-1 Suggested steps for dealing with disruptive patients. *ESRD,* End-stage renal disease. *(Adapted from reference 42.)*

importance of understanding, information, patience, and persistence. However, the bottom line for patients who are aggressive toward staff while on dialysis must be that they are taken off treatment and sent home.

RESUSCITATION AND WITHDRAWAL OF DIALYSIS

Cardiopulmonary Resuscitation

If patients are to be fully involved in decision making about their treatment, two sensitive issues need to be discussed—cardiopulmonary resuscitation (CPR) and the possibility of withdrawal of dialysis.[52] The two are not necessarily linked; patients may wish to continue with dialysis but express a desire that resuscitation not be attempted should they experience a cardiac arrest. Such a decision would be supported by evidence on the outcome of CPR in dialysis patients; only six of 74 dialysis patients who received CPR survived to hospital discharge, and at 6 months after CPR only two were still alive, significantly fewer than 23 of 247 "control" patients not on dialysis still alive at 6 months. This difference was not explained by age or comorbid conditions.[53] Successful CPR often resulted in a "poor-quality" death, with 20 of the 27 successfully resuscitated dialysis patients dying a few days later on mechanical ventilation in an intensive care unit.

A decision not to attempt CPR must be carefully documented in the patient's medical and nursing records, and all nursing staff must be made aware of it. It is important to be clear what is meant by "cardiac arrest" and for there to be agreement on how the nursing staff should respond should the patient experience a hypotensive "crash" while on dialysis. These notes may form part of a complete advance directive, as discussed later.

Withdrawal of Dialysis

As discussed earlier, it is not possible to predict accurately which patients will gain prolonged benefit from dialysis. Many nephrologists, therefore, operate a liberal policy of offering dialysis to all patients with ESRD who wish to have it. This policy ensures that no patients are denied dialysis but has the inevitable consequence that a number of patients will be started on dialysis who subsequently do not enjoy an acceptable quality of life. The possibility of withdrawing dialysis needs to be addressed if these patients are not to suffer unreasonably.

Rates of withdrawal vary widely among countries and cultures. Withdrawal rates in Italy and France are much lower than in the United Kingdom and the United States.[52] In the United States, African Americans have about one third the withdrawal rate of Caucasians. Rates of withdrawal vary among dialysis units and are significantly associated with the medical director's opinion about whether withdrawal is allowed or facilitated in that unit.[52] This suggests that patients' wishes are not always fully included in these decisions. Patients may be very reticent to express a wish to withdraw from dialysis. Many see it as their duty as a patient to go along with the treatment recommended by their physician and do not wish to appear ungrateful for the efforts that are being made to keep them alive. Their physician may be the last member of the team to learn about the patient's views, and it is very important that good communication exists within the multidisciplinary team so that any clues that the patient gives are acted on.

Staff should adopt a proactive approach and raise the issue of withdrawal of dialysis with patients who are not thriving. Qualitative research suggests that raising the subject of death with patients does not destroy their hope for the future.[54] Early discussion of these issues can lead to a more satisfactory outcome for patients, relatives, and staff when the patient eventually dies.[55] In the United States, formal advance directives play an important part in these discussions, and helpful guidance on how to conduct sensitive and interviews has been published.[56] In the United Kingdom, dialysis teams may enter patients on an at-risk register so that they can receive appropriate assessment and care.[57]

When a patient is no longer competent to make a decision, an advance directive can provide a clear legal basis for the decision to stop dialysis. Indeed, in the absence of clear and convincing written evidence, some U.S. states insist that dialysis must be continued. In other U.S. states and the United Kingdom, the physician is given the task of deciding on the patient's behalf. Helpful advice for dialysis staff and patients wishing to complete an advance directive is available in the RPA clinical practice guideline toolkit.[42]

Once a patient has expressed a wish for dialysis to be withdrawn or the issue has been raised by his or her relatives, the first priority must be to identify any reversible factors that may improve the patient's health sufficiently for the decision to be reversed. In particular, any depression must be identified and treated.[58] Once all these factors have been ruled out, the process of withdrawing dialysis should be managed according to some key principles (Box 90-2).

Withdrawing dialysis should not be seen as an admission of failure but as a final stage in the process of renal replacement therapy. The opportunity for patients to complete unfinished emotional and financial business can make the subsequent bereavement period much less traumatic. Managing this terminal phase can be uniquely rewarding, particularly if it allows a patient and his or her family and care givers to prepare themselves for the patient's death.[59]

Principles Underlying Withdrawal of Dialysis

- The ultimate responsibility for the decision rests with the physician, not the relatives or care givers.
- The patient's interests and dignity should be protected at all times.
- The process should not be rushed. If there is any doubt about the correctness of the decision, treatment should continue.
- There should be an open discussion among the multidisciplinary team to avoid any damaging disagreements.
- The psychological needs of the health care team should not be overlooked.
- Palliative care must be given in the most appropriate environment—for example, a hospice or, ideally, the patient's own home.

Box 90-2 Key principles underlying the process of withdrawal of dialysis.

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CHAPTER 91

Vascular Access for Dialytic Therapies

Jan H. M. Tordoir

Functional vascular access is needed for all extracorporeal dialytic therapies and remains the lifeline for patients with end-stage renal disease who need chronic intermittent hemodialysis (HD) therapy. The ideal HD access should have a long length of a suitable superficial vein for cannulation in two places more than 5 cm apart with a sufficient blood flow for effective dialysis, usually in excess of 400 to 1500 ml/min. A vascular access should have good primary patency, have a low risk of complications and side effects, and leave opportunities for further procedures in the event of failure. Ideally, a first access should be an arteriovenous (AV) fistula placed peripherally at the wrist. However, upper arm and lower limb access sites are increasingly used because the aging dialysis population, with multiple comorbidities, has poor and diseased arm vessels that may be unsuitable for the creation of a simple wrist fistula.

Vascular access should be performed with minimal delay by a surgeon experienced in vascular access creation and, wherever possible, in advance so that dialysis may start with permanent access rather than with use of a central venous catheter. Central venous catheter use should be minimized because of the increased risk of sepsis, the increased mortality, and the development of central venous stenosis or thrombosis, which compromises further access in the upper limbs. Unfortunately, many patients require a central venous catheter either to start dialysis or as a bridge between the failure of a permanent access and the creation of a new AV fistula.[1]

The need for revisional procedures because of access-related complications, including thrombosis, central venous obstruction, and ischemia, is increasing. A multidisciplinary approach to access creation and maintenance, involving nephrologists, interventional radiologists, access surgeons, and dialysis nurses, is mandatory to meet the burden of HD vascular access on health care facilities and costs.

EVALUATION OF THE PATIENT FOR VASCULAR ACCESS

The earlier a patient with chronic kidney disease (CKD) is seen by a vascular access surgeon, the better the chance for the patient to have a well-functioning access at the initiation of HD. An early decision on the type, side, and site of the first vascular access will be based on the following:

- *Clinical examination* with careful palpation of arterial pulses and venous vasculature. Particular attention is paid to the venous filling capacity, with use of a blood pressure cuff and variable pressures, and to the presence of venous collaterals and swelling. The dominant arm is not necessarily the preferred side, and the decision should be based on the quality of the vessels.
- *Vascular mapping by Doppler ultrasound.* This provides information about the venous vasculature, particularly in obese patients and in the upper arm, and about the diameter of the brachial, radial, and ulnar arteries; detects vascular calcifications; and reveals the blood flow volume in the brachial artery. The resistance index, a measure of arterial compliance, can be calculated from the differences between the high-resistance triphasic Doppler signal with clenched fist and the low-resistance biphasic waveform after the fist is released. A preoperative resistance index of 0.7 or higher in the feeding artery indicates insufficient arterial compliance (often associated with arterial calcification) so that the chance of successful creation of an AV fistula is reduced. Current guidelines recommend ultrasound mapping in all patients. Additional angiography is needed only in very difficult cases or in patients with previous ipsilateral central vein catheters to rule out central vein obstruction; the use of radiocontrast media should be minimized.

Preservation of veins during the earlier stages of CKD is crucial for the success of vascular access. Patients should be instructed to protect their veins, restricting blood sampling to the dorsum of the hand whenever possible.

PRIMARY AUTOLOGOUS VASCULAR ACCESS

Radiocephalic Arteriovenous Fistula

A well-functioning distal radiocephalic AV fistula in the nondominant arm is the ideal permanent access for HD. This usually gives an adequate blood flow and a long length of superficial vein for needling. It also leaves proximal sites for further procedures in the event of failure. A distal radiocephalic AV fistula should be possible in a majority of incident patients but may be compromised if the cephalic and antecubital fossa veins are unusable because of thrombophlebitis from previous intravenous cannulas or venipunctures. For this reason, it is essential that these veins be avoided for intravenous cannulas, which should be restricted to the dorsum of the hand in all patients with CKD, except in the emergency situation when rapid access to the circulation is required.

A radiocephalic AV fistula is usually created at the wrist but can be created more proximally in the forearm if distal vessels are inadequate (Fig. 91-1). On occasion, three or four radiocephalic AV fistulas can be created at progressively more proximal sites in the forearm before a brachiocephalic AV fistula is created. The radiocephalic AV fistula at the wrist was initially described by Brescia and Cimino in 1966 as a side-to-side anastomosis, but an end-to-side configuration is preferred by most to reduce the risk of venous hypertension in the radial aspect of the hand.

The primary patency of radiocephalic fistulas varies from center to center, but recent publications report high primary failure rates varying from 5% to 41% and 1-year primary patency rates of 52% to 71% (Table 91-1).[2-7] Early thrombosis and nonmaturation of an AV fistula in the older comorbid population, who have poor upper limb vessels, are the major causes of these high primary failure and low patency rates. The patency of radiocephalic AV fistulas is poorer in women, so a proximal AV fistula might be preferable if the cephalic vein or radial artery is small.

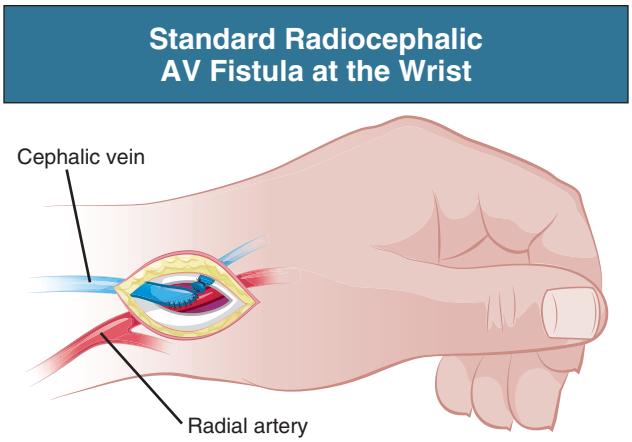

Figure 91-1 Standard radiocephalic arteriovenous (AV) fistula at the wrist. Anastomosis of end of vein to side of artery.

Early Failure and 1-Year Patency Rates of Radiocephalic Arteriovenous (AV) Fistulas

Author	Year	Number of Fistulas	Early Failure (%)	1-Year Patency (%)
Wolowczyk et al[2]	2000	208	20	65
Gibson et al[3]	2001	130	23	56
Allon et al[4]	2001	139	46	42
Ravani et al[5]	2002	197	5	71
Roijens et al[6]	2005	86	41	52
Biuckians et al[7]	2008	80	37	63

Table 91-1 Early failure and 1-year patency rates of radiocephalic AV fistulas.

Nonmaturation of Radiocephalic Arteriovenous Fistula

The autogenous radiocephalic AV fistula needs time to mature and for the vein to enlarge to a size at which it can be needled for dialysis. Usually 6 weeks for maturation is advised. Earlier cannulation can damage the thin veins. Nonmaturation rates vary from 25% to 33%. The essential components of a successful AV fistula are a sufficient vein diameter of 4 to 5 mm for needling and a high blood flow so that blood can be drawn from the fistula at 300 to 400 ml/min. In reality, this requires a fistula flow of about 600 ml/min to prevent excessive recirculation and to permit adequate dialysis within the usual 4-hour time frame of HD treatment. Fistulas that fail immediately are the consequence of poor selection of vessels or poor technique. Regular duplex ultrasound investigation early after AV fistula formation, especially in fistulas that are not maturing, can detect poor flow, stenosis, and accessory branches, guiding the interventional radiologist and surgeon to the appropriate treatment.

SECONDARY AUTOLOGOUS VASCULAR ACCESS

Although a primary radiocephalic AV fistula is preferable, the first-choice procedure is increasingly an upper arm AV fistula with use of an autogenous superficially located arm vein, especially in the dialysis population with associated comorbidities such as diabetes mellitus, coronary heart disease, and peripheral arterial occlusive disease.[1]

The upper limb is preferred to the lower limb for vascular access because of the ease of cannulation, comfort for the patient, and considerably lower incidence of complications. Similarly, autogenous conduits are preferable to the use of prosthetic grafts because of improved patency and lower risk of infection.

Forearm Cephalic and Basilic Vein Transposition and Elevation

Vein transposition or elevation increases the possibilities for creating a forearm fistula. The cephalic vein is preferred, but if it is unsuitable, the more deeply located basilic vein can be transposed from the ulnar to the radial side along a straight subcutaneous course from the elbow to the radial artery. Alternatively, a basilic vein–to–ulnar artery anastomosis can be performed with additional volar transposition to facilitate needling for dialysis.

Different surgical techniques, with or without transposition, have been advocated according to the forearm artery and vein location. In one study,[8] 91% fistula maturation was achieved with a range of techniques; 15% were suitable for a straightforward AV fistula, 33% required vein transposition from dorsal to volar for anastomosis to the appropriate artery, and the remaining 52% required superficial transposition of a vein on the volar aspect of the forearm before arterial anastomosis. Primary patency rates were 84% at 1 year and 69% at 2 years.

Needle cannulation may be difficult, particularly in obese patients. A forearm cephalic vein that is too deeply located may be made accessible for cannulation by transposition or elevation. In one study, the elevation technique was applied in obese patients with radiocephalic AV fistulas and cannulation difficulties; the primary failure rate was 15%, with a 1-year patency rate of 84%. After operation, all patients could be successfully cannulated for dialysis.[9]

Recently surgical lipectomy or liposuction has been advocated to facilitate cannulation of deeply located fistulas.[10]

Elbow and Upper Arm Cephalic Vein Arteriovenous Fistula

The brachiocephalic and antecubital fistulas are two possible AV anastomoses in the elbow region. In addition, anastomosis between the transposed cephalic vein and brachial artery 2 cm proximal to the elbow may be executed, which provides an optimal situation for cannulation along the cephalic vein (Fig. 91-2). The outcome of the brachiocephalic AV fistula is usually good, with a high primary function rate and good long-term patency; studies showed a 10% early failure rate caused by nonmaturation and an 80% 1-year patency rate.[11,12] Two-year primary, assisted primary, and secondary patency rates were 40%, 59%, and 67%, respectively. (Primary patency is functioning access without any intervention; assisted primary patency is functioning access after preemptive intervention for flow decline; secondary patency is functioning access after intervention for thrombosis.) Predictors of failure include diabetes mellitus and a history of contralateral forearm AV graft (indicating poor vessels). Therefore the primary patency of brachiocephalic fistulas is comparable to that of radiocephalic fistulas. The early failure and 1-year patency rates of brachiocephalic AV fistulas are shown in Table 91-2.[11-15]

Upper Arm Basilic Vein Arteriovenous Fistula

The upper arm basilic vein is usually inaccessible for dialysis cannulation because of its medial and deep position. Therefore the basilic vein needs to be superficialized and transposed to an

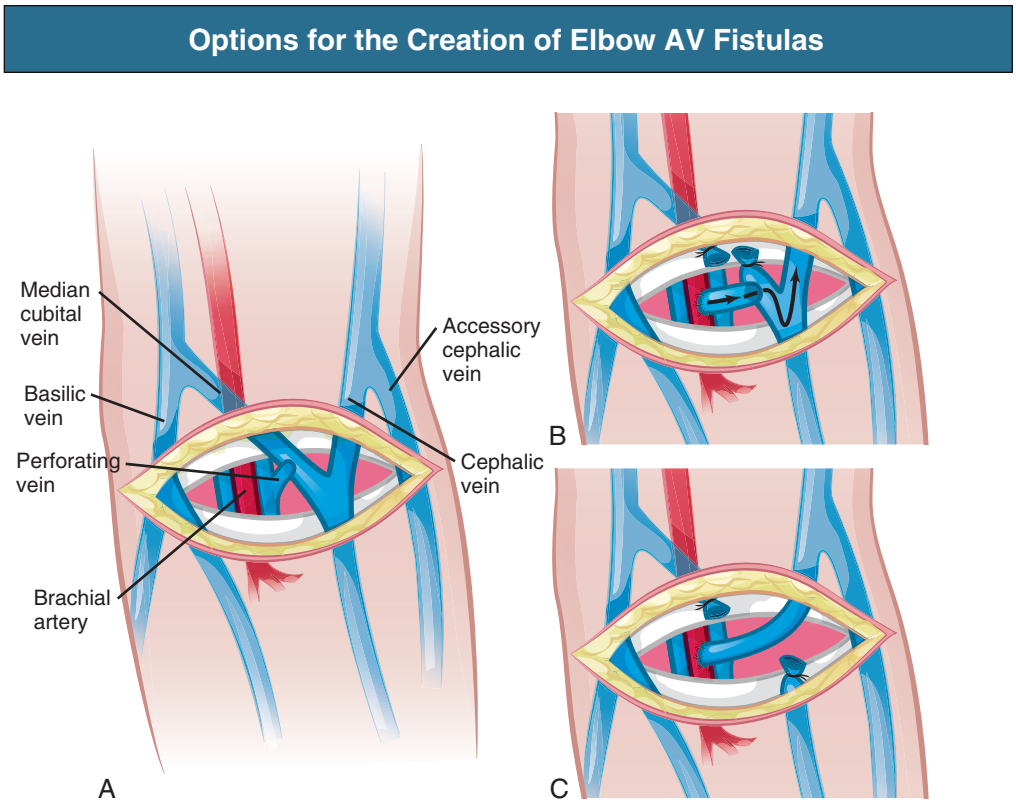

Figure 91-2 Options for the creation of elbow arteriovenous (AV) fistulas. **A,** Brachiocubital AV fistula. **B,** Brachiocubital AV fistula with ligation of proximal cubital vein. **C,** Brachiocephalic AV fistula.

Early Failure and 1-Year Patency Rates of Brachiocephalic Arteriovenous (AV) Fistulas

Author	Year	Number of Fistulas	Early Failure (%)	1-Year Patency (%)
Murphy et al[14]	2002	208	16	75
Zeebregts et al[12]	2005	100	11	79
Lok et al[11]	2005	186	9	78
Woo et al[15]	2007	71	12	66
Koksoy et al[13]	2009	50	10	87

Table 91-2 Early failure and 1-year patency rates of brachiocephalic AV fistulas.

Early Failure and 1-Year Patency Rates of Brachiobasilic Arteriovenous (AV) Fistulas

Author	Year	Number of Fistulas	Early Failure (%)	1-Year Patency (%)
Segal et al[17]	2003	99	23	64
Wolford et al[18]	2005	100	20	47
Harper et al[19]	2008	168	23	66
Keuter et al[20]	2008	52	2	89
Koksoy et al[13]	2009	50	4	86

Table 91-3 Early failure and 1-year patency rates of brachiobasilic AV fistulas.

anterolateral position. The original technique of brachiobasilic AV fistula construction is a two-step approach. First, a brachiobasilic anastomosis is constructed, and in the second operation, usually after 6 weeks, the arterialized vein is mobilized into a subcutaneous position, becoming accessible for needling (Fig. 91-3); at the present time the brachiobasilic AV fistula creation may be performed as a one-stage surgical procedure, with elevation or transposition of the vein to a subcutaneous and anterolateral position at the time of creation of the AV anastomosis. A nonrandomized study comparing the different techniques of brachiobasilic AV fistula creation reported 86% to 90% 1-year patencies in all groups, with only 5% to 7% nonmaturation rates.[16] Primary failure rates of 2% to 23% with 1-year patencies varying from 55% to 89% have been reported (Table 91-3).[13,17-20] In comparison with brachiocephalic fistulas, brachiobasilic AV fistulas are more likely to mature, although they are more susceptible to late thrombosis. However, a randomized study showed similar patencies of brachiocephalic and brachiobasilic AV fistulas.[13]

The technique of subcutaneous placement of the basilic vein has several advantages over forearm or upper arm graft implantation, with less infection and thrombosis. A meta-analysis comparing brachiobasilic AV fistulas with prosthetic grafts has shown superiority of the brachiobasilic AV fistula in primary and secondary patency rates, and it should therefore be used early in difficult access cases before the use of prosthetic grafts.[21]

NONAUTOGENOUS PROSTHETIC VASCULAR ACCESS

When autogenous AV fistula creation is impossible or the fistulas have failed, graft implantation should be considered as a vascular access conduit. Xenografts such as the ovine sheep graft (Omniflow) are popular materials as an alternative access conduit, with acceptable patency and low infection rates. The most frequently used implants are prosthetic grafts made of either polyurethane (Vectra)

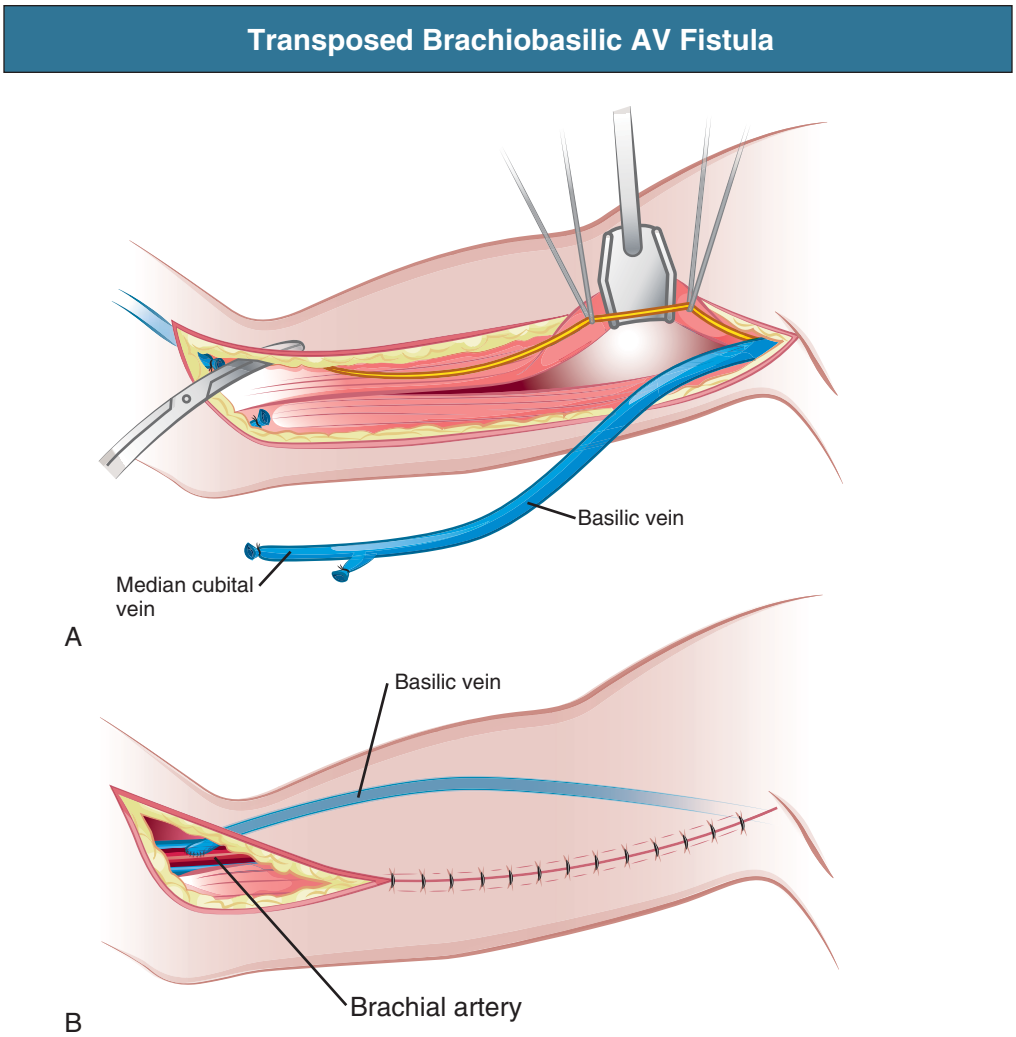

Figure 91-3 Transposed brachiobasilic arteriovenous (AV) fistula. A, Dissection of the basilic vein. **B,** Anterolateral transposition and brachial artery anastomosis.

or polytetrafluoroethylene (PTFE). These prosthetic grafts can be implanted in a wide variety of locations and configurations in the upper limb (Fig. 91-4). At present, early cannulation of PTFE grafts (within 24 hours of surgery) is feasible because of newer graft compositions. Short-term functional patency is usually good, but stenosis (mostly at the graft-vein anastomosis) may lead to thrombotic occlusion within 12 to 24 months. The primary patency rates of prosthetic AV grafts vary from 60% to 80% at 1 year and from 30% to 40% at 2 years of follow-up. Secondary patency ranges from 70% to 90% and from 50% to 70% at 1 and 2 years, respectively.[22-25] Intimal hyperplasia, with smooth muscle cell migration and proliferation and matrix deposition, is the major cause of stenosis formation and thrombosis. The cause of the intimal hyperplasia is uncertain, although the high wall shear stress, caused by the access flow, may denude the endothelial cell layer, resulting in platelet adhesion and initiation of a cascade of proteins that stimulate the smooth muscle cells to proliferate and to migrate.

Measures to Improve Graft Patency

Numerous experimental and clinical studies have defined the influence of graft material and graft design on AV graft patency. Modulating the geometry of the arterial inlet or venous outlet of the graft may have a beneficial effect on intimal hyperplasia. Clinical studies using tapered (at the arterial side of the graft) grafts did not improve patency rates, nor did cuff implantation at the venous anastomosis.[26,27] However, primary patency did improve with the use of a cuff-shaped prosthesis (Venaflo).[28] Grafts such as polyurethane, which are more distensible, could in principle influence intimal hyperplasia by the better matching of the stiff prosthesis with the compliant vein at the anastomotic site; however, in clinical studies, this feature was not of proven benefit.[29]

PHARMACOLOGIC APPROACHES FOR ACCESS PATENCY

Aspirin, ticlopidine, and dipyridamole have some beneficial effect in maintaining patency of AV fistulas and grafts but increase the risk of hemorrhage.[30] Clopidogrel may also be effective in reducing thrombosis of AV grafts and fistulas. Warfarin reduces AV graft thrombosis but increases the risk of hemorrhage.[31] A large trial showed that dipyridamole plus aspirin had a significant but modest effect in reducing the risk of stenosis and improving the duration of primary unassisted patency of newly created AV grafts.[32] In a large randomized study, clopidogrel improved primary radiocephalic fistula function but not maturation.[33] Given the available evidence, antiplatelet agents should be used routinely in patients with AV

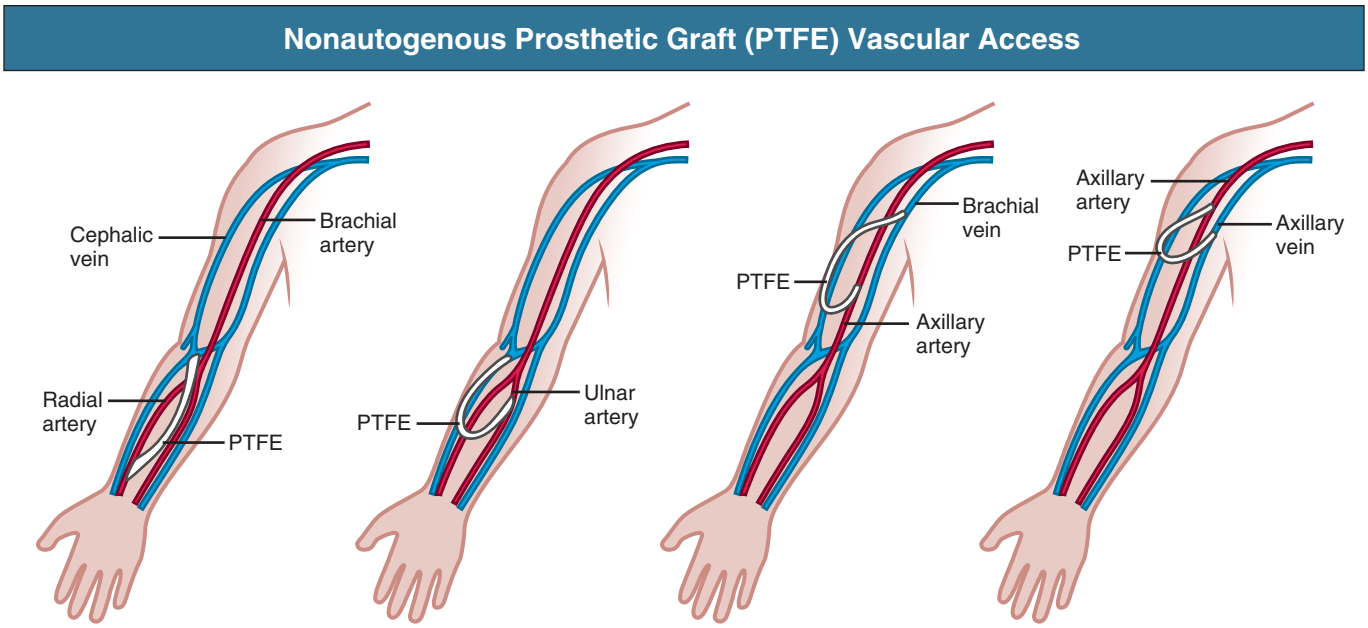

Figure 91-4 Nonautogenous prosthetic graft (polytetrafluoroethylene *[PTFE]*) vascular access. Straight and loop configuration in upper limb.

grafts but not fistula. There is no role for the routine use of warfarin (coumadin), particularly in view of the recent evidence of adverse effects of warfarin in HD patients.

There have been suggestions that other drugs, such as calcium channel blockers and angiotensin-converting enzyme inhibitors, might be associated with improved AV fistula patency, but this requires confirmation with randomized studies.[34] Fish oil reduced AV graft thrombosis in one randomized trial.[35]

Efforts have been made to inhibit the development of intimal hyperplasia pharmacologically with the cytotoxic agent paclitaxel. Paclitaxel wraps have been shown to reduce prosthetic graft intimal hyperplasia in animal models but have yet to be clinically evaluated.

LOWER LIMB VASCULAR ACCESS

Probably the only indication for lower limb vascular access is bilateral central venous or caval obstruction, which endangers the outflow of upper limb AV fistulas. Saphenous and superficial femoral vein transposition is a primary option for thigh AV fistulas, although this carries a relatively high risk of distal ischemia. If clinical evaluation indicates incipient ischemia, primary flow reduction by tapering of the anastomosis is indicated to prevent ischemia.[36] Prosthetic graft implantation in the thigh bears a high risk of infection and septicemia.

VASCULAR ACCESS COMPLICATIONS

Nonmaturation of Arteriovenous Fistulas

Fistulas that fail immediately do so as a consequence of poor selection of vessels, poor surgical technique, or postoperative hemodynamic instability. Vascular abnormalities, including stenoses, occlusions, and accessory veins, will be identified in virtually all early failures, and more than half of the stenoses are in the perianastomotic area of nonmatured fistulas. Arterial inflow stenoses of more than 50% vessel diameter reduction coupled with poor flows are seen in less than 10% of nonmaturing fistulas, but if identified, they should undergo angioplasty. If this fails to improve fistula flow rates, it is unlikely that surgical bypass will be of help. Anastomotic and swing segment (in which the vein has been mobilized and swung over to the artery) stenosis may be treated percutaneously or surgically, depending on local expertise.

The diameter of the angioplasty balloon is chosen to correspond to the diameter of the vessel next to the stenotic or occlusive lesion and is usually not smaller than 5 mm for venous stenoses and not smaller than 4 mm for arterial or anastomotic stenoses. Ultrahigh-pressure balloons inflatable up to 36 atm are used when necessary to abolish the waist of the stenosis on the balloon. Apart from local infection, contraindications to balloon angioplasty are anastomotic stenoses in fistulas less than 4 to 6 weeks after surgical construction, which increases the risk of anastomotic disruption at angioplasty. Percutaneous balloon angioplasty is further discussed in Chapter 92.

The surgical approach is to reconstruct the AV fistula, usually with use of local anesthesia. The anastomosis is exposed and ligated; the vein can then be divided, mobilized proximally, and reanastomosed to the proximal radial artery.

A prospective nonrandomized study of 64 patients showed that outcomes were similar with angioplasty or surgery.[37] Restenosis rates were significantly higher after angioplasty, but overall costs of treatment were similar.

Nonmatured fistulas are rescued by angioplasty of stenoses or occlusions, ligation of accessory veins, or both. Accessory veins can be obliterated through coil embolization, percutaneous ligation, or surgical ligation. The use of coils with a diameter of 1 mm in excess of the target vessel diameter will prevent coil dislocation. Although ligation of accessory veins is usually performed in a single surgical intervention, three variants of vein ligation in a stepped approach have also been described.[38] By use of this approach, surgery is limited to ligation of the accessory veins if the AV fistula appears to be of adequate size to allow cannulation. If the fistula is still considered to be too small, the median cubital vein is ligated. If the AV fistula is still believed inadequate, temporary banding of the main venous channel is performed. Apart from surgical ligation, accessory veins can also be ligated percutaneously. In predialysis

patients the risk of renal function deterioration as a result of radiocontrast load can be overcome by performance of ultrasound-guided angioplasty.[39]

Stenosis and Thrombosis

The development of vessel stenosis in both autogenous AV fistulas and prosthetic AV grafts is usually initiated by intimal hyperplasia caused by migrating and proliferating vessel smooth muscle cells, which form extracellular matrix. Progressive stenosis leads to access flow deterioration and subsequently thrombotic occlusion. Prophylactic repair of access stenoses may prevent thrombosis and prolong access patency.

Autogenous Fistula Stenosis or Thrombosis

Arteriovenous fistula stenosis should be treated if the vessel diameter is reduced by more than 50% and is accompanied by a reduction in access flow (25% flow decline between measurements or absolute flow below 500 ml/min) or in measured dialysis dose. Other indications for intervention are difficulties in cannulation and prolonged bleeding time after decannulation, indicating high intra-access pressure caused by outflow vein stenosis. Venous pressure above 250 mm Hg with a blood flow of 200 ml/min is also suggestive of stenosis. In AV fistulas, 55% to 75% of the stenoses are close to the AV anastomosis, 25% in the venous outflow tract and 15% in the arterial inflow. In brachiocephalic and brachiobasilic AV fistulas, the typical location for stenosis (besides the anastomosis) is at the junction of the cephalic with the subclavian vein (cephalic arch) and the basilic with the axillary vein (junctional stenosis). Initial evaluation of suspected access stenosis is by ultrasound; angiography is used subsequently when intervention is planned.

Endovascular treatment by percutaneous transluminal angioplasty (PTA) is the first option for arterial inflow and venous outflow stenoses and junctional stenoses, with the option of stent placement.[40] These techniques are discussed further in Chapter 92. Some stenoses may not be sufficiently dilated by conventional balloons (12 to 16 atm), and in these patients, cutting balloons or ultrahigh-pressure balloons (up to 36 atm) may be applied. Drug-eluting balloons may prevent restenosis; however, outcome data for this approach are not yet available. Anastomotic stenoses in forearm and upper arm fistulas are primarily treated with PTA; however, surgical revision with a more proximal reanastomosis for swing segment stenosis is indicated in failed PTA of radiocephalic AV fistula.

Fistula thrombosis should be treated as soon as possible because timely declotting allows immediate use of the access without the need for a central venous catheter; fistula salvage usually requires intervention within 6 hours (grafts may be salvaged up to 24 hours). The duration and site of AV fistula thrombosis as well as the type of access are important determinants of treatment outcome. Thrombi become progressively fixed to the vein wall, which makes surgical removal more difficult. When the clot is localized at the anastomosis in radiocephalic and brachiocephalic fistulas, the outflow vein may remain patent because of continuing flow in its tributaries, making it possible to create a new proximal anastomosis.[41]

Thrombolysis can be performed mechanically or pharmacomechanically.[42-44] Whereas the immediate success rate is higher in AV grafts than in autogenous AV fistulas (99% vs. 93% in forearm fistulas), the primary patency rate of the forearm AV fistula at 1 year is much higher (49% vs. 14%). One-year secondary patency rates are 80% in forearm and 50% in upper arm AV fistulas.

In AV fistulas, the combination of a thrombolytic agent (urokinase or tissue plasminogen activator [tPA]) with balloon angioplasty resulted in an immediate success rate of 94%.[43]

Arteriovenous Graft Stenosis or Thrombosis

The most common cause of graft dysfunction and thrombosis is venous anastomotic stenosis. Because grafts should be implanted only in patients with exhausted peripheral veins, vein-saving procedures such as PTA or patch angioplasty are preferred to graft extensions to more central venous segments. When a stent or a patch fails, graft extension is still possible. Graft monitoring by access flow measurement is recommended; with preemptive endovascular treatment, this may diminish graft thrombosis but does not extend graft patency.

Intragraft (or midgraft) stenoses are found in the cannulation segment of grafts. They result from excessive ingrowth of fibrous tissue through puncture holes. These stenoses can be treated by PTA, graft curettage, or segmental graft replacement. When only a part of the cannulation segment is replaced, the access can be used for HD without the need of a central venous catheter. When restenosis occurs in a nonexchanged part of the graft, this can be replaced after healing of the new segment.

Prosthetic graft thrombosis can be treated with various percutaneous techniques and tools, including combinations of thromboaspiration, thrombolytic agents such as tPA, and mechanical thrombectomy. An initial success rate of 73% and primary patency rates of 32% and 26% at 1 and 3 months, respectively, are reported.[45-48] It is important to perform thrombolysis as soon as possible to avoid the need for a central venous catheter and as an outpatient procedure to decrease costs, whenever possible. Postprocedural angiography to detect and to correct inflow, intra-access, or venous outflow stenosis is mandatory.

When endovascular treatment fails or is not possible, surgical thrombectomy may be performed with a Fogarty catheter after venotomy, with correction of the underlying obstruction. On-table angiography should be performed after completion of thrombectomy of both the arterial and venous limbs of the graft.

Central Venous Obstruction

In the majority of patients, central vein obstruction is a result of previously inserted central venous catheters or pacemaker wires. In 40% of patients with subclavian vein and 20% with jugular vein catheters, venous stenosis or occlusion will develop. Chronic swelling of the access arm is the most important sign, usually with prominent superficial collateral veins around the shoulder. The indications for intervention by PTA and stent placement are severe and disabling arm swelling, finger ulceration, and pain or inadequate HD. Contrast angiography of the access and complete venous outflow tract must be performed because the central veins can be difficult to examine with ultrasound in their retroclavicular position.

Endovascular Intervention

Endovascular intervention is the first option for central venous obstruction treatment. PTA alone results in low primary patency rates of 10% or less at 1 year, and numerous restenoses may develop. Primary or additional stent implantation gives a much better outcome, with 1-year patency rates up to 56% or higher.[49,50] Reinterventions are usually required to maintain patency and to achieve long-term clinical success.

Stent placement should avoid overlapping the ostium of the internal jugular vein because this vein is essential for future placement of central venous catheters. Similarly, a stent placed in the innominate vein should not overlap the ostium of the contralateral vein; otherwise, contralateral stenosis may occur and preclude future use of the contralateral limb for access creation.

Surgical Intervention

When interventional treatment of central venous obstruction fails, surgical revision with bypass grafting is indicated. Surgical bypass to the ipsilateral jugular vein or contralateral subclavian or jugular vein is the first option in these patients. Alternative surgical approaches for upper limb vascular accesses with compromised venous outflow are axillary vein to femoral, saphenous, or popliteal vein and right atrial bypasses.[51] In case of bilateral obstruction of the mediastinal veins, including the superior vena cava, it will not be possible to sustain upper limb access, and lower limb access will be required.

Ultimately, ligation of the upper limb access can be considered, which will relieve local symptoms but loses a valuable dialysis access.

Vascular Access–Induced Ischemia

Vascular access–induced upper limb ischemia is a serious complication that without prompt intervention may lead to amputation. The incidence of symptomatic ischemia varies from 2% to 8% of the HD population.[52] Elderly patients, diabetics, and patients with peripheral or coronary arterial occlusive disease are most at risk of ischemia. In addition, previous ipsilateral vascular access increases the risk. Access-induced ischemia occurs more often with proximally located fistulas. These high-flow AV fistulas induce a steal phenomenon with lowering of distal perfusion pressures, and when collateral circulation is inadequate, symptoms may occur. Pain during HD is a characteristic early symptom. A grade 1 to 4 classification for access-induced ischemia can be used to outline the severity of the disease; this ranges from minor symptoms to finger necrosis.

- Grade 1: pale and blue or cold hand without pain
- Grade 2: pain during exercise or HD
- Grade 3: ischemic pain at rest
- Grade 4: ulceration, necrosis, and gangrene

For grades 1 and 2, conservative treatment of ischemia is advocated. With grades 3 and 4, interventional treatment is mandatory.

Diagnosis of Ischemia

Physical examination, including observation and palpation of peripheral vessels, may be inadequate and misleading for the diagnosis of symptomatic ischemia. Additional noninvasive testing with measurement of digital pressures and calculation of the digit-brachial index, transcutaneous oximetry ($TcPO_2$), ultrasound of forearm arteries, and access blood flow measurement are important steps in the diagnosis and decision-making process. Finally, contrast angiography with visualization of the upper extremity arterial tree from the proximal subclavian artery to the distal palmar arches with and without AV fistula compression to enhance distal flow is obligatory to outline the strategy for treatment and to determine whether interventional or surgical options are preferred.

Endovascular and Surgical Management of Ischemia

The treatment strategy depends on the cause of the ischemia. Inflow arterial obstruction and distal arterial lesions are recanalized with small-caliber balloons or stent placement[53]; high-flow AV fistulas are suitable for flow-reducing procedures such as access banding and arterial inflow reduction by an interposition graft to a smaller forearm artery (revision using distal inflow) (Fig. 91-5).[54,55] Steal in itself may be cured by ligation of the artery distal to the AV anastomosis (distal radial artery ligation). In most patients, it is necessary to add a saphenous vein or prosthetic graft bypass to the forearm arteries to augment distal hand perfusion (distal revascularization and interval ligation; Fig. 91-6). The results of these procedures are usually good, with relief of symptoms and preservation of the access site (Table 91-4).[56-60] A simpler alternative to the distal

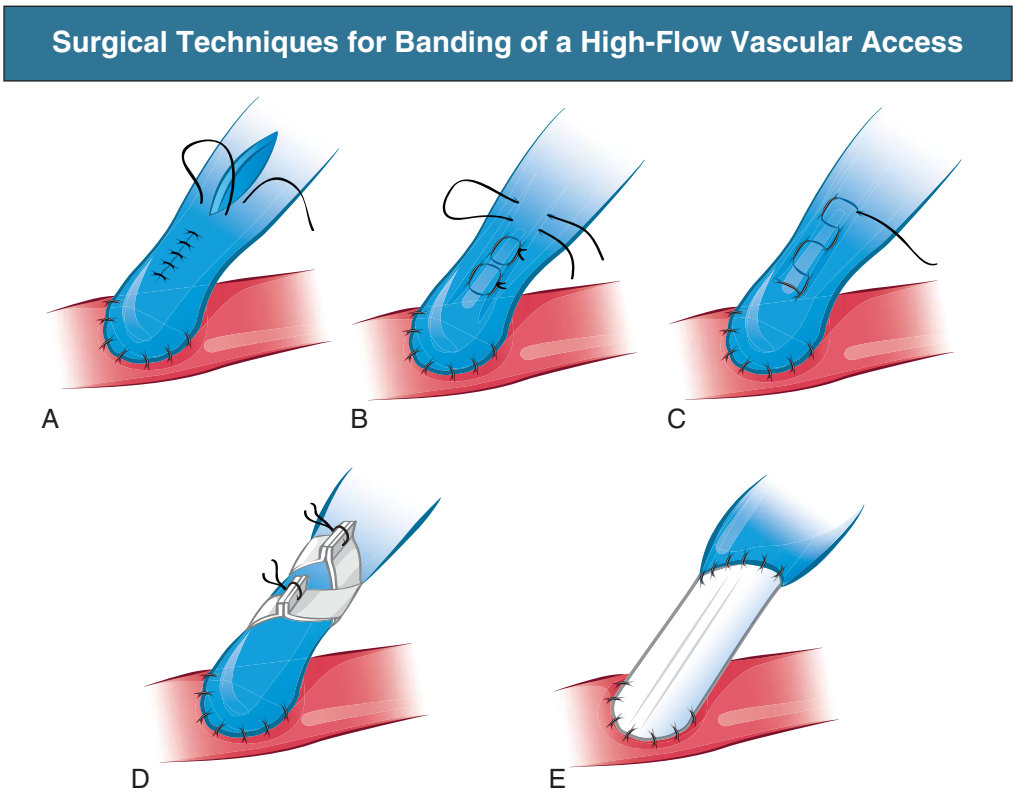

Figure 91-5 Surgical techniques for banding of a high-flow vascular access. A, Open venoplasty. **B,** Interrupted mattress suturing. **C,** Continuous mattress suturing. **D,** PTFE banding. **E,** polytetrafluoroethylene (PTFE) interposition graft. The choice of technique is made by the surgeon on a case-by-case basis.

revascularization–interval ligation procedure is the proximal AV anastomosis technique, in which the AV anastomosis at the elbow is disconnected and moved to the axilla, with anastomosis to the axillary artery by means of a graft interposition.[61] The minimally invasive limited ligation endoluminal-assisted revision procedure has been described; this procedure uses a minimally invasive percutaneous technique with banding of the access over a 4-mm balloon.[62]

Intraoperative digital pressure measurement or $TcPO_2$ is mandatory to guarantee an adequate surgical intervention with acceptable outcome. A digital-brachial pressure index above 0.60 or $TcPO_2$ above 40 mm Hg is indicative of sufficient distal hand perfusion. In some patients, AV fistula ligation and transition to chronic catheter dialysis access or a change in renal replacement modality to peritoneal dialysis may be the only solution.

Distal Revascularization-Interval Ligation (DRIL) for Ischemia in an Upper Arm Vascular Access

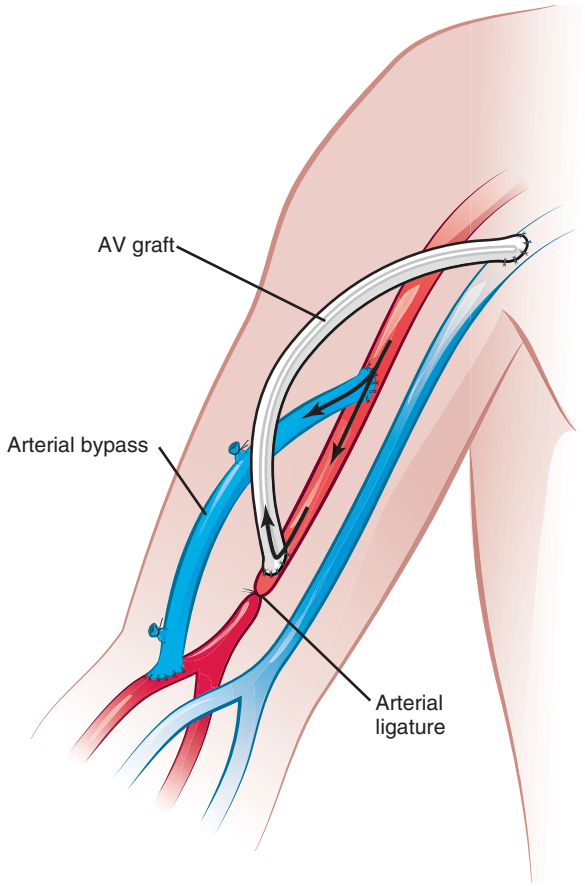

Figure 91-6 Distal revascularization–interval ligation for ischemia in an upper arm vascular access. *AV,* Arteriovenous.

CENTRAL VENOUS CATHETER ACCESS

Central venous catheters are still widely used as vascular access for HD. Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS)[63] indicate that 25% of HD patients in the United States are dialyzed with catheters; in other countries the use of catheters is even more common (Belgium, 41%; United Kingdom, 28%). Central venous catheters are the preferred vascular access only for patients who present with acute kidney injury and for patients with chronic kidney disease without permanent AV access or with failed vascular access. Two types of catheters are used in practice: nontunneled catheters for short-term dialysis, with a limited use and high morbidity; and tunneled cuffed catheters, which can be used up to several months with lower morbidity. The physical characteristics (i.e., design and geometry) not only influence the performance (blood flow rate, recirculation, and resistance) but also affect the overall efficiency of the HD therapy and the morbidity risk (infection, thrombosis).

Nontunneled Catheters

Single- or double-lumen catheters are usually made of polymers (polyethylene, polyurethane), enabling a simple and direct implant possibility. The length of the catheter must be chosen in accordance with the insertion site. The femoral route requires catheters of 30 to 35 cm in length for the distal tip to be located in the inferior vena cava. The internal jugular vein route needs shorter catheters of 20 to 25 cm in length, with tip location at the inferior vena cava–right atrium junction. The subclavian vein should not be used because of the very high risk of subsequent venous stenosis. For sufficient blood flow rates to be achieved, the diameter of these catheters must be ideally 12 to 14 French. It is recommended that the use of nontunneled catheters not exceed 7 days.

Tunneled Catheters

Tunneled central venous catheters have two lumens, each having a length of 40 cm, 10 cm of which is tunneled under the skin; the cannulae are made of synthetic polymer with a large internal lumen and a Dacron cuff to ensure subcutaneous anchoring. The catheter characteristics rely on the type of polymer, design, and geometry (double-lumen catheters, dual catheters, split catheters). The use of

Results of the Distal Revascularization–Interval Ligation (DRIL) Procedure for Angioaccess-Related Ischemia

Author	Year	Number of Fistulas	Ischemia Cured (%)	Ischemia Improved (%)	Ischemia Not Improved (%)	Access Patency (%)
Haimov et al[56]	1996	23	86	14	—	95
Knox et al[57]	2002	55	55	25	11	86
Waltz et al[58]	2007	36	100	—	—	54
Yu et al[59]	2008	24	96	—	4	88
Huber et al[60]	2008	64	78	—	NS	68

Table 91-4 Results of the DRIL procedure for vascular access–related ischemia. *NS,* Not stated.

a tunneled central venous catheter is associated with reduced morbidity as well as better and constant performance compared with uncuffed catheters.[64]

Both tunneled and nontunneled catheters are inserted percutaneously by the Seldinger technique and ultrasound guidance. These techniques are described in Chapter 92. The internal jugular vein and femoral vein routes are preferred because of ease of implantation and low risk of complications, such as central vein stenosis (Fig. 91-7).

Catheter Infection

Catheter-related bloodstream infections are a significant cause of morbidity and mortality in HD patients. Results of the Hemodialysis (HEMO) study indicate that patients with central venous catheters have an increased relative mortality risk of 3.4 compared with patients with AV fistulas. Switching from central venous catheters to AV fistulas decreases the relative mortality risk to 1.4.[65] The most likely explanation for this increased mortality risk is infection and sepsis related to the central venous catheter, including exit site infection. Typical infection rates are three episodes of infection per 1000 tunneled catheter–days and higher with nontunneled catheters.[66] These localized infections can progress to metastatic complications of osteomyelitis, septic arthritis, epidural abscess, and endocarditis. Various societies have issued recommendations for the management of catheter infections.[67] A recommended treatment algorithm is shown in Figure 91-8.

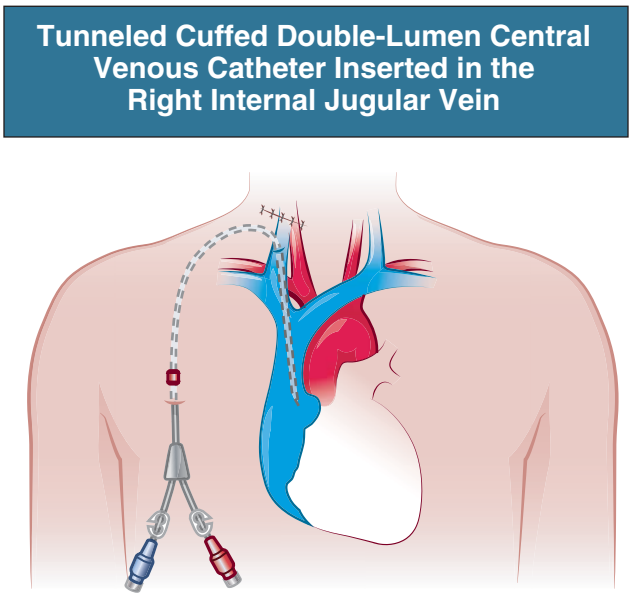

Figure 91-7 Tunneled cuffed double-lumen central venous catheter inserted in the right internal jugular vein.

Infections Involving Temporary Catheters

When a temporary dialysis catheter becomes infected, it should always be removed. There is no role for trying to salvage temporary catheters.[67]

Exit Site Versus Tunnel Track Infections

An exit site infection is a localized cellulitis confined to the 1 to 2 cm where the catheter exits the skin. The majority of these infections respond well to systemic antibiotics and meticulous exit site care, and the removal of the catheter is generally not required.[67] However, exit site infections can progress to tunnel track infections, which involve the potential space surrounding the catheter more than 2 cm from the exit site (Fig. 91-9). Patients with a tunnel track infection sometimes but not always have an associated exit site infection; untreated, they can rapidly develop bacteremia. Patients with a tunnel track infection present with fever as well as local signs of pain, swelling, fluctuance, and erythema along the track of the catheter. Because tunnel track infections involve a potential space, in an area with limited vascular supply, and an implanted synthetic material, they respond poorly to antibiotics alone and require catheter removal.[67]

Catheter-Associated Bacteremia

When a patient with a dialysis catheter has a fever, catheter infection must always be considered. If the patient does not have a clear and

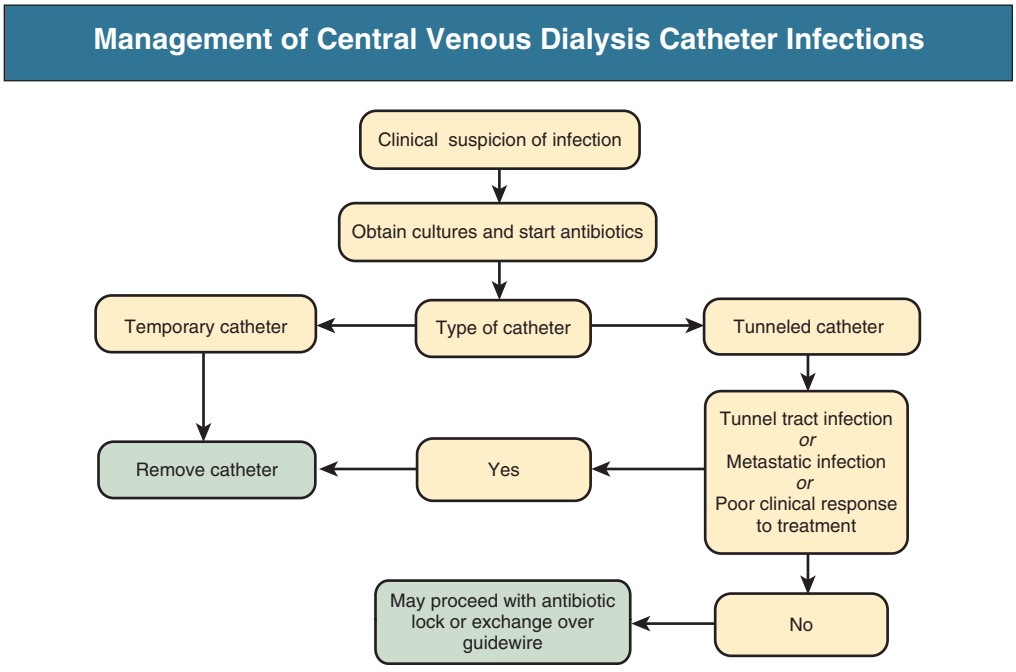

Figure 91-8 Algorithm for the management of central venous dialysis catheter infections. *(Modified with permission from reference 67.)*

Figure 91-9 Dialysis catheter tunnel infection. *(Courtesy Dr. I. M. Leidig, University Hospital Erlangen, Germany.)*

Causative Organisms in Dialysis Catheter Infections		
Polymicrobial		16%
Gram positive		89%
	Staphylococcus aureus	30%
	Staphylococcus epidermidis	37%
	Enterococcus	17%
	Corynebacterium	5%
Gram negative		33%
	Enterobacter	11%
	Pseudomonas	7%
	Acinetobacter	4%
	Citrobacter	4%
	Serratia	2%
	Klebsiella	3%
	Other gram-negative organisms	3%
Mycobacteria		2%

Table 91-5 Causative organisms in dialysis catheter infections. Numbers do not add up to 100% because 16% of infections were polymicrobial. *(Modified with permission from reference 70.)*

convincing alternative explanation for the fever, blood culture specimens should be obtained peripherally as well as through the catheter, and the patient should be started on antibiotic therapy, which is subsequently adjusted on the basis of culture results.[67] The most common organism is *Staphylococcus aureus,* although a wide range of gram-positive and gram-negative organisms have been reported (Table 91-5). The percentage of patients with methicillin-resistant *S. aureus* (MRSA) varies greatly among centers, with higher rates associated with greater antibiotic use. An aminoglycoside or a cephalosporin is a good choice for gram-negative coverage; however, local microbiologic epidemiology must be taken into consideration, especially with regard to antibiotic resistance.

Catheter Removal

The decision to remove a tunneled cuffed dialysis catheter because of an episode of catheter-associated bacteremia is not straightforward. The clinical condition of the patient and response to initial therapy, the presence of metastatic complications, the infecting organism, and the availability of other vascular access sites must all be taken into consideration before a treatment plan is selected (see Fig. 91-8).

The conventional approach is to remove the catheter with interval replacement at a different site after the infection has resolved. Although this is effective, it leads to an additional temporary catheter if dialysis is needed before the catheter can be replaced. Attempts to "salvage" an infected catheter with systemic antibiotic therapy lead to resolution of infection in only about 30% of patients. Another treatment option is to combine systemic antibiotics with antibiotic "lock" solutions. Many different cocktails of antibiotics mixed with either heparin or citrate have been tested; a popular regimen is vancomycin 2.5 mg/ml, gentamicin 1 mg/ml, and heparin 2500 U/ml. Infection clearance rates of 50% to 70% are reported with antibiotic locking.

Several studies have reported that exchange of the catheter over a guidewire 48 hours after initial antibiotic treatment is more effective than treatment with antibiotics alone and is as effective as removal of the catheter and delayed replacement, with the advantages of only one invasive procedure and preservation of the venous access site.[68] There are no published randomized trials of antibiotic locking or catheter exchange over a guidewire.

Prevention of Infection

The most important measure to prevent catheter infection is meticulous handling of the catheter at all times. The catheter should be inserted with use of maximal sterile precautions. The dialysis nurses need procedures for accessing the catheters under strict sterile conditions, and it is of the utmost importance that these catheters never be accessed by untrained personnel. Data from randomized trials indicate that antibiotic lock solutions significantly reduce the incidence of infection.[69] Topical application of mupirocin ointment to tunneled exit sites has been reported to reduce the incidence of catheter-associated bacteremia.

Catheter Obstruction

Catheter obstruction may be caused by endoluminal fibrin deposits, restricting the catheter lumen or obstructing catheter side holes at the tip, or external fibrin sleeves surrounding the catheter, resulting in inadequate flow and excessive extracorporeal blood pressure alarms during the dialysis session. Depending on the location of the fibrin clot (arterial or venous line), there may be high negative arterial pressure (obstruction at the arterial catheter line) or high positive venous pressure (obstruction at the venous catheter line).

Prevention of clot formation in the catheter tip during the interdialytic period is crucial. This is achieved by installing an antithrombotic lock solution (trisodium citrate 30% is superior to standard heparin or low-molecular-weight heparin).[70] A certain amount of the antithrombotic lock solution may leak into the circulation through side and central catheter holes, facilitating catheter clot formation while increasing risk of hemorrhage. Regular use of low-dose warfarin or antiplatelet agents has failed to improve catheter function in dialysis patients in randomized trials.

To correct catheter dysfunction, it is recommended that the catheter lumen be cleaned periodically by application of a fibrinolytic agent (urokinase) as a lock solution or by continuous infusion on both arterial and venous lines. Occluded catheters are reopened either by a mechanical method (brush) or pharmacologically (urokinase). Removal of the fibrin sleeve may be achieved by lasso wire stripping or by infusion of a fibrinolytic solution (urokinase) for 3 to 6 hours. Alternatively, the catheter may be exchanged over a guidewire.

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CHAPTER 92

Diagnostic and Interventional Nephrology

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A variety of procedures are essential to the care of nephrology patients and include ultrasound, renal biopsy, insertion of hemodialysis and peritoneal dialysis (PD) catheters, creation of arteriovenous (AV) fistulas, and diagnostic and interventional procedures on hemodialysis accesses. These procedures have traditionally been performed by other specialists, and this may lead to fragmented care. The desire to provide greater continuity of care has led an increasing number of nephrologists to perform these procedures—the field of diagnostic and interventional nephrology. It is most developed in the United States, where the American Society of Diagnostic and Interventional Nephrology (www.asdin.org) has established training standards and certification procedures. This chapter covers ultrasound, insertion of dialysis catheters, and interventions on vascular access, focusing on the applications of these procedures and their performance by nephrologists. Renal biopsy is covered in Chapter 6, and placement of AV fistulas and AV grafts in Chapter 91.

ULTRASOUND

An important reason for nephrologists to be involved in ultrasound procedures is that many of the findings on ultrasound are not specific and require clinical correlation. The role and interpretation of ultrasound are further covered in Chapter 5.

Applications and Limitations of Ultrasound

Ultrasound is an excellent tool for examination of the kidneys and urinary tract. Under optimal conditions, both kidneys, the renal artery and vein, the proximal and distal ureter (when enlarged), and the bladder can be visualized. The ureter is usually apparent only when it is dilated. The middle portion of the ureter is usually obscured by overlying bowel but still may be visible when it is very dilated. In transplants, the entire ureter can be visualized, even when it is not markedly dilated, because of the proximity to the probe and the lack of overlying bowel. In very ill patients who cannot be optimally positioned or cannot control their breathing or have abdominal wounds or distention, views of the kidneys may be limited, but it is still possible in most of these patients to determine whether hydronephrosis is present.

Chronic Kidney Disease

Ultrasound is indicated in any patient with chronic kidney disease (CKD) to establish renal size and to rule out polycystic kidney disease or urinary tract obstruction. Small, echogenic kidneys indicate severe irreversible disease, eliminating the need for a biopsy.[1]

Acute Kidney Injury

Although the diagnostic yield is very low in patients in whom the basis for renal failure is likely to be acute tubular necrosis or prerenal causes, ultrasound is still indicated in certain patients to rule out obstruction and to identify preexisting CKD.[2]

Renal Transplant

Ultrasound is indicated when there is an acute decline in renal transplant function, because urinary obstruction is common in this setting.[3] In the immediate post-transplantation period, Doppler evaluation of renal blood flow should also be performed to rule out thrombosis. Additional indications in transplant patients are pain, swelling, ipsilateral leg edema, and infection. Another important indication in both native and transplanted kidneys is guidance for percutaneous biopsy, nephrostomy, or drainage of fluid collections.

Renal Biopsy

Ultrasound is the method of choice to guide percutaneous renal biopsy.[4] Except in rare patients, computed tomography offers no advantages over ultrasound[5] and results in unnecessary irradiation. This is discussed further in Chapter 6.

Urinary Bladder

Ultrasound is the procedure of choice for measurement of postvoid residual volume because it is painless and sufficiently accurate[6] and, when a scanner is readily available, a simple task. Additional indications include checking the location and patency of Foley catheters and examination of the distal ureters. Placement of the catheter in the proximal urethra is uncommon but not rare, and obstruction of catheters is frequent, so examination of the bladder should always be considered when urine output decreases. Prostatic hypertrophy, prostatitis, bladder carcinoma, mucosal edema, blood clots, stones, stents, and other foreign bodies can be recognized with ultrasound, but transabdominal ultrasound is not the appropriate test to rule out bladder cancer (which requires cystoscopy) or prostatic cancer (which requires transrectal ultrasound and biopsy).

Hemodialysis Access

Ultrasound is essential in the management of vascular access, including guidance of catheter insertion, evaluation of fistula dysfunction, preoperative vein mapping, and monitoring of access flow. Of these, the first two can be readily performed by nephrologists. Guidance of catheterization is best performed with a dedicated scanner but can be done with any scanner that has a vascular probe and does not require Doppler imaging. Examination of dysfunctional fistulas is also straightforward and does not necessarily require Doppler analysis. Vein mapping and monitoring of access flow are both best performed by an experienced vascular technician.

Renovascular Ultrasound

Doppler ultrasound of renal arteries and veins is a difficult study requiring an experienced operator and is not usually practical for nephrologists. Tracings from segmental arteries are more easily obtained and can be useful in diagnosis of renal artery stenosis and vein thrombosis. However, measurement of resistive index can be unreliable and nonspecific (it can be influenced by external factors such as systemic blood pressure and heart rate) and is of questionable usefulness in the evaluation of acute renal failure either in native

kidneys or transplanted kidneys. Doppler ultrasound is useful in distinguishing between cystic and vascular lesions and between renal vein and ureter.

Equipment

Important considerations in the choice of equipment are image quality, probe type and frequency, cost, size, portability, and output. Image quality is difficult to quantitate and is related to the number of elements (crystals) in the probe and the number of channels that can be processed. Probes should be electronic and in the frequency range of 2.0 to 5.0 MHz (up to 7.5 MHz for pediatric use) for abdominal imaging. Preferably, these should be variable frequency, curvilinear probes. Probes for vascular imaging are usually linear probes with a frequency of 7.5 to 12 MHz. For grayscale renal ultrasound, portable, lightweight scanners with good image quality are available; Doppler capability can add to the cost but is increasingly being offered as a standard feature. Larger and more expensive scanners are difficult to maneuver and have additional features that are of little use to the nephrologist. Controls on the scanner allow adjustment of scanning depth, focal length, time-gain compensation, sound intensity, and grayscale. Although this seems a daunting number of variables, adjustment is usually straightforward and mostly empiric. Images can be printed directly or digitally stored.

Procedure

Description of the scanning procedures cannot substitute for hands-on training because scanning is an acquired skill that requires practice. Ideally, the patient should be fasting for abdominal scanning to minimize interference from intestinal gas, but this is not essential for examination of kidneys and is of no consequence for examination of the bladder or transplanted kidneys. There must be an airtight connection between the probe and the skin, which is accomplished by placing gel on the probe or skin and applying firm pressure against the skin. To avoid compression of the vessels, minimal pressure should be applied for vascular examinations, with the use of more gel. Gel specifically designed for ultrasound should be used because other gels, such as lubricating gel, give poorer image quality. Ambient light should be dimmed to optimize viewing of the monitor.

The patient should be flat in the supine or lateral decubitus position with imaging through the abdomen for examination of native kidneys. Initial attempts should be made with the patient in the supine position before resorting to the lateral decubitus position. Imaging through the back is not recommended for diagnostic imaging because of sound attenuation by muscle and fascia and limitations on angling of the probe. Placement of the ipsilateral arm over the head, removal of pillows from under the head, and deep inspiration aid in moving overlying ribs superiorly. Transplanted kidneys and the urinary bladder are examined with the patient in the supine position, but he or she need not be completely flat.

Initially, longitudinal images should be obtained to determine maximal kidney length. On the right side, this view should be obtained through the liver if possible (Fig. 92-1, *A*). The probe should be oriented so that the upper pole is toward the left side of the image. The probe should then be rotated 90 degrees to obtain transverse views (Fig. 92-1, *B*), and the kidney is scanned from pole to pole to ensure visualization of the entire kidney. Examination of each kidney should include longitudinal images with adjacent liver or spleen if possible as well as transverse images through the mid-kidney and each pole.[7] Measurements other than length are of no clinical usefulness, and measurements of kidney volume are inaccurate and no better than length in judging kidney size.[8] Sagittal and transverse views of the urinary bladder are obtained with the probe just superior to the symphysis pubis and angled inferiorly (Fig. 92-1, *C* and *D*). Volume is obtained by multiplying the two transverse dimensions and the sagittal length by 0.523.[6] The technique for renal biopsy is discussed in Chapter 6.

Training and Certification

There are no data on what constitutes adequate training for renal ultrasound. Training is required for both performance and interpretation and should include didactic, hands-on, and supervised components. The last can vary considerably, depending on case volume and particularly type because any quantity of studies will be inadequate if the findings are all normal. Thus, the number of studies required for competence is inversely related to the frequency of pathology. Minimal qualifications for physician-sonographers have been established by the American Institute of Ultrasound in Medicine[9] and the American College of Radiology,[6] but neither organization has developed guidelines for limited abdominal ultrasound. The American Society of Diagnostic and Interventional Nephrology (www.asdin.org) has established training standards for ultrasound limited to kidneys and bladder that specify 50 hours of training and 125 studies (at least 80 being supervised and the remaining having confirmatory follow-up).[10] Because renal ultrasound is not usually a formal component of nephrology training, a course for nephrologists has been established in the United States (http://medicine.emory.edu/divisions/renal_medicine/renal-ultrasound/index.html).[7] Training and certification are available in vascular ultrasound but are not limited to applications specific to nephrology. Such training is important for vascular studies of kidneys but is not necessary for examination of dysfunctional AV fistulas and grafts (unless flow is measured) because this does not require Doppler analysis. There are currently no guidelines or training established for vascular ultrasound related to nephrology.

PERITONEAL DIALYSIS CATHETERS

Successful PD is dependent on proper catheter insertion and management. The feasibility, safety, and success of these procedures when they are performed by nephrologists have been well documented,[11-13] and this leads to greater use of PD. Chronic PD catheters are constructed of silicone rubber with a 5-mm external diameter and internal diameters of 2.6 to 3.5 mm. Some commonly used designs of PD catheters are shown in Figure 96-6. The intraperitoneal portion can be straight, straight with perpendicular silicone disks, or curled with side holes or T shaped with linear grooves or slots rather than side holes. These designs are created to diminish outflow obstruction. The subcutaneous portion is either straight or bent and has one or two extraperitoneal Dacron cuffs that prevent fluid leaks and bacterial migration around the catheter. The subcutaneous catheter shapes all provide a lateral or downward direction of the exit site. An upwardly directed exit site collects debris and fluid, increasing the risk of exit site infection. Currently, the method of placement of the catheter has more effect on the outcome than catheter choice does.

Catheter Insertion

The four techniques for PD catheter insertion are dissection (surgical), the Seldinger technique (blind or with fluoroscopy), peritoneoscopic, and laparoscopic.[14] The Seldinger and peritoneoscopic techniques are most frequently used by nephrologists. Peritoneoscopic insertion is a single-puncture technique using a small (2.2-mm

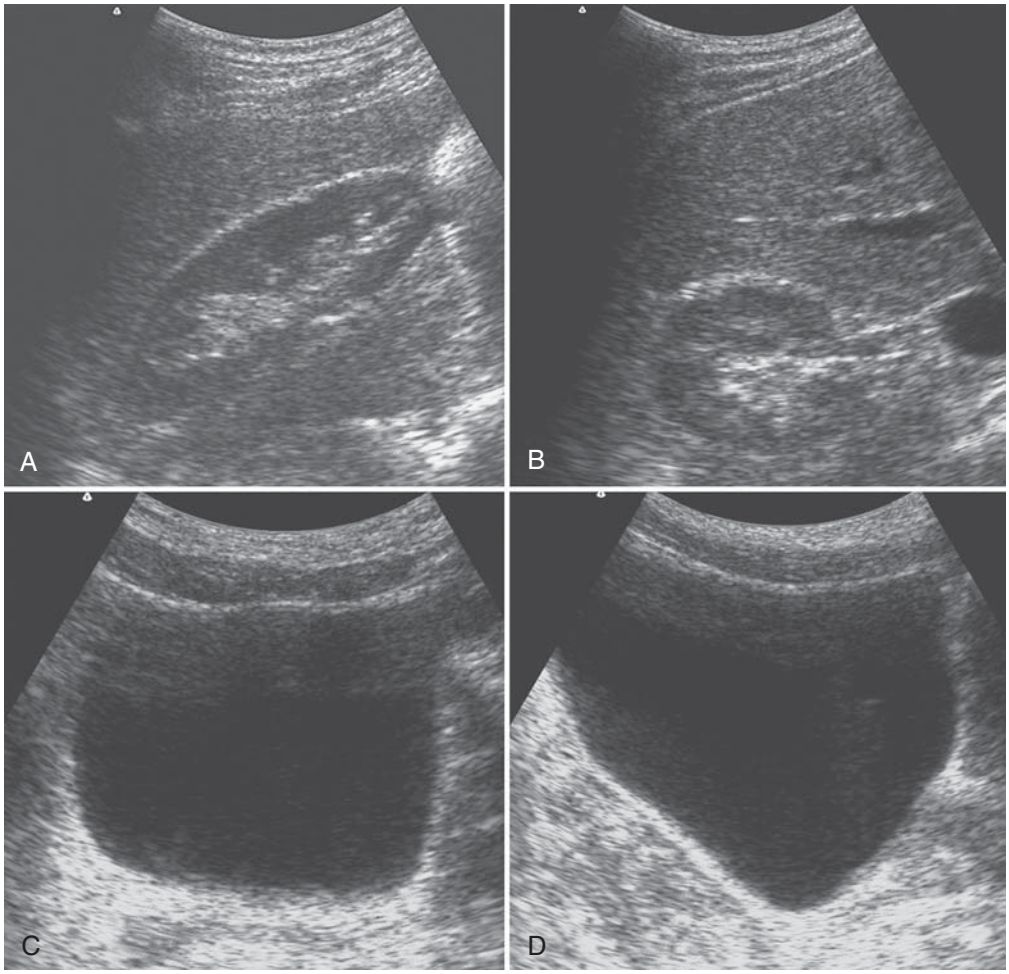

Figure 92-1 Imaging planes for renal and bladder sonography. A, Longitudinal image of right kidney. Upper pole should be on left side of the image. **B,** Transverse image of right kidney through the renal hilum. **C,** Transverse image of urinary bladder. Anteroposterior and mediolateral dimensions are obtained in this plane. **D,** Sagittal image of the urinary bladder. Superior portion of the bladder is to the left. Superoinferior dimension is obtained in this plane.

diameter) optical peritoneoscope for direct inspection of the peritoneal cavity and identification of a suitable site for the optimal intraperitoneal portion of the catheter. Peritoneoscopic placement is usually performed with local anesthesia (sometimes with conscious sedation) and manual infusion of about 1 liter of air. Laparoscopic techniques are performed with the patient under general anesthesia, with larger scopes, multiple insertion sites, and automated gas infusion. Both peritoneoscopic and laparoscopic techniques allow direct visualization of intraperitoneal structures.

The choice of technique must take into account the local experience with complications (pericatheter leakage, outflow failure, exit site and tunnel infection) and long-term catheter function associated with each technique, costs, ease and timely insertion of the catheter, and factors contributing to mortality risk (local vs. general anesthesia). Both randomized and nonrandomized studies have documented that the peritoneoscopic and fluoroscopic Seldinger techniques result in fewer catheter complications (infection, outflow failure, pericatheter leak) and improved catheter survival compared with surgical placement.[12,15] The superior results with peritoneoscopic placement may relate to direct visualization of the abdominal cavity, less tissue dissection, and avoidance of general anesthesia. Because tissue dissection is minimal, the catheter can be used immediately (after 36 hours), although a 2- to 3-week delay is recommended.[16]

For peritoneoscopic insertion (Fig. 92-2), a small skin incision (2 to 3 cm) is made and dissection is carried down only to the subcutaneous tissue.[23] The anterior rectus sheath is identified but not incised. A preassembled cannula with trocar and a spiral sheath is then inserted at a 40- to 50-degree angle into the abdominal cavity through the rectus muscle (Figs. 92-2, *A*, and 92-3). The trocar is then removed and replaced by the peritoneoscope to confirm the intra-abdominal position of the cannula (Figs. 92-2, *B*, and 92-4). Air is then infused (600 to 1000 ml) to separate visceral and parietal peritoneum. Alternatively, a Veress needle can be used.[17] Bowel loops, the dome of the bladder, and any intra-abdominal adhesions are identified. The cannula and spiral sheath are advanced into the pelvis (Fig. 92-2, *C*). The cannula and the peritoneoscope are then removed, the spiral sheath is dilated to 6-mm diameter (Fig. 92-2, *D*), and the catheter is inserted through the sheath by a stylet (Fig. 92-2, *E*). The deep cuff is implanted into the rectus muscle with use of an implanter tool without dissection of the anterior rectus sheath or the muscle (Fig. 92-2, *F*). A tunnel and an exit site are created (Fig. 92-5), and the superficial cuff is implanted into the subcutaneous tissue. The subcutaneous tissue is sutured with absorbable material; the skin is closed with nylon. No sutures are placed on the external rectus sheath or at the skin exit site.

The Seldinger technique using fluoroscopy begins with blunt dissection down to the level of the lateral border of the rectus sheath. A 22-gauge needle from a 5-French micropuncture set is inserted at an angle of 45 degrees, directed toward the lower pelvis into the peritoneum (ultrasound can be helpful). The location of the needle

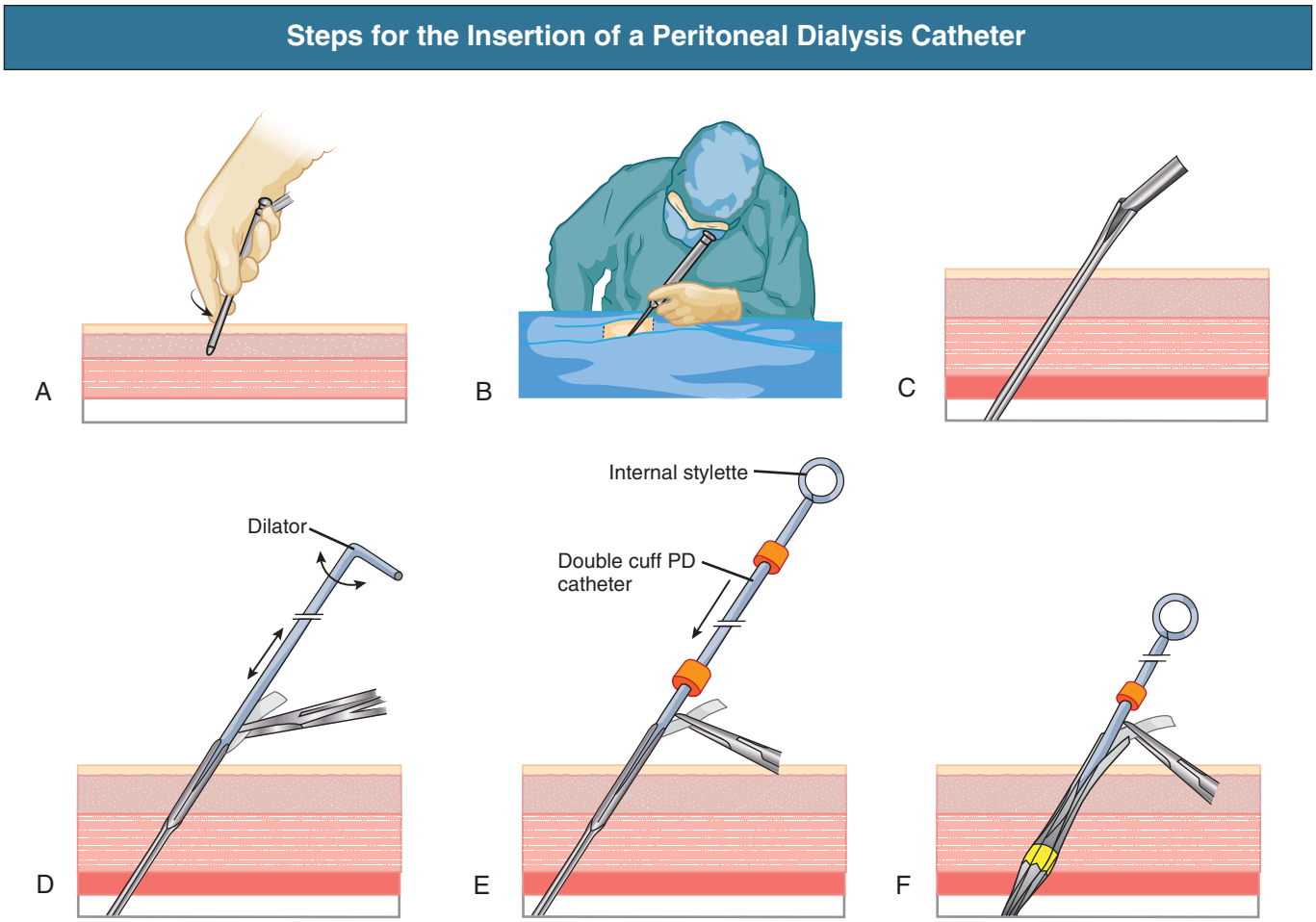

Figure 92-2 Steps for the insertion of a peritoneal dialysis *(PD)* catheter by peritoneoscopy. A, A trocar and cannula with a sheath are inserted into the abdominal cavity. **B,** A peritoneoscope is passed through and locked into the cannula. **C,** The sheath has been passed into the abdominal cavity and the peritoneoscope and cannula removed sequentially. **D,** The sheath is secured with forceps while it is being dilated. **E,** A PD catheter (with double cuff) is passed through the dilated sheath by use of an internal stylet. **F,** The deep cuff is implanted into the rectus muscle. *(Redrawn from Y-Tec Instructions: Laparoscopic and Peritoneoscopic Placement of Peritoneal Dialysis Catheters. Oswego, IL: Medigroup Inc. [division of Janin Group, Inc.]; 2004:1-5.)*

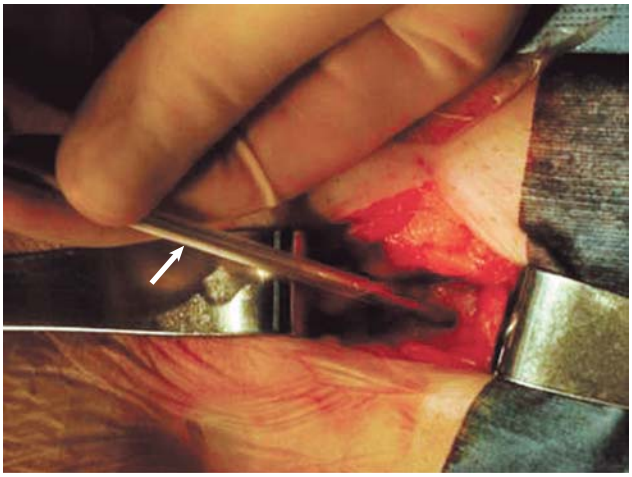

Figure 92-3 Peritoneoscopic insertion of a peritoneal dialysis catheter. During peritoneoscopic insertion of a peritoneal dialysis catheter, a Quill guide trocar and cannula *(arrow),* with its wrapped spiral sheath, is being inserted through the rectus muscle under local anesthesia.

Figure 92-4 Peritoneoscopic insertion of a peritoneal dialysis catheter. A peritoneoscope has been introduced into the abdominal cavity through the cannula, and the fiberoptic light source is being connected to the scope.

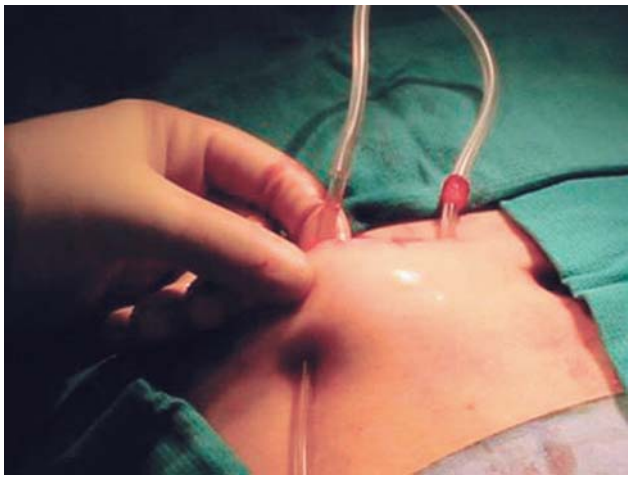

Figure 92-5 Peritoneoscopic insertion of a peritoneal dialysis catheter. With use of a disposable tool, a subcutaneous tunnel is created for the catheter. The superficial cuff shown will be implanted in the subcutaneous tunnel.

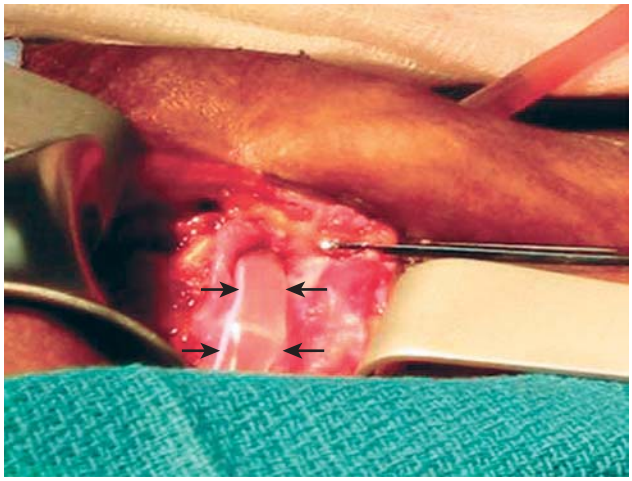

Figure 92-6 Peritoneal dialysis catheter removal. The catheter (*arrows* show lateral margins of catheter) has been exposed by dissection of the subcutaneous tunnel.

within the peritoneal cavity is confirmed by injecting 3 to 5 ml of contrast material, which is seen surrounding bowel loops. A micropuncture 0.018-inch wire is then inserted through the needle under fluoroscopy. Once it is in the lower pelvis, a 5-French catheter is placed over the wire. Contrast material can again be injected to confirm the position. A 0.035-inch guidewire is then passed through the catheter, and dilators are advanced sequentially up to the final 18-French dilator and peel-away sheath. The guidewire is removed and the PD catheter is inserted over a metal stylet through the sheath, splitting the sheath as the deep Dacron cuff advances. This cuff is pushed into the rectus muscle while the sheath is in place, and the sheath is then removed around the cuff and catheter. The catheter is tunneled laterally with a tunneling tool.[18,19]

Burying the Peritoneal Dialysis Catheter

If the catheter will not be used immediately, it can be implanted (buried) under the skin for weeks to months before it is tunneled to the outside and used. The catheter is placed in the usual manner, then blocked with a plug and tunneled in a straight line under the skin. In some centers the catheter is tied off with silk suture and coiled into a pouch under the exit site. This allows ingrowth of tissue into the cuffs of the catheter without an opportunity for bacterial colonization and diminishes the incidence of early pericatheter infections.[20,21] Catheters buried in this fashion have been successfully used more than 1 year after insertion.[22] We recommend burial when the catheter will not be used for at least a month.

Complications of Peritoneal Dialysis Catheter Insertion

Bowel perforation is the most feared complication of catheter insertion. The incidence is 1% to 1.4% with surgical insertion[12,13] but 0% to 0.8% with the peritoneoscopic insertion.[11,13] The diagnosis is established by direct peritoneoscopic visualization of bowel mucosa, bowel contents, or hard stool or return of fecal material or emanation of foul-smelling gas through the cannula. Whereas some investigators suggest that this complication should be treated with surgical intervention,[24] successful conservative management of bowel perforation with bowel rest and intravenous antibiotics has also been reported.[19,25] To minimize the risk of perforation, a needle (such as a Veress needle) that is smaller and has a blunt, self-retracting end can be used instead of a trocar to gain access to the abdominal cavity.[17] Previous abdominal surgery is mentioned as a relative contraindication to PD because of intraperitoneal adhesions.[26,27] However, with peritoneoscopy, which can be used to identify intraperitoneal adhesions, assess their extent, and locate a suitable site for catheter placement, the incidence of bowel perforation is no higher than in patients without prior abdominal surgery, and the success rate exceeds 95%.[11,13]

Catheter Repositioning

Migration of the PD catheter to the upper abdomen is a frequent cause of catheter failure. A variety of techniques have been used for repositioning, including guidewire or stylet insertion, Fogarty catheters, and laparoscopy, and are feasible for nephrologists. The long-term success rate is only 27% to 48%,[28,29] probably because the migration of the catheter is the result of encasement by the omentum. Thus, insertion of a new catheter is required in many patients. Fogarty catheter manipulation is perhaps the most cost-effective, safe, and simple method. A Fogarty catheter is advanced into the PD catheter, and the balloon is inflated. Manipulation is performed by tugging movements to reposition the catheter into the pelvic area. Infusion and drainage of dialysate as well as radiography are performed to determine patency and position of the PD catheter, respectively.

Removal of Peritoneal Dialysis Catheters

A Tenckhoff curled or straight PD catheter can be safely removed without need for an operating room or general anesthesia.[16] Local anesthetic is infiltrated at the site of the primary incision, and dissection is carried down to the subcutaneous portion of the catheter by longitudinal incisions with scissors while the catheter is held with toothed forceps. The catheter is clamped with a hemostat, a nylon suture is placed in the catheter beyond the hemostat as a tag, and the catheter is cut between the two. Dissection is continued toward the deep cuff (Fig. 92-6), and additional anesthetic is infiltrated around the deep cuff. For catheters that have been in place for less than a month, blunt dissection is usually sufficient to free the deep cuff. Older catheters require sharp dissection. Exposure of the deep cuff

and the anterior rectus sheath is required. Once the deep cuff is separated from the surrounding tissue, the intraperitoneal portion of the catheter is gently withdrawn from the peritoneal cavity, and the defect in the rectus sheath is closed with an absorbable purse-string suture. The nylon tag is then pulled to expose the remaining subcutaneous portion of catheter segment, and dissection is performed in the direction of the superficial cuff. Once the superficial cuff is free, this portion of the catheter is removed through the primary incision site or the exit site. Absorbable suture material is used to close the subcutaneous tissue; nylon is used to close the skin. The exit site is not sutured.

Training and Certification

The American Society of Diagnostic and Interventional Nephrology has established training guidelines and criteria for certification of physicians in the insertion of PD catheters (www.asdin.org).[10] In addition to appropriate didactic training, there should be two practice insertions (into models, animals, or human cadavers), observation of two insertions into patients, and then six successful insertions into patients as primary operator.

TUNNELED HEMODIALYSIS CATHETERS

Central venous catheters are used as a temporary hemodialysis access, as a bridge to AV fistula or graft use, and when all other permanent access sites have been exhausted. Nontunneled catheters are used when a limited number of dialysis sessions is anticipated or there are contraindications to tunneled catheters (systemic infection, risk of bleeding) and are appropriate for use only in the inpatient setting. Tunneled catheters can be placed in both inpatient and outpatient settings, can be inserted at multiple vein locations, are relatively low in cost, and provide immediate access. However, there are significant disadvantages, including morbidity from infection and thrombosis and the risk of central vein stenosis or occlusion.[30,31] The role of the tunneled dialysis catheter in the provision of vascular access for hemodialysis is discussed further in Chapter 91.

Catheter Insertion

The right internal jugular vein is the preferred catheter location compared with the left internal jugular and subclavian vein sites; it provides a straight route to the right atrium, thereby reducing the risk of central vein stenosis. Catheters may also be placed in the femoral veins.

Catheter insertion is performed in a sterile setting, ideally in an operating room environment with fluoroscopy available or at a minimum in a dedicated procedure room with cardiac monitoring. Before cannulation the vein should be located by ultrasound to detect anatomic variation or venous thrombosis. The patient's neck is then prepared and draped in sterile fashion; under ultrasound guidance, the vein is cannulated with a micropuncture needle (18 to 22 gauge), and a micropuncture guidewire is inserted and positioned in the superior vena cava. The needle is then removed, and the micropuncture dilator is inserted over the guidewire so that it can be replaced with a standard guidewire. The use of the smaller needle rather than the standard 15-gauge needle minimizes trauma to the vein. A small subcutaneous incision is made adjacent to the dilator or guidewire, additional dilation is performed, and the catheter is placed over the guidewire, with care taken to hold the guidewire in place. If a tunneled catheter is to be placed, a catheter exit site is selected inferior to the clavicle and sufficiently lateral to the venotomy to avoid a kink in the catheter. A 1-cm superficial incision is made at this point, and a subcutaneous track adjacent to the venotomy is infiltrated with lidocaine. A double-lumen catheter, generally 28 or 32 cm in length, is attached to the tunneling device and pulled through the subcutaneous tunnel in a curved path. A guidewire is passed through the dilator and into the inferior vena cava. The venotomy site is then serially dilated over the guidewire. The catheter can then be inserted over the guidewire through the venous port. When a split-tip catheter is used, the guidewire is passed in and out of the two venous ports and through an arterial port or through a hollow intracatheter stiffener. Alternatively, a peel-away sheath is placed over the guidewire and the catheter inserted through the sheath after the removal of the guidewire; however, this method has greater potential for blood loss and air embolism. Fluoroscopy is used to confirm tip placement at the level of the right atrium, with the arterial port facing away from the atrial wall, and to ensure that there are no kinks in the catheter (Fig. 92-7). Each port of the catheter is then flushed with saline and locked with the appropriate amount of heparin based on catheter length and priming volume designation, followed by placement of the catheter hub caps.

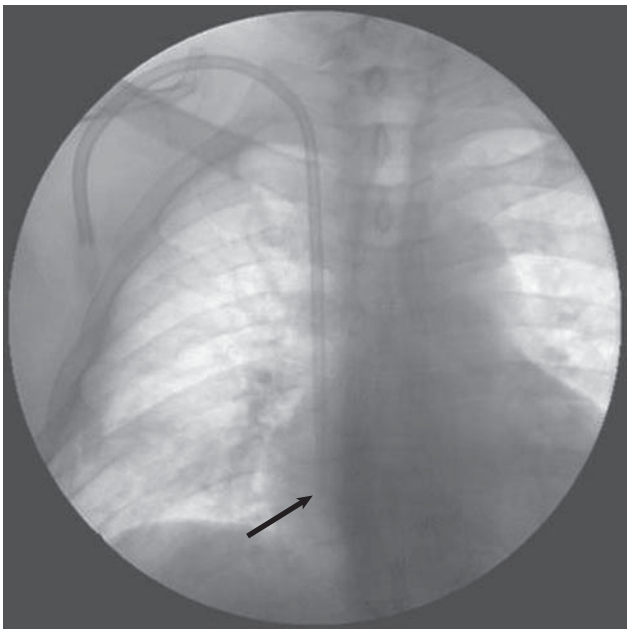

Figure 92-7 Insertion of a venous catheter for hemodialysis. Chest radiograph confirming that the tip of the catheter *(arrow)* is at the junction of the superior vena cava and the right atrium.

Catheter Dysfunction

Catheter dysfunction is defined as the failure to maintain a blood flow sufficient to perform hemodialysis without significantly extending treatment time; this is usually 300 ml/min.[39] Causes of immediate dysfunction include a kink in the catheter, incorrect position or orientation (arterial port against the vessel wall), and errant venous cannulation. These problems should be ascertained and corrected at the time of catheter placement. Catheter thrombosis is the most common cause of late dysfunction. Extrinsic thrombosis is less common than intrinsic thrombosis and is caused by central vein, mural, or right atrial thrombosis. Intrinsic obstruction results from thrombus within the catheter lumen or tip or most commonly from a fibrin sheath. Fibrin sheaths typically develop weeks to months after catheter insertion and result when a sleeve of connective tissue forms at the venotomy site and extends and

encases the catheter tip, creating a flap-valve. First-line treatment of catheter thrombosis includes forceful flush of the catheter with saline. If flow is not restored, a fibrinolytic agent should be instilled. Tissue plasminogen activator (tPA) is commonly used and appears more effective than urokinase in restoring patency and adequate flow.[32,33] Typically, 2 mg of tPA is instilled per occluded catheter lumen with 0.9% sodium chloride without preservative to fill the internal volume of each lumen and is allowed to dwell 30 minutes. If this fails, the catheter should be exchanged. Strategies to minimize dialysis catheter thrombosis are discussed in Chapter 91.

Catheter Exchange and Fibrin Sheath Removal

Catheter exchange over a guidewire is useful in the setting of catheter thrombosis or bacteremia and allows the preservation of the venotomy, tunnel, and exit sites. The tunnel and exit sites must appear free of infection if the same sites are to be used. Catheter exchange should take place within 72 hours of the initiation of antibiotic therapy.[39] Under sterile conditions, the exit site is anesthetized and the cuff is freed. Once the catheter is pulled back 8 to 10 cm, contrast material is injected through the catheter under fluoroscopy to check for a fibrin sheath (Fig. 92-8). To obliterate a sheath, a guidewire is passed down the venous port of the catheter and into the inferior vena cava. The catheter is then removed, and a balloon catheter is inserted over the guidewire to the sheath location and inflated to disrupt the sheath. The guidewire is then wiped with povidone-iodine (Betadine), and a new catheter is inserted over the guidewire. When the catheter tip is beyond the venotomy site, near the superior vena cava, contrast material can be injected again to check for sheath removal before proceeding with catheter insertion.

Training and Certification

The American Society of Diagnostic and Interventional Nephrology guidelines for hemodialysis vascular access procedure certification specify formal didactic training in central venous anatomy, sonographic examination of central veins, fluoroscopy, and catheter design and complications. In addition, practical training for certification includes satisfactory insertion of 25 tunneled long-term catheters. More information may be obtained at www.asdin.org.

PROCEDURES ON ARTERIOVENOUS FISTULAS AND GRAFTS

The most common indications for intervention are inadequate flow during dialysis, thrombosis, and failure of AV fistulas to mature. Specific interventions include angiography, thrombectomy, angioplasty, and stenting. All of these procedures require a dedicated facility, either inpatient or outpatient, with fluoroscopy, monitoring equipment, and staff to assist with the procedures and to deliver conscious sedation. There are many different techniques for AV access procedures and few data to indicate superiority of one method over the other, so the choice is generally one of personal preference and cost. However, the first step should always include a careful physical and ultrasound examination of the access. An examination will generally identify the problem and allow detection of access infection, an absolute contraindication to intervention. Appropriate intervention can then be planned. Monitoring and management of vascular access to minimize stenosis, thrombosis, and failure are discussed further in Chapter 91.

Percutaneous Balloon Angioplasty

Stenosis in AV grafts and fistulas is routinely managed by percutaneous balloon angioplasty, which can be safely performed on an outpatient basis, causes minimal discomfort, and allows immediate use of the access. Not all stenotic lesions are responsive, however, and some require repeated treatment. In fistulas, the stenosis is most commonly located at the "swing point," the portion of the native vein mobilized during creation of the AV anastomosis (Fig. 92-9); in

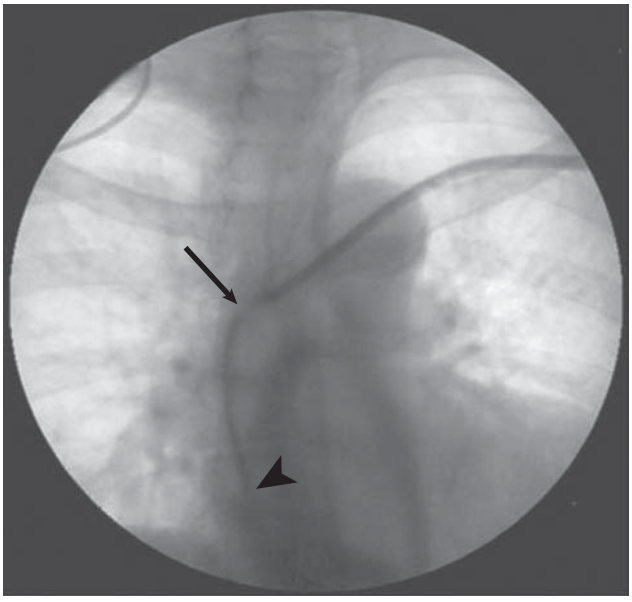

Figure 92-8 Fibrin sheath on a tunneled venous catheter. Contrast material has been injected into a tunneled catheter after the tip *(arrow)* has been pulled back into the innominate vein. The contrast material fills a sheath that extends from the catheter tip as far as the arrowhead.

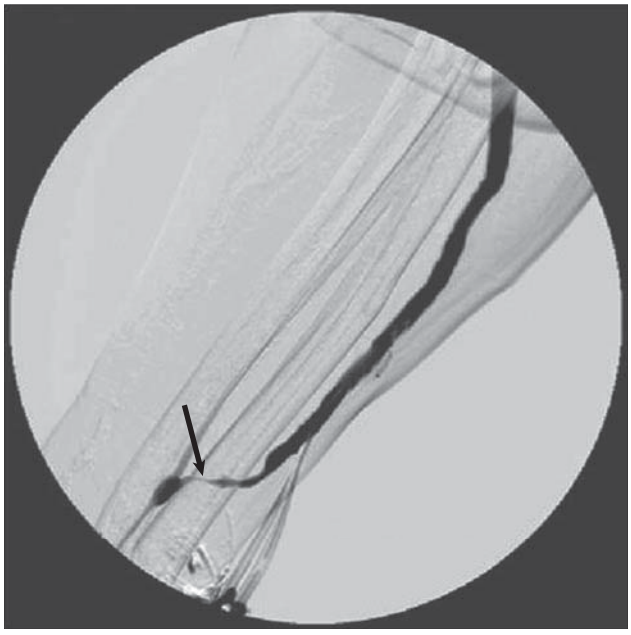

Figure 92-9 Juxta-anastomotic stenosis in a radiocephalic arteriovenous fistula. Contrast material was injected at the arterial anastomosis *(bottom left of image)* and demonstrates a narrowing in the initial portion of the fistula *(arrow)*.

grafts, the venous anastomosis is the most common site of stenosis.[34-38] Angioplasty is indicated if the stenosis is 50% or more and is associated with clinical or physiologic abnormalities.[39] Treatment of stenosis increases access blood flow and longevity, reduces access thrombosis, and reduces vascular access–related hospitalization.[38,40,41] A relative contraindication to angioplasty is a newly created access (<4 to 6 weeks old).

The access is cannulated with an introducer needle, a sheath is inserted, and initial angiography is performed. This should include views of the access, draining veins (peripheral and central), and arterial anastomosis and is used to confirm the location and degree of stenosis. Unless contraindicated, sedation and analgesia are then given with short-acting agents once a lesion has been identified on initial angiography, because angioplasty is painful.

A guidewire is passed through the sheath and across the stenosis. An angioplasty balloon catheter is passed over the guidewire, positioned at the stenotic site, and inflated with a syringe to 18 to 20 atm (Fig. 92-10). A variety of sheaths, guidewires, balloon sizes, and maximum pressures are available. The guidewire is left in place, and angiography is repeated to identify residual stenosis or any complications. Angioplasty is repeated for residual stenosis or when multiple lesions are present and may require a second cannulation of the access in the opposite direction for inflow stenoses. After removal of all devices, hemostasis at the cannulation site is achieved by manual pressure or suture placement. There is no evidence to support the use of antiplatelet agents or anticoagulation after intervention. According to Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, a successful angioplasty is achieved when there is no more than 30% residual stenosis and physical indicators of stenosis have resolved.[39]

Percutaneous Thrombectomy

A variety of techniques are used for thrombus removal. In thromboaspiration—the least costly method, and as effective and efficient as mechanical and pharmacomechanical thrombolysis—low-dose tPA is instilled into the thrombosed access, the clot is manually macerated, flow returns, and angioplasty is used to dilate access stenoses.[42] Thrombectomy by thromboaspiration combines angiography with balloon angioplasty and thrombectomy by clot aspiration. Absolute contraindications to thromboaspiration include access infection and known right-to-left cardiac shunt; relative contraindications include a large clot burden and longstanding access occlusion.

The access is cannulated in an antegrade direction, and a guidewire is passed to the level of the central veins. A straight catheter is inserted over the wire to the central veins, and angiography is performed to confirm central venous patency. Anticoagulation and short-acting sedative and analgesic medications are administered in the central circulation. An angiogram is then obtained as the catheter is pulled back to identify the location of stenosis. The guidewire is then inserted beyond the stenotic lesion, followed by an angioplasty balloon catheter. The balloon catheter is insufflated by hand with a syringe, and the stenotic lesion is dilated. The access is then cannulated in the retrograde direction, a sheath is inserted, and a Fogarty catheter is passed across the arterial anastomosis, inflated, and pulled back through the entire length of the access while clot fragments are aspirated. On return of flow through the access, angiography is performed to evaluate the inflow and the arterial anastomosis, and angioplasty is repeated if necessary. Hemostasis is achieved by manual pressure or a suture at the cannulation sites.

Stents

The precise role of the endovascular stent in AV fistulas and grafts has not been defined. Results from nonrandomized studies differ as to the patency benefit of primary stent use versus angioplasty alone within a stenotic access or central vein.[43-46] Stents are expensive and have often been used in situations in which their use will not extend the life of the access. Stents should be considered in the setting of failed balloon angioplasty (an elastic lesion), when there are few remaining access sites, if the patient is not a surgical candidate for a new access, or when an outflow vein ruptures after balloon angioplasty (Figs. 92-11 and 92-12).[47,48] Finally, a stent may be useful in the setting of an expanding pseudoaneurysm.[49,50]

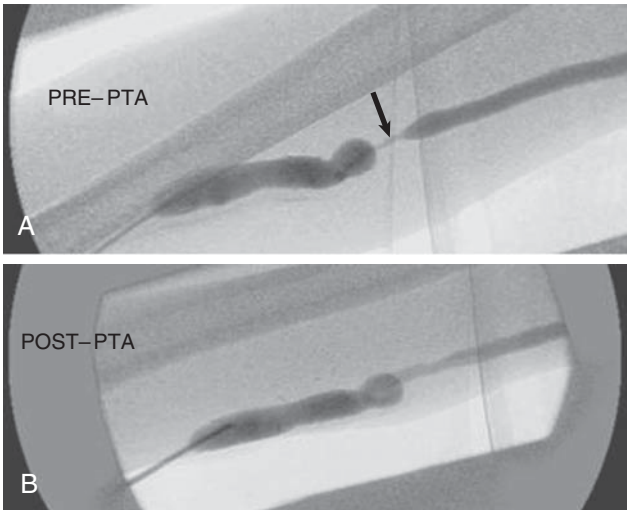

Figure 92-10 Arteriovenous graft stenosis. A, Stenosis in the outflow vein of an upper arm arteriovenous graft *(arrow)*. **B,** Angiogram performed immediately after percutaneous angioplasty. *PTA,* Percutaneous transluminal angioplasty.

Figure 92-11 Vein rupture. Postangioplasty angiogram of an arteriovenous fistula showing extravasation of dye *(arrow)* indicative of a vein rupture. *(Courtesy Dr. G. Beathard, Austin, Texas.)*

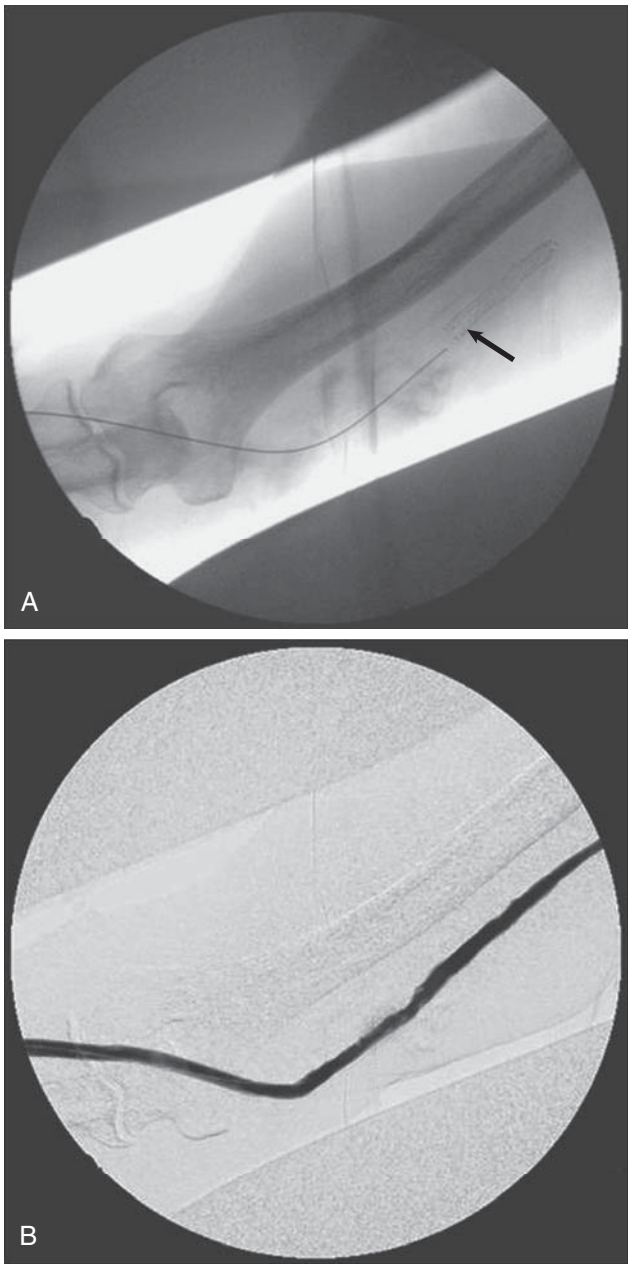

Figure 92-12 Treatment of vein rupture with an intraluminal stent. **A,** Placement of the stent *(arrow).* **B,** An angiogram obtained after stent placement showing that venous outflow has been reestablished. *(Courtesy Dr. G. Beathard, Austin, Texas.)*

Training and Certification

The American Society of Diagnostic and Interventional Nephrology guidelines for hemodialysis vascular access procedure certification specify didactic training in venous anatomy, fluoroscopy, procedural equipment, and sedation and analgesia. Requirements for practical training include 25 procedures in both fistulas and grafts of each of the following: angiography, angioplasty, and thrombectomy as primary operator (refer to www.asdin.org for more information). In general, several times that number as secondary operator will be required before one can become a primary operator.

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CHAPTER 93

Hemodialysis: Principles and Techniques

Peter Kotanko, Martin K. Kuhlmann, and Nathan W. Levin

Despite the widespread use of peritoneal dialysis and renal transplantation, hemodialysis (HD) remains the main renal replacement therapy in most countries. Currently more than 2 million patients are treated with HD in about 28,500 dialysis units worldwide. Despite substantial advances in our understanding of the biology of chronic kidney disease (CKD) and the risk factors for poor outcome on HD and improvements in dialysis technology, the annual mortality in HD patients varies from 5% to 25% internationally, depending on demographic and possibly genetic factors.

DIALYSIS SYSTEM

The aim of the HD system is to deliver blood in a fail-safe manner from the patient to the dialyzer, enable the efficient removal of uremic toxins and excess fluid, and deliver the cleared blood back to the patient. The main components of the dialysis system are the extracorporeal blood circuit, the dialyzer, the dialysis machine, and the water purification system.[1] The dialysis machine delivers dialysis fluid with the intended flow rate, temperature, and chemical composition. It has monitoring and safety systems for air, blood, conductivity, and pressure; blood and dialysate pumps; a heating system; a dialysate mixing and degassing unit; and a volumetric ultrafiltrate balancing system. The role of the water purification system is to produce water for dialysis that complies with international chemical and microbiologic standards.

DIALYZER DESIGNS

The dialyzer provides controllable transfer of solutes and water across a semipermeable membrane. The flows of dialysate and blood are separated and countercurrent. The dialyzer has four ports, one inlet and one outlet port each for blood and dialysate. The semipermeable dialysis membrane separates the blood compartment from the dialysate compartment. The transport processes across the membrane are diffusion (dialysis) and convection (ultrafiltration). The removal of small solutes occurs primarily by diffusion, whereas larger components such as β_2-microglobulin are more effectively removed by convection. The hollow fiber dialyzer is currently the most effective design; it delivers high dialysis efficiency with low resistance to flow in a small device.

DIALYSIS MEMBRANES

Membranes vary with respect to chemical structure, biophysical properties such as transport characteristics, and biocompatibility (Table 93-1).

Materials

The original widely used membrane material was cellulose, which is made up of repetitive polysaccharide units containing hydroxyl groups. In cellulose acetate 80% of the hydroxyl groups are replaced by acetate radicals. Synthetic tertiary amino compounds are added during cellulose membrane synthesis to form cellulosynthetic membranes. More recent membranes are not cellulose based but instead are built of entirely synthetic materials, such as polyacrylonitrile, polysulfone, polycarbonate, polyamide, and polymethylmethacrylate. These synthetic membranes provide superior biocompatibility and are widely used.

Transport Properties

Transport of molecules across the dialysis membrane occurs because of (1) the concentration gradient (diffusive transport) and (2) the hydrostatic pressure gradient across the membrane (convective transport) and is dependent on membrane pore size. Dialyzer efficiency in terms of urea removal depends on the surface area (usually 0.8 to 2.1 m^2). High-efficiency dialyzers have a high surface area irrespective of pore size and possess a superior clearance for small molecules but may have small pores and thus a low ability to remove large molecules such as β_2-microglobulin. The dialyzer mass transfer area coefficient (K_oA) for urea is a measure of the theoretically maximal possible urea clearance (in milliliters per minute) at infinite blood and dialysate flow rates. Dialyzer efficiency can be categorized according to K_oA for urea as low (<500 ml/min), moderate (500 to 700 ml/min), and high (>700 ml/min). In contrast to the dialyzer clearance of a substance, its K_oA is independent of flow rates in the blood and dialysate compartments. High-flux dialyzers have pores large enough to allow the passage of larger molecules such as β_2-microglobulin (molecular weight 11800 d). Water permeability is defined by the ultrafiltration coefficient (K_{uf}) in milliliters of transmembrane ultrafiltration per hour per millimeter of mercury of transmembrane pressure (ml/h/mm Hg). K_{uf} is high in high-flux dialyzers, with K_{uf} up to 80 ml/h/mm Hg. During high-flux HD, backfiltration (the flow of dialysate into the blood because of higher hydrostatic pressure on the dialysate side) can occur at the distal end of the dialyzer blood compartment and may result in a transfer of 5 to 10 liters of dialysate into the blood during a treatment; it is compensated for by an increased blood water removal at the proximal part of the dialyzer. Therefore, water quality is of paramount importance when high-flux dialyzers are used.

In the prospective, randomized Membrane Permeability Outcome (MPO) study a survival benefit of high-flux membranes was seen among patients with serum albumin levels of 4 g/dl or lower, and in diabetic patients.[2] These results are in contrast with the results of the Hemodialysis (HEMO) study, which did not show any effect in patients with hypoalbuminemia, but did show survival benefit in

Dialysis Membrane Properties			
Membrane	**Membrane Name (Example)**	**High or Low Flux**	**Biocompatibility**
Cellulose	Cuprophane	Low	Low
Semisynthetic cellulose			
Cellulose diacetate	Cellulose acetate	High and low	Intermediate
Cellulose triacetate	Cellulose triacetate	High	Good
Diethylaminoethyl-substituted cellulose	Hemophane	High	Intermediate
Synthetic polymers			
Polymethylmethacrylate	PMMA	High	Good
Polyacrylonitrile methacrylate copolymer	PAN	High	Good
Polyacrylonitrile methallyl sulfonate copolymer	PAN/AN-69	High	Good
Polyamide	Polyflux	High and low	Good
Polycarbonate-polyether	Gambrane	High	Good
Ethylene vinyl alcohol copolymer	EVAL	High	Good
Polysulfone	Polysulfone	High and low	Good

Table 93-1 Dialysis membrane properties.

patients on dialysis for longer than 3.7 years before the trial.[3] These differences may be related in part to population characteristics (race, recruitment of incident of prevalent patients), or to the fluxes achieved.

SAFETY MONITORS

Safety monitors are integral parts of the dialysis machine. Pressure monitors are integrated in most machines to monitor the system pressure in critical positions (Fig. 93-1)[1]:

- Between the arterial side and the blood pump (prepump arterial pressure) to assess the suction pressure; overly negative values may signal reduced arterial inflow and access problems.
- Between the blood pump and the dialyzer inlet (postpump to assess the dialyzer inflow pressure); a high pressure may signal dialyzer clotting.
- Between the dialyzer outlet and the air trap (venous pressure) to control the return pressure; a high pressure may point toward an obstruction in the venous limb. It is important to consider that in the event of venous needle displacement, the venous pressure will remain positive because of the needle's flow resistance, and a pressure alarm may not occur.

A venous air detector and air trap are located downstream of the venous pressure monitor. A positive signal at the air detector automatically clamps the venous line and stops the blood pump. A blood leak detector is placed in the dialysate outflow line. Dialysate temperature is constantly monitored. Dialysate is produced by a proportioning system that mixes acid and bicarbonate concentrates with purified water. The osmolarity of the dialysate translates into conductivity, which is measured by the dialysis conductivity monitor. The ultrafiltration rate must be controlled precisely, in most machines by a volumetric control system.

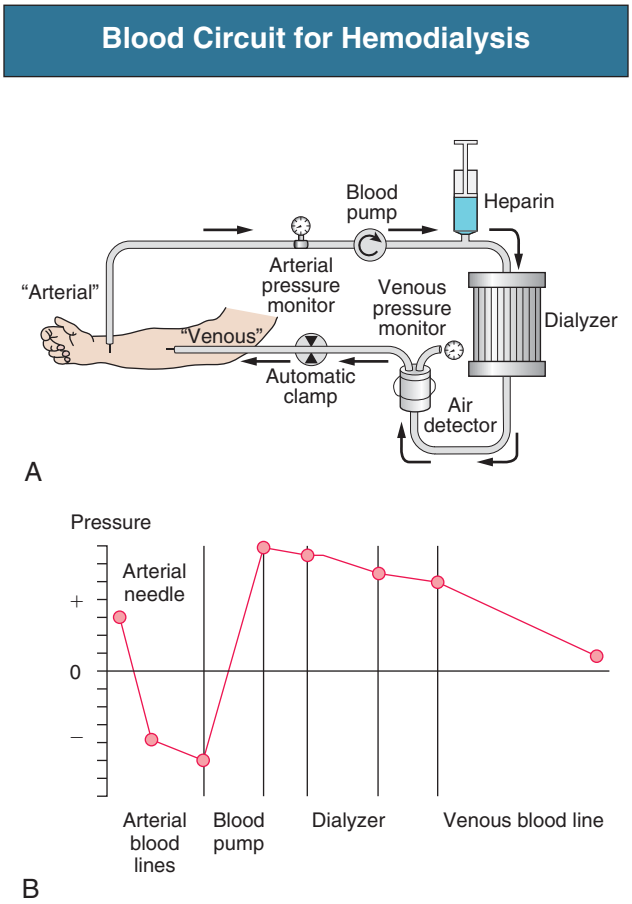

Figure 93-1 Blood circuit for hemodialysis. A, The blood circuit. **B,** The pressure profile in the blood circuit with an arteriovenous fistula as the vascular access.

ANTICOAGULATION

Either unfractionated heparin or, in some countries, low-molecular-weight heparin (LMWH) is used to prevent blood clotting in the extracorporeal circuit. Constant infusion of heparin, repeated boluses of heparin, or a single bolus of LMWH may be used. LMWH has not been approved by the U.S. Food and Drug Administration (FDA) for use in dialysis patients in the United States. A number of alternative modalities are available for patients at high risk for bleeding or who have contraindications to heparin, such as saline flushes, regional citrate anticoagulation (RCA), prostacyclin, danaparoid, argatroban (direct thrombin inhibitor), and lepirudin (recombinant hirudin). Lepirudin has the disadvantage of an extremely prolonged half-life in dialysis patients. In some institutions, RCA is used routinely, especially in patients with recent surgery, coagulopathies, thrombocytopenia, active bleeding, pericarditis, or heparin-associated side effects (such as heparin-induced thrombocytopenia type 2, pruritus, rapidly progressive osteoporosis,

and alopecia). Neutrophil activation may be reduced with RCA compared with heparin anticoagulation. Heparin requirements may be reduced with the use of citrate-containing dialysate.[4]

A typical routine prescription of constant infusion heparin is to administer an initial bolus of 2000 IU followed by a heparin infusion (800 to 1200 IU/h) ending 30 to 60 minutes before the end of the session. Applying the repeated-bolus method, an initial heparin bolus of, for example, 4000 IU is followed by, for example, 1000 to 2000 IU after 2 hours. Although the half-life of LMWH may be prolonged in renal failure, it has proved safe with fewer bleeding episodes, if appropriate dose reductions are made. LMWH has become the anticoagulant of choice in many centers for routine HD. LMWH is given as a bolus at the beginning of the session. Routine monitoring of whole-blood partial thromboplastin time, activated clotting time, or factor Xa is usually not necessary.

DIALYSATE FLUID

Water and Water Treatment

A standard 4-hour HD session exposes the patient to 120 to 160 liters of water. Therefore, water quality is of paramount importance to the patient's well-being. A typical water purification plant is shown in Figure 93-2. Water from municipal sources is filtered to remove particulate matter. Activated carbon, with high surface area, adsorbs substances such as endotoxins, chlorine, and chloramines. Downstream water softeners use a resin coated with sodium ions, which are exchanged for calcium and magnesium ions, before the water enters the reverse osmosis (RO) system. During RO, water is pumped at high pressure (15 to 20 bar) through a tight membrane. The small pore size of these membranes (0.05 to 0.5 nm) provides an absolute barrier for molecules larger than 100 to 300 d. This process rejects over 99% of all bacteria, viruses, pyrogens, and organic materials. Thereafter water is pumped into the RO storage tank and from there into a loop that supplies the dialysis stations. Common faults include carbon filters with inadequate capacity and recharging with inadequate frequency. Optional ultraviolet irradiation, to be placed upstream of a filter, is used to damage bacteria.

Standards for chemical quality of water are widely accepted, but there is less consensus regarding acceptable levels of bacterial and endotoxin contamination.[5] At the very least, endotoxin concentrations below 0.25 endotoxin units (EU)/ml are suggested, and many support the use of 0.06 EU/ml or lower. Municipal water supplies may contain a variety of contaminants that are toxic to HD patients. Substances added to the water supply such as aluminum and chloramines cause significant morbidity. Aluminum accumulation may result in a severe neurologic disorder (speech abnormalities, muscle spasms, seizures, and dementia), bone disease, and erythropoietin-resistant anemia. Plasma aluminum concentration should be monitored regularly; levels should be below 1 µmol/l, and levels above 2 µmol/l should prompt the search for excessive exposure. Chloramines have been associated with hemolysis and methemoglobinemia. Copper and zinc may leach from plumbing components and may cause hemolysis. Lead has been associated with abdominal pain and muscle weakness. Nitrate and nitrite may cause nausea and seizures. High concentrations of calcium may cause the hard water

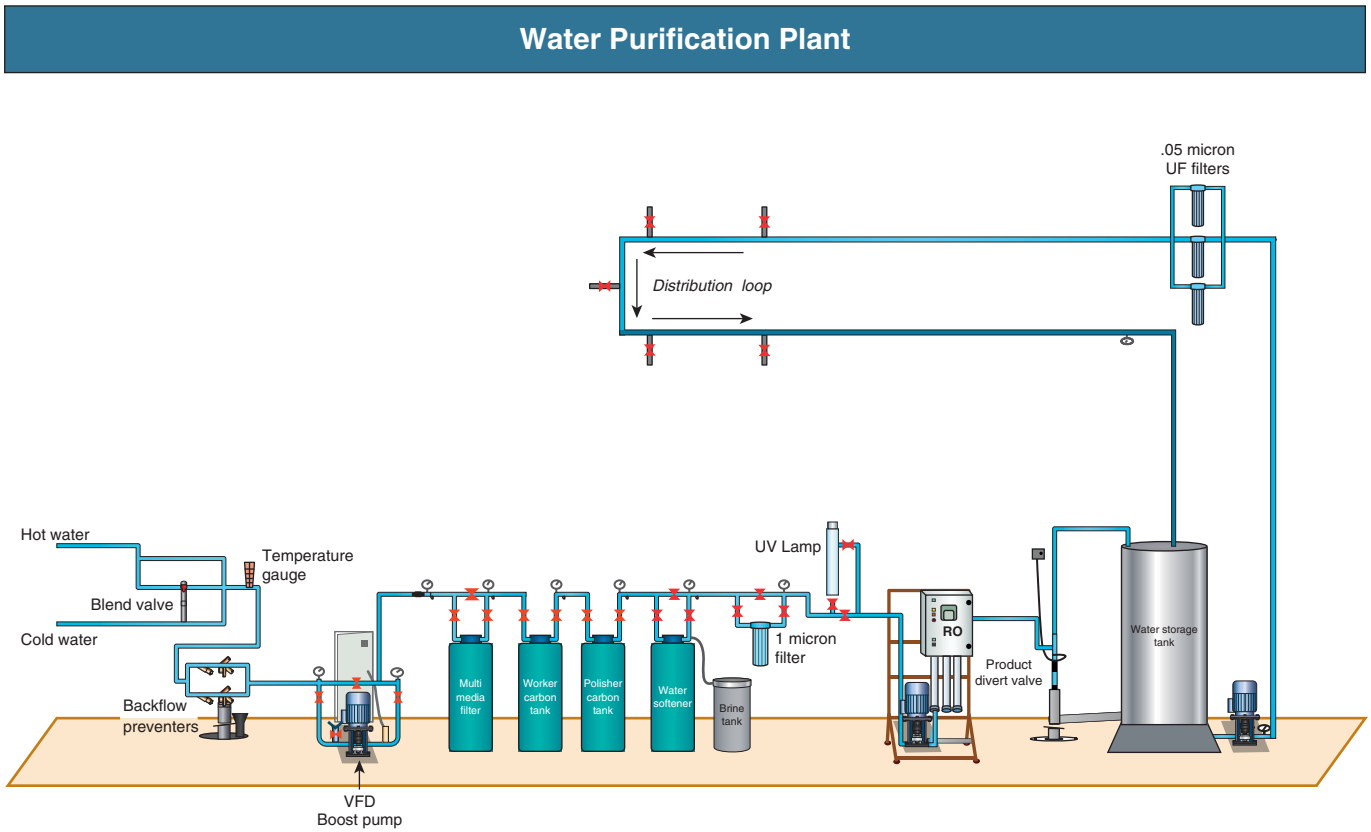

Figure 93-2 Water purification plant. The four main functional domains are water supply, water pretreatment, primary purification, and delivery to the loop. A series of filters and water softeners are the key technical pretreatment components, whereas reverse osmosis (RO) is the main component of the primary purification. Note that several features are optional, for example, the water storage tank. *UF,* Ultrafiltration; *UV,* ultraviolet light; *VFD,* variable frequency drive. *(Original artwork by Rob Levin and Randy Hux, New York, USA.)*

Microbiologic Standards for Water, Concentrates, and Dialysis Fluids[4]

National and International Standards	Year Issued	Microorganisms (CFU/ml)	Endotoxins (EU/ml)
Water			
EDTA-ERA	2001	<100	<0.25
USA (AAMI RD 52)	2004	200 (alert 50)	2 (alert 1)
ISO/DIS 13959 (draft)	2009	100	0.25
Concentrates (Acid and Basic)			
USA (AAMI RD 52)	2004	200 (alert 50)	2 (alert 1)
Ph Eur, 5th ed	2005	—	<0.5*
Dialysis Fluid			
EDTA-ERA	2001	<100	<0.25
USA (AAMI RD 52)	2004	200 (alert 50)	2 (alert 1)
ISO/DIS 11663 (draft)	2009	100 (alert 50)	0.5
Ultrapure Dialysis Fluid Before Last Filter for Hemodiafiltration On-line			
EDTA-ERA	2001	<0.1	<0.03
USA (AAMI RD 52)	2004	0.1	0.03
ISO/DIS 11663	2009	<0.1	<0.03
Substitution Fluid On-line			
EDTA-ERA	2001	$<10^{-6}$	<0.25
USA (AAMI RD 52)	2004	$<10^{-6}$	<0.03
ISO/DIS 11663	2009	Sterile	Nonpyrogenic

Table 93-2 Microbiologic standards for water, concentrates, and dialysis fluids. *AAMI,* Association for the Advancement of Medical Instrumentation; *EDTA-ERA,* European Dialysis and Transplant Association–European Renal Association; *ISO/DIS,* International Organization for Standardization/Draft International Standard; *Ph Eur,* European Pharmacopoeia; *RD,* renal disease. *Diluted to user concentration.

syndrome, characterized by acute hypercalcemia and hypomagnesemia, hemodynamic instability, nausea, vomiting, muscle weakness, and somnolence.

Gram-negative bacteria produce endotoxins (pyrogenic lipopolysaccharides from the outer bacterial cell wall), and fragments of these endotoxins may be responsible for some dialysis-related symptoms. Exposure to bacteria and endotoxin is associated with rigors, hypotension, and fever. Low levels of microbiologic contaminants may be a major cause of chronic inflammation in HD patients. Extracellular matrix secreted by bacteria forms the biofilm, a coating on surfaces, which protects them from antibiotics and disinfectants. The microbiologic standards for HD water, dialysis fluid, and substitution fluid vary among countries (Table 93-2).[5] The harm done by endotoxins passing through the dialysis membrane by backfiltration includes stimulation of inflammation, decreased response to erythropoiesis-stimulating agents, and possible aggravation of atherosclerosis. Use of a polysulfone or polyamide filter in the dialysate line may be adequate to remove endotoxins, but smaller molecules including bacterial DNA fragments may pass through the dialyzer and stimulate immune cells. In the absence of routine hot water disinfection of the machine and the connections to the water loop, the only way that endotoxin concentration can be kept low is by frequent measurement and disinfection of the entire system when concentration exceeds accepted standards.

Composition of Dialysates for Bicarbonate Dialysis

Component	Concentration	
	Range	Typical
Electrolytes (mmol/l)		
Sodium	135-145	140
Potassium	0-4.0	2.0
Calcium	0-2.0	1.25
Magnesium	0.5-1.0	0.75
Chloride	87-124	105
Buffers (mmol/l)		
Acetate	2-4	3
Bicarbonate	20-40	35
pH	7.1-7.3	7.2
P_{CO_2} (mm Hg)	40-100	
Glucose	0-11 (0-200 mg/dl)	5.5 (100 mg/dl)

Table 93-3 Composition of dialysates for bicarbonate dialysis.

Ultrapure water is recommended by international guidelines for use with high-flux dialyzers. Ultrapure water represents a basic prerequisite for convective dialysis modalities in which online production of substitution fluid is used (online hemofiltration or hemodiafiltration).

Liquid bicarbonate dialysis fluid concentrate distributed in a central distribution system may be a source of bacterial growth and should be replaced daily; acid concentrates in canisters and bicarbonate powder represent no bacterial growth risk.

Dialysis Solution

Dialysis fluid can be considered as a drug to be adjusted to the individual patient's needs (Table 93-3). In modern machines, dialysate is made by mixing two concentrate components, which may be provided as liquid or dry (powder) concentrates. The base concentrate contains sodium bicarbonate and sodium chloride; the conventional acid concentrate typically contains chloride salts of sodium, calcium, magnesium, and potassium, glucose monohydrate, and an organic acid. The organic acid can be in the form of acetic acid, citric acid, or lactic acid. The acid concentrate may also contain the salt of an organic acid, such as sodium acetate. The purpose of the acid is to lower the pH of the dialysate to below 7.3 so that calcium and magnesium do not precipitate as carbonate salts when bicarbonate is added. Base and acid components are mixed simultaneously with purified water to make the dialysate. Dialysate proportioning pumps ensure proper mixing. One typical mixing relationship is 1 : 1.72 : 42.28 (acid concentrate–base concentrate–water; also known as *45X preparation*). The relative amounts of water, bicarbonate, and acid component define the final dialysate composition. It is important to note that some dry acid concentrates contain sodium diacetate (8 mmol/l), which is made up of equal parts of acetic acid and sodium acetate. After mixing with bicarbonate, the final dialysate contains 8 mmol of sodium acetate per liter.[6] The addition of sodium acetate increases the total buffer load and may foster metabolic alkalosis. Dialysate composition can be further modified by small changes in the mixing ratio and by adding salt solutions; potential advantages and disadvantages of dialysate modifications are shown in Table 93-4.

Advantages and Disadvantages of Modifications of Dialysate Composition		
Component	**Advantage**	**Disadvantage**
Sodium		
Increased	Hemodynamic stability	Thirst; intradialytic weight gain; high blood pressure; sodium toxicity?
Decreased	Reduced osmotic stress in the presence of predialytic hyponatremia	Intradialytic hemodynamic instability
Potassium		
Increased	Fewer arrhythmias in digoxin intoxication with hypokalemia; may improve hemodynamic stability	Hyperkalemia
Decreased	Increased dietary potassium intake	Arrhythmias; risk of sudden death
Calcium		
Increased	Suppresses PTH, increased hemodynamic stability	Hypercalcemia, vascular calcification, adynamic bone disease resulting from PTH suppression
Decreased	Permits more liberal use of calcium-containing phosphate binders	Stimulation of PTH, reduced hemodynamic stability
Bicarbonate		
Increased	Acidosis control improved	Postdialytic alkalosis; increased mortality
Decreased	No postdialytic alkalosis	Promotes acidosis; increased mortality
Magnesium		
Increased	Hemodynamic stability, fewer arrhythmias, suppresses PTH	Altered nerve conduction, pruritus, renal bone disease
Decreased	Permits use of magnesium-containing phosphate binders; improved bone mineralization; less bone pain	Arrhythmias, muscle weakness and cramps, elevated PTH
Glucose		
Decreased	Avoidance of intradialytic hyperglycemia and hyperinsulinemia	Increased risk of disequilibrium (rare), hypoglycemia
Increased	Lower risk of disequilibrium	Intradialytic hyperglycemia and hyperinsulinism
Citrate	Heparin-sparing effect	High blood citrate levels in liver failure

Table 93-4 Advantages and disadvantages of modifications in the dialysate composition. *PTH,* Parathyroid hormone.

BIOCOMPATIBILITY

The contact of blood with some lines and membranes triggers an inflammatory response akin to that seen in infection. *Biocompatibility* is the property of a membrane that does not produce a toxic, injurious, or immunologic response on contact with blood. Although many components of the dialysis procedure contribute to the degree of biocompatibility, it is the membrane itself that is most important. Biocompatibility is of particular importance with the use of cellulose membranes, whereas synthetic membranes and reused membranes activate complement to a much lesser extent (Fig. 93-3). Activation of complement peaks at 15 minutes after the start of dialysis and lasts up to 90 minutes. RCA may improve biocompatibility because of reduced granulocyte degranulation.[7] Dialyzer reprocessing with appropriate antibacterial substances such as peracetic acid is also associated with improved biocompatibility, but also with reduced diffusion of larger molecules.

HEMOFILTRATION

Hemofiltration (HF) differs markedly from HD by the mechanisms by which the composition of the blood is modified (Fig. 93-4). HF is mainly used in the intensive care setting. In the simplest form of HF, blood under pressure passes down one side of a highly permeable membrane, allowing both water and substances up to a molecular weight of approximately 20 kd to pass across the membrane by convective flow, depending on membrane permeability. During HF, the filtrate is discarded and the patient receives a substitution fluid either before (predilution) or after (postdilution) the dialyzer. The substitution fluid contains the major crystalloid components of the plasma at physiologic levels. Both bicarbonate and lactate are used as buffers. The rate of fluid removal and substitution fluid infusion can be adapted to the patient's need. HF is particularly useful as a continuous renal replacement therapy in an intensive care setting.[8]

HEMODIAFILTRATION

Hemodiafiltration (HDF) combines the benefits of HD (high transport rate of low-molecular-weight solutes by diffusion) and HF (high convective transport of substances) (Fig. 93-5). HDF is used both as a continuous and an intermittent renal replacement therapy. HDF offers potential benefits with regard to anemia correction, inflammation, oxidative stress, lipid profiles, and calcium-phosphate product[9] and possibly the prevention of long-term complications such as dialysis (β_2-microglobulin) amyloidosis. Two randomized controlled trials (RCTs) did not show improved survival but suggested that higher substitution volumes would be beneficial. This notion was corroborated by a recently reported large RCT of high-efficiency postdilution on-line HDF in patients who all achieved a high substitution volume. This trial demonstrated that, compared with patients who continued on high-flux HD, those assigned to on-line HDF had a 30% lower risk of all-cause mortality, a 33% lower risk of cardiovascular mortality, and a 55% lower risk of infection-related mortality (see Chapter 94 for further discussion).[10]

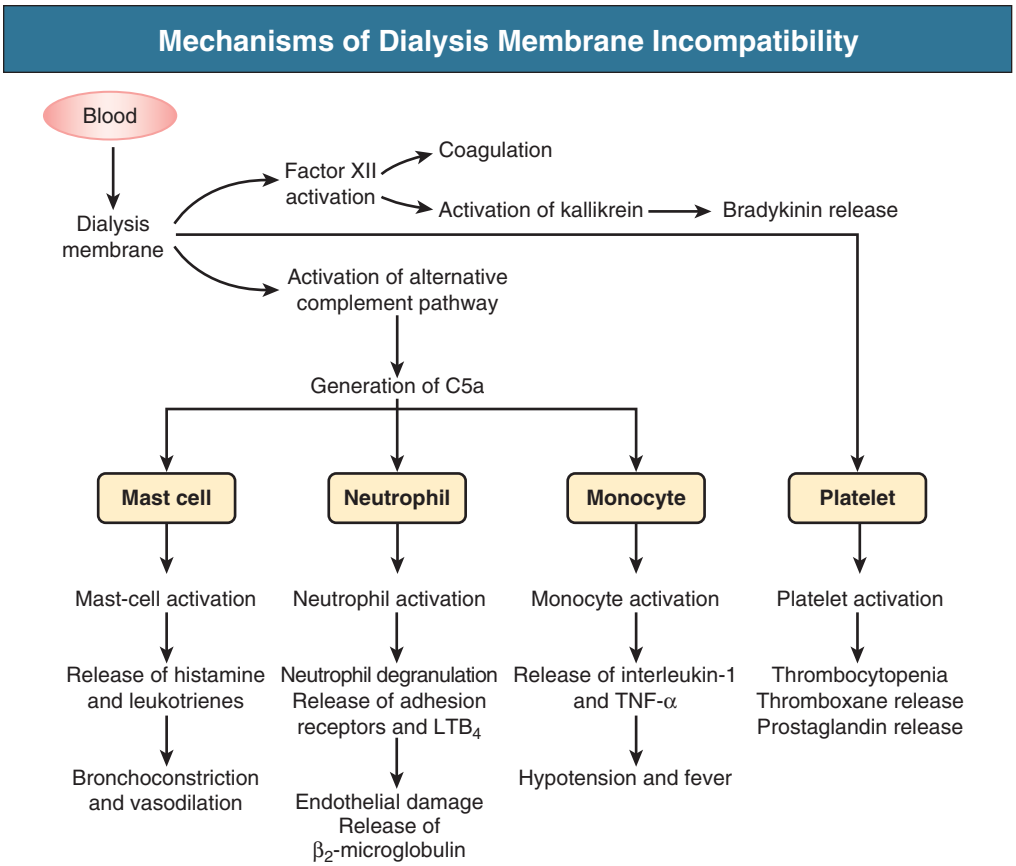

Figure 93-3 Mechanisms of dialysis membrane incompatibility. Pathways involved in the body's response to dialysis membranes. *LTB_4*, Leukotriene B_4; *TNF-α*, tumor necrosis factor α.

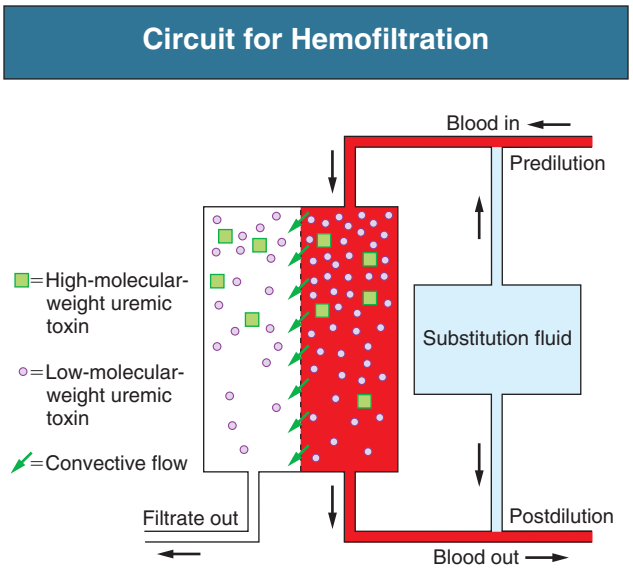

Figure 93-4 Circuit for hemofiltration.

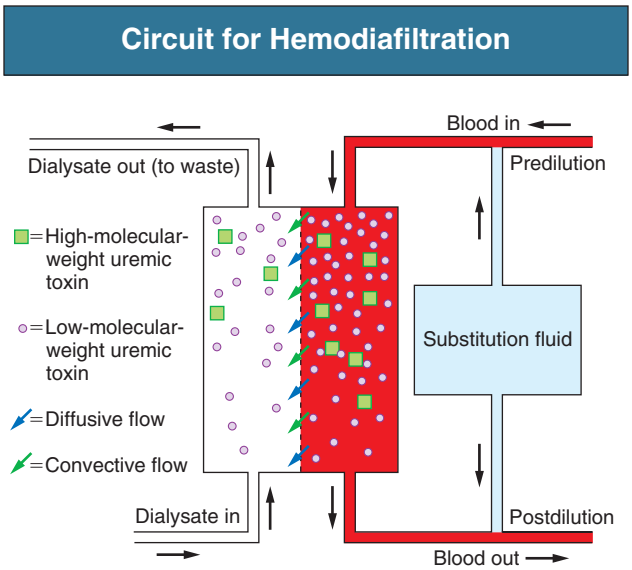

Figure 93-5 Circuit for hemodiafiltration.

DIALYSIS TIME AND FREQUENCY

Hemodialysis has conventionally been delivered in three treatment sessions per week. This developed as a practical compromise between the physiologic benefits of replacing renal function by HD ("the more, the better") and the practicalities of delivering HD, in terms of both patient tolerance and facility organization. There is good evidence that twice-weekly HD provides inferior outcomes to three times weekly, except in some patients with substantial residual renal function. Treatment times of 3 to 5 hours per session are now typical, but a growing number of centers also offer longer hours (up to 8 hours per session), originally necessary because of the relative inefficiency of the available HD techniques. It remains controversial whether the excellent long-term outcomes of patients receiving prolonged HD are related to selection bias rather than real advantages.

Two RCTs investigated the effect of increased HD frequency on changes in left ventricular mass, as measured by magnetic resonance

imaging, and quality of life including cognitive measures.[11,12] Frequent HD, as compared with conventional HD, was associated with positive results with respect to the composite outcomes of death or change in left ventricular mass and death or change in a physical health composite score. However, the number of access complications (but not access failures) increased with frequent HD.

ADDITIONAL DEVICES AND TECHNOLOGIES

Relative Blood Volume Monitoring

A decrease in blood volume because of ultrafiltration is one of the main causes of intradialytic hypotension. Blood volume monitors provide continuous noninvasive monitoring of relative changes in blood volume by continuous measurement of plasma protein concentration by ultrasound or hematocrit by optical scattering. Too rapid changes in blood volume from baseline indicate decreased plasma refilling rates and may precede intradialytic hypotension. Blood volume monitoring can be particularly useful for monitoring hemodynamically unstable dialysis patients. In some dialysis machines the rate of blood volume change is used to automatically adjust ultrafiltration rates or to warn of marked reduction in relative blood volume. This approach has been shown to reduce the frequency of symptomatic intradialytic hypotension.[13]

Ultrafiltration Profiling

The ultrafiltration rate is usually kept constant but can be changed during the dialysis session in a preprogrammed manner (ultrafiltration profiling). It may be advantageous to remove a large proportion, for example two thirds, of the ultrafiltration volume in the first half of the HD session. Because of a high initial plasma refilling rate, severely fluid-overloaded patients may tolerate a higher ultrafiltration rate in the early stages and normal fluid status may be reached more easily. In some machines, predefined ultrafiltration profiles are incorporated. The clinical benefits of ultrafiltration profiling have not been adequately evaluated.

Sodium Profiling

Normally the dialysate sodium concentration is kept constant throughout the dialysis treatment. The variable sodium option allows dynamic changes of the dialysate sodium concentration during the treatment (sodium profiling). Some patients with hemodynamic instability may benefit from this option if the initial sodium concentration is kept high and then the concentration is slowly reduced to avoid residual sodium loading. In the absence of appropriate reductions in dialysate sodium concentrations, the ensuing thirst may increase intradialytic weight gain.

Online Clearance Monitoring

Sodium and urea clearances are identical for practical purposes. Because the conductivity of the dialysate is largely a function of the dialysate sodium concentration, online clearance monitors can use this feature to compute the urea clearance *(K)* of a dialyzer during a dialysis treatment. Changes in inflow dialysate sodium concentration are related to the respective changes of conductivity in the dialysate outflow. The conductivity clearance is equivalent to urea clearance, and *Kt,* the product of *K* and treatment time *(t),* is easily calculated. Together with estimates of *V* (total body water), *Kt/V* can be determined during each treatment.

Blood Temperature Monitoring

During standard HD, the core body temperature usually increases. Because the thermoregulatory response to rising core temperature (dilation of thermoregulatory vessels) may offset the vascular response to hypovolemia (vasoconstriction), this increase in internal heat production might be in part responsible for the intradialytic hemodynamic instability. Cool dialysate has been shown to improve vascular stability during dialysis. The core temperature can be controlled by a blood temperature monitor, which adapts the dialysate temperature according to the desired core temperature. When no blood temperature monitor is available, the dialysate temperature can be set initially to the patient's core temperature. If this is well tolerated and intradialytic hypotension still occurs, the dialysate temperature may be reduced up to 0.5° C below the patient's core temperature, unless cold discomfort occurs. A meta-analysis of 22 studies concluded that intradialytic hypotension occurred seven times less frequently with cool dialysis[14] without reduction in urea clearance.

Bioimpedance

Bioimpedance devices are increasingly used to determine fluid status in HD patients. A recent RCT in 156 chronic HD patients indicated that assessment of fluid overload with whole body bioimpedance spectroscopy provides better management of fluid status, leading to regression of left ventricular mass index, decrease in blood pressure, and improvement in arterial stiffness compared with standard care.[15] Calf bioimpedance spectroscopy (cBIS) methods have been developed to identify normal fluid status in HD patients, and a recent study shows that cBIS compares favorably with whole-body bioimpedance methods.[16]

Sorbents, Nanotechnology, Wearable Artificial Kidney

Use of sorbents to absorb nondialyzable molecules will allow testing of the relevance of uremic toxins and of many protein-derived substances that accumulate in the plasma of uremic patients. Nanotechnologic approaches to dialysis therapy are under intensive investigation. A recent study reported the successful short-term use of a wearable artificial kidney.[17]

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CHAPTER 94

Hemodialysis: Outcomes and Adequacy

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From an idealistic clinical perspective, an adequately treated hemodialysis (HD) patient is physically active, well nourished, euvolemic, and normotensive with a maintained good quality of life and a life expectancy that is not inferior to that of healthy patients. Despite these optimistic goals, outcomes for dialysis patients expressed in terms of mortality, hospitalization, and quality of life regrettably remain comparable to those observed in patients with solid organ cancer. The mean life expectancy of an average 60-year-old HD patient currently can be estimated at 5 to 7 years, with an annual mortality rate of 13% to 20% (www.usrds.org). Mortality in HD patients differs by gender and race; for example, in the United States there is lower mortality in African Americans compared with Caucasians, in Hispanics compared with non-Hispanics, and in Asians compared with any other racial group. Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) suggest that variations in practice patterns, such as prescribed dialysis treatment time, average erythropoietin dose, preferred vascular access type, and number of patients with central venous catheters, may account for some of these differences. Outcomes are also directly related to comorbid factors occurring during evolution of chronic kidney disease (CKD), such as atherosclerotic vascular disease, diabetes, and arterial hypertension, and to background cardiovascular mortality of the respective general population.[1] Indeed, the majority of CKD patients die mainly of cardiovascular causes before reaching end-stage renal disease (ESRD). In addition to cardiovascular disease (discussed further in Chapter 82), other major factors influencing outcome that are common to all patients with ESRD include anemia (see Chapter 83) and control of bone and mineral metabolism (see Chapter 85).

In this chapter, we discuss dialysis-related factors influencing outcome in patients receiving maintenance HD and measures to influence these factors clinically (see summary in Table 94-1). A key factor influencing outcome is "adequacy" of dialysis, a term which was originally used exclusively to describe dialysis dosage measured by small solute removal, but now has a broader meaning encompassing all aspects of the replacement of excretory and endocrine functions of the kidney that affect outcome.

ADEQUACY OF DIALYSIS DOSE

Uremic Toxins

The retention in the body of compounds that normally are metabolized by healthy kidneys or filtered and secreted into the urine results in the uremic syndrome. These retained compounds are called *uremic retention solutes* or *uremic toxins* when they interact negatively with biologic functions. Uremic toxins include a small group of inorganic compounds, such as water, potassium, phosphate, and trace elements, and a much larger group of organic compounds that are further subdivided into small water-soluble solutes (<500 d), middle molecules (>500 d), and protein-bound solutes (Table 94-2).

A continuously updated list of uremic toxins is provided at www.uremic-toxins.org. The catalogue of uremic toxins is long, and a growing number of compounds have been associated with outcomes. Mortality has repeatedly been shown to be associated with reduced clearance of urea. Of commonly measured middle molecular size substances, serum concentrations of β_2-microglobulin have been associated with mortality, as have concentrations of *p*-cresyl sulfate among protein-bound uremic solutes.[2] Although it is evident that uremic toxicity is more than the retention of urea or water-soluble compounds alone, current dialysis and dialysis-related treatments do not remove any significant quantity of substances larger than 10 to 15 kd. Future means of removing higher-molecular-weight toxins or protein-bound substances may include the use of sorbents in addition to traditional diffusive and convective dialysis strategies.

Urea as a Surrogate Marker of Uremic Toxicity

Among all potential uremic toxins, only urea, a 60-dalton small water-soluble compound, is established as a marker of uremic solute retention and removal. Urea, which itself shows little toxicity, is a metabolite of amino acid metabolism; urea generation therefore depends on protein intake and the balance between protein anabolism and catabolism. The removal of urea was originally considered to be representative for the removal of other water-soluble solutes with a higher pathogenic impact, but it is now clear that urea removal does not closely parallel that of other small water-soluble compounds, protein-bound solutes, or middle molecules. This is because urea, in contrast to other uremic solutes, is freely diffusible through cell membranes, which allows rapid equilibration of urea concentration within whole body water after urea has been removed from the blood compartment. For other uremic toxins the intercompartmental transfer rate is much slower, leading to a protracted equilibration between the intravascular and other tissue compartments. Nevertheless, knowledge of urea kinetics is essential for the general understanding of the physics of solute removal during dialysis.[3]

Assessment of Dialysis Dose

Adequacy in terms of dialysis dose refers to delivery of a treatment dose that is considered sufficient to promote optimal long-term outcome. The delivered dose of dialysis is conventionally assessed by the removal of urea and expressed either by the urea reduction ratio (URR) or by the treatment index *Kt/V* (see later for detailed explanation). Simply following predialysis blood urea nitrogen (BUN) or serum urea concentration is misleading; low serum urea may much more reflect malnutrition from inadequate protein intake than adequate dialysis urea removal. If urea removal is inadequate, then dialysis is inadequate, regardless of the serum urea level.

Factors Related to Dialysis Outcome	
Factors	**Ways to Address These Factors**
Patient Characteristics	
Age	None
Gender	None
Race/ethnicity	None
Body size	Target BMI above 23 kg/m^2; treat malnutrition if BMI is falling
Social status	Social and family support
Dialysis vintage	Early renal transplantation
Comorbidities	
Diabetes mellitus	Prevent hypoglycemia, target HbA1c below 7.5%
Arterial hypertension	Optimize target weight, decrease dietary salt intake, avoid intradialytic positive sodium balance
Congestive heart failure	Optimize fluid status by gradual postdialysis target reduction, decrease dietary salt intake, avoid intradialytic positive sodium balance
Depression	Treat medically
Peripheral vascular disease	Aspirin, lipid-lowering substances, management of hyperphosphatemia
Transplant eligibility	Living donor transplantation
Frailty	Nephrologic rehabilitation program, exercise during dialysis to avoid falls and fractures
Physical activity	Nephrologic rehabilitation program, exercise during dialysis; avoid immobilization
Arrhythmias	Avoid hypokalemia and prevent hyperkalemia; do not use zero-K^+ dialysate bath
Obstructive sleep apnea	Optimize fluid status; use CPAP if indicated
Anemia	
Hemoglobin concentration	Target Hb level 10-11 g/dl
EPO resistance	Surveillance of iron status; target transferrin saturation >25%; identify and treat sources of inflammation
CKD-MBD	
PTH	Lower phosphate levels toward normal range, use vitamin D and calcimimetics
FGF-23	Lower phosphate levels toward normal range
Hyperphosphatemia	Optimize dialysis phosphate elimination; phosphate binder therapy, dietary phosphate restriction
Nutrition and Inflammation	
Inflammation	Ultrapure dialysate, avoid central venous catheters and graft access
Low serum albumin	Ultrapure dialysate, avoid central venous catheters and graft access
Protein-energy malnutrition	Nutritional counseling, enteral supplements
Fluid overload	Define post-HD target weight, bioimpedance?
Vascular access	Avoid central venous catheters and graft access
β_2-Microglobulin	Increase middle molecule clearance, HDF
Dialysis Treatment Factors	
Session length	Session length more important than urea clearance once minimum *Kt/V* has been achieved; minimum session length 4 h?
Frequency	Four to seven sessions per week; short daily in-center HD, daily or every-other-day nocturnal home HD
Long interdialytic interval	Every-other-day dialysis or four sessions per week
Dialysis dose	Target *Kt/V* >1.3; URR >65% per treatment
Dialysis modality	High efficiency on-line HDF; target convective volume >22 l per treatment
Hemodialysis membrane biocompatibility	Biocompatible membranes
Hemodialysis membrane type	High-flux membranes
Dialysate quality	Ultrapure dialysate
Dialysate composition (acidosis, hyperkalemia)	Individualized dialysate bicarbonate, potassium, calcium, and sodium concentration
Acidosis	Target pre-HD HCO_3^- >22 mmol/l, avoid severe post-HD alkalosis

Table 94-1 Factors related to dialysis outcome and ways to address these factors. *BMI,* Body mass index; *CKD-MBD,* chronic kidney disease–mineral and bone disorder; *CPAP,* continuous positive airway pressure; *EPO,* erythropoietin; *FGF-23,* fibroblast growth factor 23; *Hb,* hemoglobin; *HbA1c,* hemoglobin A1c; *HD,* hemodialysis; *HDF,* hemodiafiltration; *Kt/V,* dialysis treatment index; *PTH,* parathyroid hormone; *UFR,* ultrafiltration rate; *URR,* urea reduction ratio.

Factors Related to Dialysis Outcome	
Factors	**Ways to Address These Factors**
Hyperkalemia	Nutritional counseling, oral bicarbonate supplementation
Timing of dialysis initiation	Avoid early dialysis initiation without clinical symptoms of uremia
Intradialytic hemodynamic stability	Thermoneutral dialysis, avoid high UFR
Residual renal function	Avoid intradialytic hypotension, volume depletion, and high UFR

Table 94-1 Factors related to dialysis outcome and ways to address these factors—cont'd

Organic Uremic Solutes					
Free Water-Soluble Low-Molecular-Weight Solutes	**MW**	**Protein-Bound Solutes**	**MW**	**Middle Molecules**	**MW**
Guanidines		**AGEs**		**Cytokines**	
ADMA	202	3-Deoxyglucosone	162	Interleukin-1β	32,000
Argininic acid	175	Fructoselysine	308	Interleukin-6	24,500
Creatinine	113	Glyoxal	58	Tumor necrosis factor α	26,000
Guanidine	59	Pentosidine	342	**Peptides**	
Methylguanidine	73	**Hippurate**		Adrenomedullin	5729
Peptide		Hippuric acid	179	ANP	3080
β-Lipotropin	461	**Indoles**		β_2-Microglobulin	11,818
Polyols		Indoxyl sulfate	251	β-Endorphin	3465
Erythritol	122	Melatonin	126	Cholecystokinin	3866
Myoinositol	180	Quinolinic acid	167	Cystatin C	13,300
Sorbitol	182	**Phenols**		Delta sleep-inducing peptide	848
Threitol	122	Hydroquinone	110	Hyaluronic acid	25,000
Purines		*p*-Cresol	108	Leptin	16,000
Cytidine	234	Phenol	94	Neuropeptide Y	4572
Hypoxanthine	136	**Polyamines**		PTH	9225
Uracil	112	Putrescine	88	Retinol-binding protein	21,200
Uric acid	168	Spermidine	145	**Other**	
Xanthine	152	Spermine	202	Complement factor D	23,750
Pyrimidines		**Other**			
Orotic acid	174	Homocysteine	135		
Thymine	126				
Uridine	244				
Ribonucleosides					
1-Methyladenosine	281				
Pseudouridine	244				
Xanthosine	284				
Others					
Malondialdehyde	71				
Oxalate	90				
Urea	60				

Table 94-2 Organic uremic solutes. *ADMA,* Asymmetric dimethylarginine; *AGEs,* advanced glycation end products; *ANP,* atrial natriuretic peptide; *PTH,* parathyroid hormone.

Intradialytic Urea Kinetics

Dialyzers are highly efficient at removal of urea from the blood, reducing the urea concentration during one passage by 80% to 90%. Intradialytic serum urea kinetics were originally described by single-compartment (single-pool) models, assuming that full equilibration between blood and tissue compartments occurs immediately and without time delay. In such models, the change in serum urea follows first-order kinetics, with a linear decline and no urea rebound (Fig. 94-1, *dashed line*). *In vivo,* however, intercompartmental urea redistribution is somewhat delayed, and therefore the intradialytic urea concentration in the blood compartment is always lower than in tissue compartments. Full equilibration among all compartments is reached within 30 to 60 minutes after the end of a dialysis treatment. These features of urea kinetics are more accurately described by double-pool models that take into account the intercompartmental urea redistribution rate and postdialysis urea rebound (Fig. 94-1, *solid line*).

Current methods for assessment of dialysis dose are based on the predialysis and postdialysis difference in serum urea and include URR, single-pool *Kt/V (spKt/V),* equilibrated *Kt/V (eKt/V),* and weekly standard *Kt/V (std-Kt/V).*

Urea Reduction Ratio

Urea reduction ratio refers to the treatment-related reduction of serum urea concentration and is computed as follows:

$$\text{URR}\,(\%) = (1 - C_t/C_0) \times 100\%$$

where C_t is postdialysis and C_0 is predialysis serum urea concentration.

Urea reduction ratio is a simple but rather imprecise way to quantify dialysis dose because it does not take into account intradialytic urea generation and convective urea removal by ultrafiltration. Despite these limitations, URR correlates well with dialysis outcome

and is an accepted method for assessment of dialysis adequacy. A minimum URR of 65% to 70% is recommended for adequate HD.

Single-Pool *Kt/V (spKt/V)*

The treatment index *Kt/V* is the most widely used parameter to assess dialysis dose. *Kt/V* is a dimensionless number representing the total plasma volume cleared ($K \times t$, in liters) divided by volume of distribution (V, in liters). The concept of *Kt/V* may be applied to any substance but in clinical practice is used almost exclusively for urea, where K is the dialyzer blood water urea clearance (liters per hour), t is dialysis session length (hours), and V is the distribution volume of urea (liters), which equates closely to total body water. A delivered *Kt/V* of 1.0 implies that the volume of plasma cleared of urea ($K \times t$) during a dialysis session is equal to urea distribution volume *(V)*.

In daily clinical practice *spKt/V* may be computed according to the classic Daugirdas equation, which is based on URR and accounts for intradialytic urea generation and ultrafiltration volume.[4] The Daugirdas equation is validated for a *Kt/V* range of 0.8 to 2.0 and is widely used because of its simplicity and accuracy.

$$\text{spKt/V} = -\ln(\text{R} - 0.008 \times \text{t}) + (4 - 3.5 \times \text{R}) \times \text{UF/W}$$

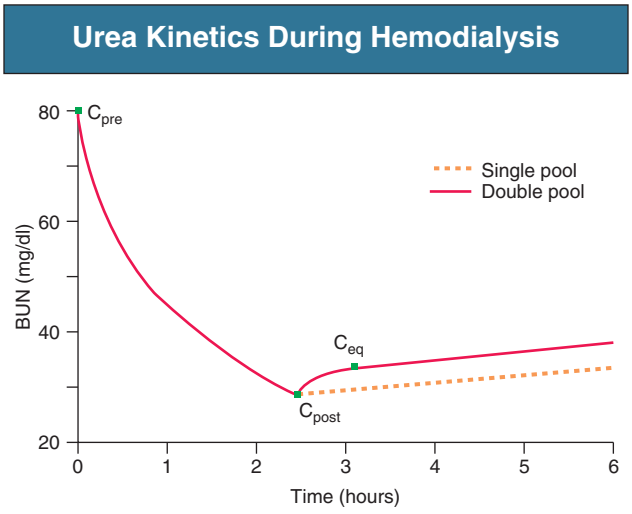

Figure 94-1 Urea kinetics during hemodialysis. Urea kinetics is determined by the difference between predialysis *(C_{pre})* and postdialysis *(C_{post})* blood urea nitrogen *(BUN)*. The single pool Kt/V model assumes no relevant change in BUN concentration after termination of dialysis except for a slow constant increase due to BUN generation *(yellow dashed line)*. The double pool *Kt/V* model *(red line)* more accurately describes the *in vivo* situation, where intercompartmental urea redistribution leads to a urea rebound until full equilibration between blood and tissue compartments is reached. Equilibrated postdialysis BUN concentration (C_{eq}) can be mathematically predicted from postdialysis BUN (C_{post}).

where ln is the natural logarithm, R is the postdialysis-predialysis serum urea ratio, t is treatment time (hours), *UF* is ultrafiltration volume (liters), and W is the patient's postdialysis body weight (kilograms).

The most accurate method for prescription and assessment of dialysis dose is formal urea kinetic modeling (UKM), where *spKt/V* is modeled from prescribed dialyzer clearance *(K)*, blood and dialysate flow rates, ultrafiltration volume, treatment time, and assumed urea distribution volume. Through comparison of modeled *Kt/V* with delivered *Kt/V*, problems in the accuracy of the delivery of dialysis dose, such as vascular access recirculation, can be identified. Because of its mathematical complexity, UKM requires advanced computer support.

Single-pool *Kt/V* regularly overestimates the delivered dialysis dose because nonequilibrated post-HD urea concentration is used for computation. A more accurate estimate of delivered dialysis dose can be achieved by taking into account the equilibrated post-HD urea concentrations. The difference between equilibrated and nonequilibrated urea concentration depends on the intensity of dialysis; the shorter and more intense a treatment, the higher the rebound. Simple equations can be applied for computation of *eKt/V* from *spKt/V*. Because nonequilibrated post-HD serum urea concentrations are lower than equilibrated concentrations, results for *eKt/V* will always be lower than for *spKt/V*. Typical results of *spKt/V* and *eKt/V* for identical treatment characteristics are shown in Table 94-3.

Computation of *spKt/V* requires accurate timing of blood collections. Predialysis blood samples must be collected right at the start of the treatment, and postdialysis samples immediately at the end of the treatment after the blood flow rate is slowed to reduce any potential effect of recirculation. Blood sampling procedures should be standardized in each center (for recommendations, see the Kidney Disease Outcomes Quality Initiative [KDOQI] clinical practice guidelines for HD adequacy, update 2006[5]). URR, *spKt/V*, or *eKt/V* should be assessed monthly, and dialysis prescription adjusted accordingly. In large cross-sectional studies, mortality increased when *spKt/V* fell below 1.2, and a target *spKt/V* of 1.3 is recommended for conventional thrice-weekly dialysis schedules.[5] Dose comparisons with more frequent dialysis schedules or peritoneal dialysis can be made by computation of a weekly dialysis dose.

Weekly Standard *Kt/V (std-Kt/V)*

The weekly HD dose is not equivalent to the product of session *Kt/V* and the number of treatments per week because the total urea mass removed per time unit decreases with increasing dialysis treatment time and dose as a result of lowering of serum urea concentration over time. This is exemplified by looking at a doubling of *Kt/V* from 1.0 to 2.0 per session, when the total mass of urea removed is not doubled but only increased by about 24% (Fig. 94-2). With the weekly *std-Kt/V* concept, the intermittently provided dialysis urea

Computation of Dialysis Dose: Results Derived from Different Model Equations

Formula	Result	Comment
$\text{URR} = (1 - C_t/C_0) \times 100\%$	67%	Urea rebound, urea generation, and ultrafiltration not taken into account
$\text{Kt/V} = \ln(C_0/C_t)$	1.10	Urea rebound, urea generation, and ultrafiltration not taken into account
$\text{spKt/V} = -\ln(\text{R} - 0.008 \times \text{t}) + (4 - 3.5\,\text{R}) \times \text{UF/W}$	1.33	Single-pool model; urea rebound not taken into account
$\text{eKt/V} = \text{spKt/V} - 0.6 \times \text{spKt/V/t} + 0.03$	1.16	Double-pool model for arteriovenous access including urea rebound
$\text{eKt/V} = \text{spKt/V} - 0.47 \times \text{spKt/V/t} + 0.02$	1.20	Double-pool model for central venous access including urea rebound

Table 94-3 Computation of dialysis dose: results derived from different model equations. Calculations based on dialysis duration *(t)* = 4 hours; predialysis blood urea nitrogen (BUN) (C_0) = 90 mg/dl; nonequilibrated postdialysis BUN (C_t) = 30 mg/dl; ultrafiltration volume *(UF)* = 3 liters; postdialysis body weight *(W)* = 72 kg; $R = C_t/C_0$. *URR,* Urea reduction ratio.

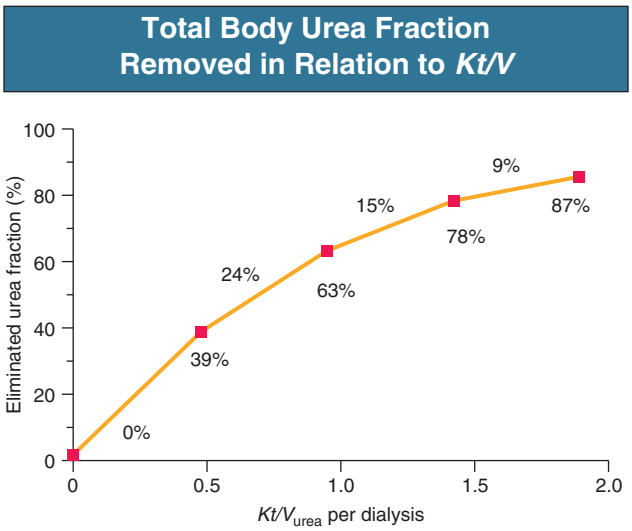

Figure 94-2 Total body urea fraction removed in relation to *Kt/V*. In this example, 63% of total body urea fraction is removed with *Kt/V* of 1.0; doubling of *Kt/V* to 2.0 increases the removed urea fraction by an additional 24%.

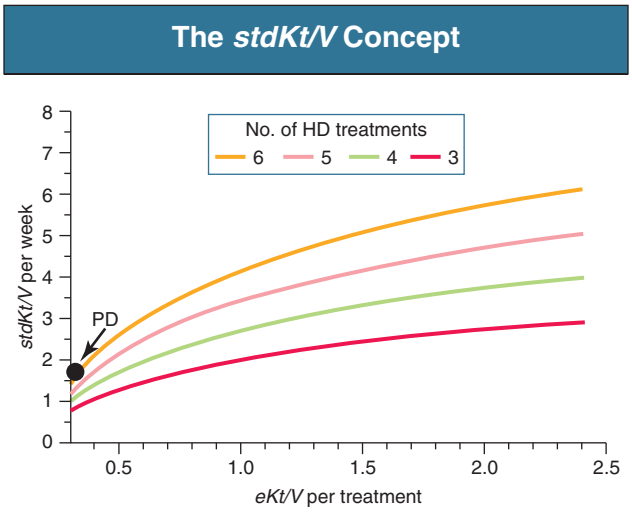

Figure 94-3 The weekly *std-Kt/V* concept. The weekly *std-Kt/V* for any hemodialysis *(HD)* frequency is derived by plotting *eKt/V* of a representative dialysis session onto the respective frequency curve. *CAPD,* Continuous ambulatory peritoneal dialysis.

clearance during 1 week is converted to an equivalent continuous "extracorporeal" urea clearance (in milliliters per minute), then multiplied by 10,080 (minutes per week) and divided by urea distribution volume *V* (in milliliters).[6] The resulting dimensionless *std-Kt/V* value is directly compatible with peritoneal dialysis weekly *Kt/V* and with native residual renal *Kt/V.* Weekly *std-Kt/V* can be derived graphically by plotting *eKt/V* of a representative dialysis session onto the respective frequency curve (Fig. 94-3). A maximum *std-Kt/V* of approximately 3.0/wk can be achieved with conventional thrice-weekly dialysis. To further increase the weekly dose, dialysis frequency needs to be altered. Residual renal function (RRF) expressed as weekly renal *Kt/V* is added to dialysis *std-Kt/V.* Independent of the treatment schedule, a minimum target *std-Kt/V* of 2.0/wk including renal *Kt/V* is recommended for all patients. This is exactly the value that is achieved with an *spKt/V* of 1.2 or *eKt/V* of 1.0 given three times per week in anuric patients.

Prescription of Dialysis Dose

Delivered dialysis dose depends on dialysate and blood flow rates, dialyzer efficiency (K_oA), session length *(t),* and the distribution volume *(V)* of the uremic toxin studied. As mentioned earlier, urea is distributed in total body water volume; but for other small-molecular-weight compounds, *V* may be substantially different. A standard dialysis prescription should include a minimum treatment time of 4 hours, a blood flow rate of at least 250 ml/min, and a dialysate flow rate of 500 to 800 ml/min. In a new dialysis patient, *V* is unknown and needs to be estimated (men, 58% of body weight; women, 55% of body weight).

Example

Male, body weight 76 kg; *V* = 58% of body weight = 44 liters
Target blood flow rate, 300 ml/min; effective dialyzer urea clearance (K_d) = 240 ml/min; target *spKt/V* = 1.3
Required treatment time (min): 1.3 × *V* (ml)/ K_d (ml/min) = 238 min

Once dialysis is delivered and *Kt/V* has been measured, the prescription is adjusted to meet the *Kt/V* target. In severe and longstanding uremia, the target dose is approached slowly during the course of several sessions to avoid the dialysis disequilibrium syndrome.

Is *V* the Adequate Denominator for *Kt/V*?

Patients with small urea *V,* typically women, tend to do poorly relative to larger people. Because total body water is much more closely related to muscle mass than to body weight, small urea *V* is a good indicator for low muscle mass. It is interesting to note that in the Hemodialysis (HEMO) study, a beneficial effect of higher *Kt/V* was reported for women but not for men. This implies that individuals with low muscle mass may require a higher clearance in relation to *V* and therefore raises the question of whether *V* is the appropriate denominator for dialysis dose. Native renal clearances, in contrast, are commonly related to body surface area (BSA), not to total body water. By analogy, it has been proposed to relate dialysis clearances to BSA. The ratio of BSA to urea *V* is generally higher in women than in men and decreases with an increment in *V.* Prescribing dialysis dose in relation to BSA ($K \times t$/BSA) would result in more dialysis for smaller patients of either gender and for women of any size. Rescaling dose of dialysis to BSA in the HEMO population supported this hypothesis by showing that the delivered dose in women was substantially lower than in men, which may explain some of the outcome differences observed in the trial.[7] Although not yet fully validated, a higher target dose of dialysis may be recommended for subpopulations with low muscle mass and associated high mortality risk.

Factors Affecting Delivered *Kt/V*

The effective dialyzer urea clearance K_d depends on the flow rates within the blood and dialysate compartments, dialyzer K_oA, effective membrane surface area, hematocrit, anticoagulation, and recirculation. Treatment time *t* is important for reaching the *Kt/V* target. Effective treatment time can be substantially shorter than prescribed treatment time because of intermittent pump stops or patient demand. *V* does not substantially change during a single HD session but may change over time. Dialysis dose needs to be adjusted for an increase in *V.* On the contrary, if there is a loss in body mass, which is associated with a decrease in *V, Kt/V* should not be reduced but rather adjusted to the higher, ideal patient *V* or, as pointed out before, to BSA.

Confronted with an inadequate delivered URR or *Kt/V,* it is sensible to check whether the studied session was representative of an

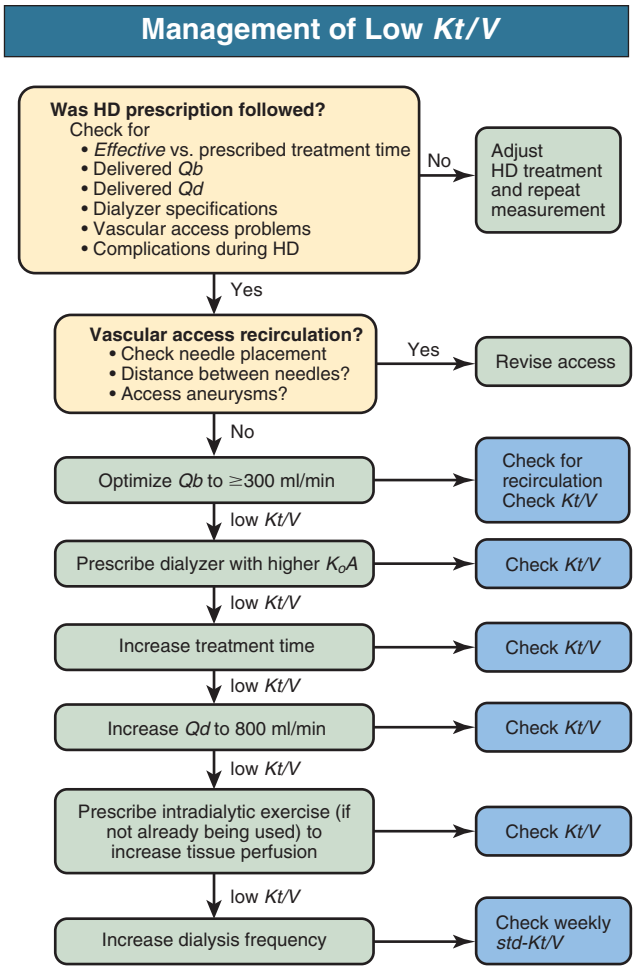

Figure 94-4 Management of low and inadequate *Kt/V*. *HD,* Hemodialysis; K_oA, the dialyzer urea mass transfer area coefficient; *Qb,* blood flow rate; *Qd,* dialysate flow rate.

average session because unusual problems may have occurred (e.g., shortened time, single-needle HD). Frequent causes of inadequately low delivered dialysis dose are vascular access problems leading to recirculation. Blood sampling errors should also be considered because delayed post-HD sampling will reduce *Kt/V* results. If a low *Kt/V* remains unexplained, treatment time should be increased and a more efficient dialyzer and higher blood and dialysate flow rates should be considered (Fig. 94-4). Active or passive muscle stimulation during dialysis improves *Kt/V* by increasing blood supply to poorly perfused muscle tissue and facilitates urea and phosphate removal.[8] Delivered *Kt/V* should be checked whenever the dialysis prescription has been modified substantially. Online clearance monitoring tools allow assessment of *Kt/V* during each single dialysis session without blood sampling.

Recommendations for Dialysis Dose Adequacy

Current European Best Practice Guideline recommendations[9] for dialysis strategies include the following:

- Dialysis should be delivered at least three times per week and the total duration should be at least 12 h/wk, unless supported by significant renal function.
- Delivered dialysis dose should be measured at least monthly.
- In anuric patients treated with three-times-per-week dialysis, the prescribed target *eKt/V* should be at least 1.2. Higher doses up to 1.4 should be considered in female patients and in patients with high comorbidity.
- For patients with renal function or those with dialysis schedules other than three times per week, weekly dialysis dose should be at least equivalent to an *std-Kt/V* of 2.0.

OTHER DIALYSIS FACTORS RELATED TO OUTCOMES

Middle Molecule Removal

It is widely held that retention solutes of middle molecular size may play an important role in the pathogenesis of the uremic state and contribute significantly to the high mortality of dialysis patients. Because of higher membrane porosity, high-flux dialyzers have the capacity to remove larger amounts of middle molecules than low-flux dialyzers do, and this may even be further increased by the use of convective dialysis strategies, such as hemodiafiltration (HDF). Because of slower intercompartmental equilibration rates, middle molecule removal is limited during conventional 4-hour dialysis sessions. Serum β_2-microglobulin, a surrogate for uremic middle molecules, can only be effectively removed by high-flux dialysis, and predialysis β_2-microglobulin levels were found to be related to mortality in patients treated randomly with high-flux or low-flux dialyzers.[10] Certain subgroups of dialysis patients, such as diabetics, and incident patients with serum albumin levels below 40 g/l, may benefit most from high-flux dialysis.[11,12] The European Best Practice Guidelines recommend the use of synthetic high-flux membranes to reduce the cardiovascular risk and to improve control of hyperphosphatemia and anemia.[9]

On-line HDF has the potential to provide the most extensive removal of the widest range of low and middle molecular size solutes. Documented advantages of on-line HDF include a higher removal rate for creatinine, phosphate, β_2-microglobulin, and some protein-bound uremic compounds. Three prospective randomized controlled studies have recently examined outcomes in on-line HDF compared with low- or high-flux HD. In two of these studies no statistically significant benefit was observed for on-line HDF in intention-to-treat analyses of the whole study populations.[13,14] However, in both studies *post hoc* on-treatment analyses revealed a significantly better outcome for subgroups of patients treated with a mean delivered convective volume of more than 18 to 22 liters per session. Results of a third randomized controlled trial from Spain (ESHOL trial)[15] confirmed these observations. Compared with patients who continued on HD, those assigned to high-efficiency on-line HDF with a mean delivered volume of 22 to 24 liters had a 30% lower risk of all-cause mortality, a 33% lower risk of cardiovascular mortality, and a 55% lower risk of infection-related mortality. Based on these three studies, high-efficiency HDF with a delivered substitution fluid volume exceeding 22 liters per session may well become a standard dialysis modality in the future.

Phosphate Removal

Hyperphosphatemia is a major problem in HD (see Chapter 85).[16] Management of hyperphosphatemia is based on phosphate removal by dialysis, dietary phosphate restriction, and intestinal phosphate binding with use of phosphate binder medication. Intradialytic phosphate kinetics differ significantly from urea kinetics, with serum phosphate levels steeply falling during the first 90 to 120 minutes into dialysis and stabilizing thereafter (Fig. 94-5). The intradialytic plateau is explained by phosphate mobilization from various compartments at a rate similar to that of dialyzer phosphate removal.

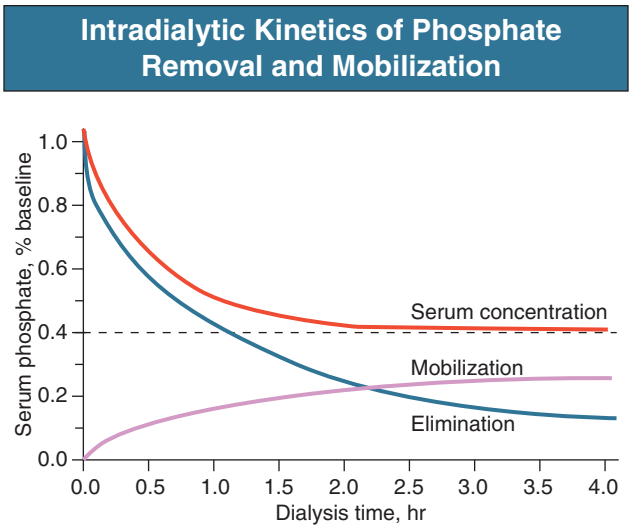

Figure 94-5 Intradialytic kinetics of phosphate removal and mobilization.

Phosphate removal can be improved by high-flux HD and HDF, by the use of a larger dialyzer surface area, and, most dramatically, by higher-frequency dialysis schedules, such as short daily or daily nocturnal HD. Long frequent dialysis schedules may even result in hypophosphatemia so that phosphate has to be added to the dialysate. In all patients, predialysis serum phosphate levels should be reduced toward the normal range.

Preservation of Residual Renal Function

Most patients starting dialysis still have considerable RRF; but by the end of the first year, the majority have lost RRF completely. Only 10% to 20% of patients still have RRF after more than 3 years of dialysis. RRF of 2 to 3 ml/min urea clearance contributes significantly to the elimination of uremic toxins.[17] This translates into lower serum β_2-microglobulin, phosphate, potassium, urea, creatinine, and uric acid levels, as well as maintained endocrine, metabolic, and antioxidative stress functions; higher hemoglobin concentration; enhanced nutritional status; better quality-of-life scores; and a reduced need for dietary and fluid restrictions. Loss of RRF, in contrast, is associated with left ventricular hypertrophy. To assess the relative contribution of RRF to total delivered dialysis dose, weekly dialysis dose should be expressed as *std-Kt/V*. For a patient with an estimated total body water of 40 liters, a residual urea clearance of 2 to 3 ml/min is equivalent to an *std-Kt/V* of 0.5 to 0.75/week. Risk factors for the loss of RRF include activation of the immune system by cellulose-based membranes and dialysate water impurities; intradialytic hypotension; use of angiotensin-converting enzyme inhibitors or nephrotoxic agents, such as radiocontrast media, aminoglycosides, and nonsteroidal anti-inflammatory drugs; and hypercalcemia. Loss of RRF may be delayed by adequate target post-HD weight prescription and prevention of intradialytic hypotensive episodes.

Dialysate Composition

During a standard treatment session, a patient's blood is exposed to 120 to 200 liters of dialysate. The several ingredients of dialysate should therefore be prescribed with great care.

Sodium

Sodium retention is a typical feature of ESRD and an important factor in the pathogenesis of hypertension in HD patients. Judicious control of sodium balance is effective in normalizing blood pressure, and dietary sodium intake should be restricted to 6 g salt or 100 mmol sodium per day. Sodium is mainly removed through ultrafiltration; but depending on the ratio of dialysate to plasma water sodium concentration, it will be additionally removed from or delivered to the patient by diffusion. For prevention of a positive sodium balance, either dialysate and serum sodium concentrations should be aligned or care should be taken that dialysate sodium does not exceed the patient's average predialysis serum sodium concentration by more than 2 to 3 mmol/l.

Potassium

Potassium removal during dialysis should ideally be equal to the amount accumulated during the interdialytic period. The dialysate potassium concentration has to be set at a level that avoids pre-HD hyperkalemia as well as intradialytic hypokalemia, which may provoke dialysis-induced arrhythmia. The typical dialysate potassium concentration is set to 2.0 to 4.0 mmol/l. Prescription of potassium dialysate concentrations below 2.0 mmol/l has been associated with an increased risk for tachyarrhythmia and sudden cardiac death and should therefore be avoided.[18]

Calcium

In light of the interdialytic positive calcium balance and accelerated vascular calcification as a major cardiovascular risk factor in ESRD, intradialytic calcium delivery to the patient should be avoided. In patients using calcium salts as phosphate binders, a negative intradialytic calcium mass balance is desirable.[19] A standard dialysate calcium concentration of 1.25 to 1.50 mmol/l is recommended by Kidney Disease: Improving Global Outcomes (KDIGO), but some patients will be in positive balance even at 1.25 mmol/l.[20] These and higher dialysate calcium concentrations may be associated with tissue calcium accumulation, whereas lower dialysate calcium will stimulate parathyroid hormone (PTH) secretion.

Bicarbonate

Chronic metabolic acidosis is associated with decreased protein synthesis and increased protein catabolism and contributes to mineral and bone disorders. Normalized pre-HD bicarbonate levels in the range of 20 to 23 mmol/l are associated with improved survival. Dialysate bicarbonate concentration is typically set at 35 to 40 mmol/l to generate a transmembrane concentration gradient favoring bicarbonate delivery to the patient. Data from DOPPS indicate that both high (>27 mmol/l) and low (<17 mmol/l) serum bicarbonate levels are associated with increased risk for mortality and hospitalization.[21]

Treatment Time

Conventional three-times-a week dialysis remains the standard of care in most countries; treatment time is typically governed by dialysis dose *(Kt/V),* with the consequence of longer dialysis in patients with higher urea distribution volumes. Acknowledging the difficulties in removing adequate amounts of low and middle molecular size uremic solutes during short dialysis sessions, a minimum treatment time of 4 hours per HD session is recommended in various countries, such as Germany. Even with similar *Kt/V,* longer treatment times are associated with higher mass removal of urea, creatinine, phosphate, and β_2-microglobulin compared with shorter treatment times.[22]

Weekly treatment time is the one factor with the potentially highest impact on dialysis dose and outcome. More frequent in-center dialysis and longer dialysis hours delivered by in-center or home nocturnal dialysis are increasingly used alternatives to

conventional thrice-weekly treatment. Both modalities offer the opportunity for improved solute clearance and complete removal of interdialytic weight gain with fewer problems because ultrafiltration rates are lower and hypotension is less likely. The randomized controlled Frequent Hemodialysis Network (FHN) study[23] demonstrated that short daily in-center HD is associated with a reduction in left ventricular mass and an improvement of the physical health score. Although it is assumed that this may translate into reduced mortality rates, survival advantages of daily HD over conventional HD still need to be demonstrated. Several retrospective epidemiologic studies in larger patient populations suggest a survival advantage for patients treated with extended time and/or frequency dialysis schedules, such as daily nocturnal or thrice-weekly nocturnal HD, over conventional HD.[24-26]

Fluid Status

Fluid overload, which is found in the majority of HD patients, is an established risk factor for the development of arterial hypertension, left ventricular hypertrophy, and cardiovascular mortality. It is the goal of an adequate HD treatment to normalize body water homeostasis and extracellular volume to a level comparable with that of patients of similar age and normal renal function. In clinical practice, this idealized postdialysis body weight is termed *dry weight,* and it may differ substantially from the target weight prescribed by the physician. Because of the difficulties in detecting fluid overload of 2 to 3 liters clinically from the presence of edema, high blood pressure, dyspnea, and increased jugular venous pressure, technical methods such as ultrasound (diameter of inferior vena cava), chest radiography, lung ultrasound, and whole-body bioimpedance should be applied regularly.[27] The prescribed post-HD target weight is achieved by ultrafiltration. Ultrafiltration rates above 1000 ml/h are associated with an increased risk of intradialytic hypotension, which in turn is associated with an increased long-term mortality risk. Transient myocardial ischemia appears to occur regularly during dialysis in relation to ultrafiltration rates exceeding 500 ml/h. Intradialytic hemodynamics can be stabilized by isothermic HD, in which the physiologic intradialytic rise in body core temperature, a key factor in the pathogenesis of intradialytic hypotension, is prevented through cooling of the dialysate.[28] In hemodynamically unstable patients, only low ultrafiltration rates and therefore longer dialysis treatment times can accomplish the goal of adequate fluid removal.

Dialysis patients are advised to limit daily fluid intake to 0.5 to 0.75 liter in excess of their average daily diuresis and to control dietary salt intake. A positive interdialytic and intradialytic sodium balance is a major factor governing thirst and interdialytic water intake. Dietary salt restriction to 6 g salt per day is recommended to prevent high interdialytic weight gain and the development of arterial hypertension and congestive heart failure. This often requires constant education including the family. A gradual reduction in interdialytic weight may reflect poorer appetite and diminished food intake and, together with a decrease in systolic blood pressure, serum albumin, and C-reactive protein, has been identified as a marker of imminent death within 1 year.[29]

Nutritional Status

Hemodialysis patients are at risk of malnutrition from protein-energy wasting, decreased appetite, infection, intercurrent illnesses, hospital admissions, and missed meals after dialysis.[30] The recommended daily intake of 1.0 to 1.2 g protein per kilogram of ideal body weight and 35 kcal/kg ideal body weight is often not met. The nutritional status of dialysis patients should be assessed regularly by clinical and biochemical means, including measurement of protein nitrogen appearance (see Chapter 87).

Vascular Access

The choice of vascular access strongly affects outcome in dialysis patients. A functioning vascular access is a major precondition for adequate dialysis treatment. Native fistulas should always be the first-line vascular access. In patients in whom a native fistula cannot be created, a vascular graft may be an alternative. Central venous catheters may be used for bridging until a vascular access can be used for dialysis. Only when a native fistula or a graft is not available and conversion to peritoneal dialysis appears not feasible should subcutaneous tunneled central venous catheters be used as permanent access. Worldwide, there are large differences in the fraction of patients with central venous catheters used as permanent access. Long-term catheter use is associated with a higher rate of chronic inflammation and acute infection, lower serum albumin levels, impaired response to erythropoietin, and higher hospitalization and mortality rates, mainly because of infection (see Chapter 91). The quality of the vascular access should be assessed regularly by clinical means, such as inspection, palpation, and auscultation, as well as by technical means, including intradialytic measurement of recirculation or access flow rate and Doppler ultrasound technology.

Quality of Life

Quality-of-life measures may be among the most sensitive indicators of the efficacy of dialysis therapies. Measures of physical and mental aspects of quality of life are recognized to assess the physical and psychological disturbances that can accompany the uremic state and can be modified by renal replacement therapy.[31] Various standardized quality of life tests are now routinely used in clinical trials involving HD patients. In addition to dialysis adequacy, quality of life may also be significantly affected by factors related to organizational issues—for example, travel delays, waiting time at the dialysis facility for treatment to start, time of dialysis in relationship to work or educational needs, and lack of exercise.

Depression is one of the major mental aspects affecting quality of life and may be assessed separately by validated standardized questionnaires, such as the Beck Depression Inventory.[32] Depression is frequently associated with biochemical evidence of inflammation or infection and may improve with appropriate treatment. One potential way to make some impact on some of these issues is to modify the "assembly line" character of many dialysis centers with variations including physical exercise and occupational therapy programs and opportunities for the patients to have regular meetings with staff to discuss their questions.

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CHAPTER 95

Acute Complications During Hemodialysis

Kevan R. Polkinghorne and Peter G. Kerr

Although technical advances in hemodialysis (HD) have made the procedure increasingly safe and well tolerated, there are still important acute complications that will be encountered by physicians responsible for patients receiving HD in both acute and chronic clinical settings. These complications with their causes and management are discussed in this chapter.

CARDIOVASCULAR COMPLICATIONS

Intradialytic Hypotension

Intradialytic hypotension, which occurs in 10% to 30% of treatments, ranges from asymptomatic episodes to marked compromise of organ perfusion resulting in myocardial ischemia, cardiac arrhythmias, vascular thrombosis, loss of consciousness, seizures, or death.[1] Furthermore, in patients with acute kidney injury, intradialytic hypotension may induce more renal ischemia and retard recovery of renal function. Intradialytic hypotension and postdialysis orthostatic hypotension have been shown to be independent risk factors for mortality.[2] The pathogenesis of intradialytic hypotension is complex[3] and is summarized in Figure 95-1. Most commonly, however, intradialytic hypotension results from the need to deal with excessive fluid weight gain between dialysis treatments. The subsequent rate of fluid removal required exceeds the achievable rate of intravascular filling, resulting in relative intravascular volume depletion.

The immediate treatment is to restore the circulating blood volume by placing the patient in the Trendelenburg position, reducing or stopping ultrafiltration, and infusing boluses of 0.9% isotonic saline (100 ml or more, as necessary). Salt-poor albumin and other hypertonic solutions offer no advantage over isotonic saline and cost more. Blood flow rate should not be routinely reduced to manage hypotension, because this has not been shown to be beneficial. If the blood pump rate is reduced transiently, particular attention should be paid to minimizing underdialysis from such a practice. Of course, in the setting of excessive weight gain, the administration of boluses of saline makes achieving the target dry weight more difficult. Because cardiac factors can precipitate intradialytic hypotension, the clinician should maintain a high index of suspicion for cardiac ischemia, especially if hypotension is accompanied by chest pain or dyspnea, and an electrocardiogram and serum troponins should be obtained. Similarly, recurrent and unexplained episodes of hypotension might warrant echocardiography to rule out pericarditis or pericardial effusion.

Preventive strategies include correction of anemia and hypoalbuminemia and treatment of congestive heart failure or arrhythmias, avoidance of antihypertensive drugs before dialysis, and avoidance of food before and during dialysis. Patients should be counseled to avoid excessive interdialytic weight gain, and accurate assessment of the patient's dry weight is required. Particular attention should be given to ensuring minimal salt intake. Midodrine, an oral selective α_1-agonist, 5 to 10 mg predialysis, is a useful preventive therapy.[4]

Preventive strategies through modification of the dialysis procedure include in the first instance use of bicarbonate dialysate, volumetric control of ultrafiltration, and sodium modeling. Subsequently, reducing the ultrafiltration rate by increasing either the number of hours or the frequency of dialysis can be tried.[5] I On-line blood volume monitoring and biofeedback techniques have been developed in an attempt to improve intradialytic cardiovascular stability.[6] Although on-line blood volume devices have been shown to decrease the incidence of intradialytic hypotension in an at-risk population, there is limited evidence that blood volume monitoring can predict intradialytic hypotension in individual patients or produce a long-term morbidity and mortality benefit, especially in the wider HD population.[7] Cooling of dialysate to 35.5°C to 36°C (95.9°F to 96.8°F), a measure that induces release of catecholamines, resulting in vasoconstriction or at least preventing vasodilation, may lessen hypotension. A systematic review of the randomized controlled trials using biofeedback modulating dialysate temperature demonstrated significant reductions in the incidence of intradialytic hypotension compared with conventional dialysis.[8] Modulation of dialysate temperature is achieved by measuring the blood temperature in the arterial and venous circuits and feeding back the information to the arterial and venous thermostats in the dialysis machine. The machine can be programmed to allow either a constant body temperature and a negative overall energy transfer, so-called *isothermic hemodialysis,* or thermoneutral hemodialysis, which aims to prevent energy transfer between the dialysate and extracorporeal blood. Both isothermic and thermoneutral HD have been shown to reduce intradialytic hypotension in randomized trials compared with conventional HD.

Intradialytic Hypertension

Intradialytic hypertension occurs in 8% to 30% of treatments.[9] Hypertension during or immediately after HD constitutes an important risk factor for cardiovascular mortality. Moreover, an intradialytic increase in systolic blood pressure is associated with an increased risk of hospitalization or death.[10]

In most circumstances, an intradialytic elevation of blood pressure indicates significant volume overload. However, in a number of patients, blood pressure remains elevated despite fluid removal, a syndrome called *dialysis-refractory hypertension.* These patients are usually young with preexisting hypertension and have excessive interdialytic weight gain and a hyperactive renin-angiotensin system in response to fluid removal.[11] In these patients the hypertension is still mediated by the previous volume expansion, but there is often a lag of days to 2 or more weeks before the blood pressure becomes normal (known as the dialysis "lag phenomenon"). Often patients can discontinue most of their antihypertensive agents once this occurs.

Erythropoietin (EPO) and other erythropoiesis-stimulating agents have been associated with a 20% to 30% incidence of new onset or exacerbation of hypertension. Furthermore, among patients

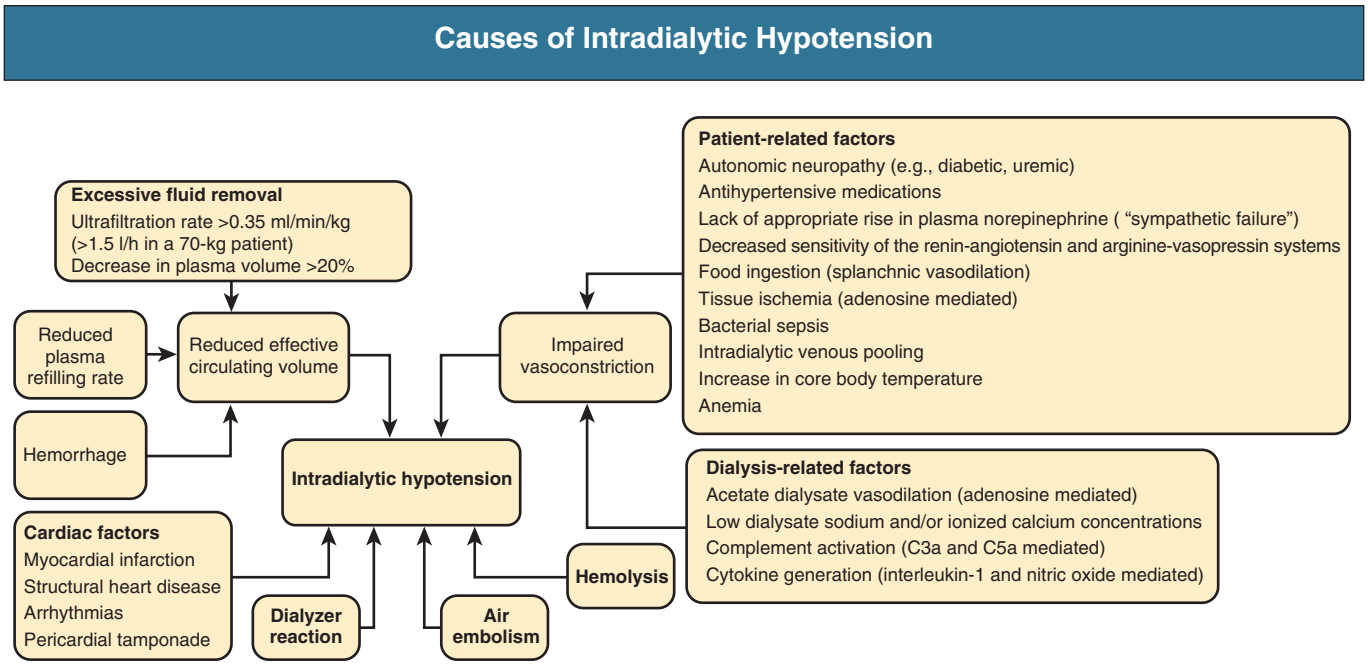

Figure 95-1 Pathogenesis and causes of intradialytic hypotension.

receiving intravenous (not subcutaneous) EPO, elevated levels of endothelin-1 (a potent vasoconstrictor) have been shown to correlate with increased blood pressure. Predominantly, such EPO-induced rises in blood pressure are associated with a rapid rise in hemoglobin and can be avoided by a more conservative approach to correcting the hemoglobin.

Intradialytic hypertension can be precipitated by the use of high sodium dialysate, which is intended to mitigate the intradialytic decrease in serum osmolality that occurs with the diffusive removal of urea and sodium.[12] Although this approach stabilizes blood pressure during dialysis by improving intravascular filling, high sodium dialysate results in a positive intradialytic sodium balance and is associated with increased postdialysis thirst, resulting in significant weight gain in the interdialytic period. To circumvent these problems, sodium modeling has been adopted as an approach that uses variable sodium concentrations in the dialysate, generally with sodium reduced in a continuous or stepwise manner from an initial level of 150 to 154 mmol/l to 138 to 142 mmol/l. Although sodium modeling has been widely promoted, randomized trial evidence for definite benefits of this approach is lacking.[13] Other hypothesized mechanisms of intradialytic hypertension include hyperactivity of the sympathetic nervous system[14] and increased cardiac output resulting from fluid removal, particularly among patients with cardiomyopathy.[15] Clinicians should also be aware of possible dialytic removal of certain antihypertensive drugs, such as angiotensin-converting enzyme (ACE) inhibitors and beta blockers.

Increasing hypertension during a dialysis session requires intervention if systolic blood pressure is greater than 180 mm Hg. This is best treated with a centrally acting agent such as clonidine or a short-acting ACE inhibitor such as captopril. Successful treatment of hypertension for a longer period requires an accurate determination of the patient's dry weight and its achievement by gradual ultrafiltration during several weeks of dialysis. Once dry weight is achieved, optimization of antihypertensive drug therapy is warranted, including the use of minimally dialyzable or nondialyzable medications such as angiotensin receptor blockers, calcium channel blockers, clonidine, and carvedilol. However, it should be remembered that use of antihypertensive agents may make achievement of dry weight difficult because of induced intradialytic hypotension. Evidence from the Dry-Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) trial[16] would suggest that optimal control of blood pressure in HD patients is via volume control, not the use of antihypertensive agents. One common error in management is to treat dialysis hypertension with increasing blood pressure medications as opposed to opting to achieve dry weight. The use of vasodilator drugs (hydralazine, minoxidil) can lead to increased fluid retention that worsens hypertension and volume overload. Minoxidil can also be associated with the development of pleural and pericardial effusions.

Cardiac Arrhythmias

Intradialytic arrhythmias are common and are often multifactorial in origin.[17,18] Left ventricular hypertrophy, congestive cardiomyopathy, uremic pericarditis, silent myocardial ischemia, and conduction system calcification are frequently encountered in adult dialysis patients. In addition, polypharmacy coupled with the constant alterations in fluid, electrolyte, and acid-base homeostasis may precipitate intradialytic arrhythmias. The range of electrocardiographic abnormalities that may be encountered in renal failure is shown in Table 95-1. QTc dispersion, the difference between maximum and minimum QTc interval on a standard 12-lead electrocardiogram, is prolonged after HD and has been proposed as a prognostic indicator of cardiac complications in dialysis patients.[19]

Preventive measures include the use of bicarbonate dialysate and careful attention to dialysate potassium and calcium levels. There are very few trials of the most appropriate dialysate potassium level, although recent observational evidence suggests that dialysate potassium levels below 2 mmol/l should be avoided in most patients.[20] Zero potassium dialysate should be avoided because of its arrhythmogenic potential, particularly in patients receiving digoxin, should serum potassium concentration decrease to less than 3.5 mmol/l. Serum digoxin levels should be regularly monitored and the need for the drug regularly reassessed.

Electrocardiographic Abnormalities in Renal Failure

Function	Abnormality Seen in Renal Failure
PR interval	Usually normal; prolongation in long-term hemodialysis Calcification of mitral valve annulus may involve His bundle, resulting in complete heart block
QRS interval	
Amplitude	Increases during ultrafiltration (correlates with reduction in left ventricular [LV] dimensions) LV hypertrophy (LVH) on voltage criteria found in up to 50%
Duration	Prolonged (within normal range) by hemodialysis Late potentials increased only in patients with preexisting coronary heart disease Prolonged in hyperkalemia
ST segment	Depression during hemodialysis does not predict coronary artery disease Depression or elevation may occur in hyperkalemia Depression during ambulatory monitoring poorly predictive of coronary artery disease
QTc interval	Increases during hemodialysis (correlates with reduction in K^+ and Mg^{2+}) Increased QT dispersion reported in patients on dialysis
T wave	Peaking or inversion may occur in hyperkalemia Inversion in anterolateral leads in LVH with strain pattern
Rhythm	High incidence of atrial and ventricular arrhythmias during hemodialysis

Table 95-1 Electrocardiographic abnormalities in renal failure. Risk factors include LV dysfunction, wall motion abnormalities, known coronary artery disease, abnormal perfusion scans (even without coronary artery disease), use of cardiac glycosides, and low dialysate potassium concentration.

Sudden Death

Cardiac arrest occurs at a rate of 7 per 100,000 HD sessions and is more common in the elderly, patients with diabetes, and patients using central venous catheters.[21] Some 80% of sudden deaths during dialysis are caused by ventricular fibrillation, more frequently observed after the long interdialytic interval on thrice-weekly dialysis, presumably because of more marked fluid and solute accumulation.[22-24] Consistent with this hypothesis, both peritoneal dialysis patients and patients undergoing long-duration HD do not show this high event rate on a particular day of the week.[24] Although coronary heart disease increases the risk of sudden death, other catastrophic intradialytic events need to be ruled out. The prompt recognition and treatment of hyperkalemia, often encountered in young, noncompliant patients, is imperative. Profound generalized muscle weakness may be a warning sign of imminent life-threatening hyperkalemia.

When cardiopulmonary arrest occurs during dialysis, an immediate decision must be made as to whether the collapse is the result of an intrinsic disease or technical errors, such as air embolism, unsafe dialysate composition, overheated dialysate, line disconnection, or sterilant in the dialyzer. Air in the dialysate, grossly hemolyzed blood, and hemorrhage caused by line disconnection can be easily detected. However, if no obvious cause is identifiable, blood should not be returned to the patient, particularly if the arrest occurred immediately on initiation of dialysis. A patient exposed to formaldehyde may have complained earlier of burning at the access site; fortunately this agent is rarely used today. If the possibility of a problem with dialysate composition is remote, blood may be returned to the patient. However, blood and dialysate samples should be immediately sent for electrolyte analysis, the dialyzer and blood lines saved for later analysis, and the dialysis machine replaced until all its safety features have been thoroughly evaluated for possible malfunction. It should be a standard practice to have defibrillators in dialysis units. The management of cardiopulmonary arrest during dialysis should follow the standard principles of cardiopulmonary resuscitation; the diagnosis and management of technical errors are discussed later.

Prevention of sudden cardiac death in HD patients, including the role of implantable defibrillators, is further discussed in Chapter 82.

Dialysis-Associated Vascular Steal Syndrome

Clinical Presentations (Symptoms Often Aggravated on Dialysis)
- Hand numbness, pain, or weakness
- Coolness of distal arm
- Diminished pulses
- Acrocyanosis, gangrene

Differential Diagnosis
- Dialysis-associated cramp
- Polyneuropathy—diabetes, uremia
- Entrapment neuropathy—$A\beta_2M$ amyloid
- Reflex sympathetic dystrophy
- Calciphylaxis

Evaluation of Steal Severity
- Pulse oximetry
- Plethysmography
- Doppler flow
- Angiography

Treatment Options (Depending on Severity)
- Symptomatic (e.g., gloves)
- Surgical, with preservation of vascular access: banding to reduce flow, distal revascularization–interval ligation (DRIL) procedure (see Fig. 91-6)
- Surgical, with loss of vascular access: ligation

Box 95-1 Dialysis-associated vascular steal syndrome.

Pericarditis

The management of pericarditis in dialysis patients is discussed in Chapter 82.

Dialysis-Associated Steal Syndrome

The construction of an arteriovenous fistula or graft frequently results in reduction of blood flow to the hand. Although clinically significant ischemia does not usually result, symptoms are by no means rare, particularly in diabetic or elderly patients with peripheral vascular disease. Dialysis-associated steal syndrome is more common in upper arm arteriovenous fistulas (about 4%) compared with both arteriovenous grafts and forearm arteriovenous fistulas (about 1%). The clinical presentation, differential diagnosis, and evaluation of dialysis-associated steal syndrome are summarized in Box 95-1 and are discussed further in Chapter 91.[25,26]

Treatment depends on the clinical severity of ischemia and vascular access anatomy.[26] Severe ischemia can cause irreparable injury to nerves within hours and must be considered a surgical emergency. Mild ischemia, manifested by mild pain during HD, subjective coldness and paresthesias, and objective reduction in skin temperature

but with no loss of sensation or motion, is common and generally improves with time.[27] Patients with mild ischemia should undergo symptom-specific therapy (e.g., wearing a glove) and frequent physical examination, with special attention to subtle neurologic changes and muscle wasting.[28] Failure to improve may necessitate surgical or radiologic intervention (see Chapter 91). Persistence of symptoms after an apparently successful correction of the vascular access flow should alert the clinician to other unrelated causes.

NEUROMUSCULAR COMPLICATIONS

Muscle Cramps

Muscle cramps occur in 5% to 20% of patients late during dialysis and frequently involve the legs. They account for 15% of premature discontinuations of dialysis.[30] Electromyography shows increased tonic muscle electrical activity throughout dialysis, and serum creatine kinase may be elevated.

Although the pathogenesis is unknown, dialysis-induced volume contraction and hypo-osmolality are common predisposing factors. Indeed, the onset of muscle cramps may give an indication that the target weight has been reached. However, hypomagnesemia and carnitine deficiency may also play a role.

The acute management is directed at increasing plasma osmolality. Cessation of ultrafiltration is not useful. Parenteral infusion of 23.5% hypertonic saline (15 to 20 ml), 25% mannitol (50 to 100 ml), or 50% dextrose in water (25 to 50 ml) is equally effective. However, hypertonic saline may result in postdialytic thirst, and both hypertonic saline and mannitol cause transient warmth and flushing during the infusion. Furthermore, large and repetitive infusions of mannitol may lead to increased thirst, interdialytic weight gain, and fluid overload. Overall, dextrose in water is preferred, particularly in nondiabetics.

Preventive measures include dietary counseling about excessive interdialytic weight gain. In patients without clinical signs of fluid overload, it is reasonable to increase the dry weight by 0.5 kg and to observe the clinical response. Quinine sulfate (250 to 300 mg) or oxazepam (5 to 10 mg) given 2 hours before dialysis may also be effective. Although the U.S. Food and Drug Administration regards quinine sulfate as both unsafe and ineffective for the prevention of cramps, this drug works well in some patients, and it is used freely in most parts of the world. Some reports also promote the use of vitamin E in this role.[31] The use of sodium gradient during dialysis may have some benefit as well. Proposed strategies include starting with a dialysate sodium concentration of 145 to 155 mmol/l and a linear decrease to 135 to 140 mmol/l by the completion of the treatment. A comparison of sodium modeling with an exponential, linear, or step program has yielded similar results.[32] In anecdotal reports, 5 mg of enalapril twice weekly may be effective, presumably by inhibiting angiotensin II–mediated thirst. Stretching exercises, magnesium, creatine monohydrate (12 mg before dialysis),[33] and L-carnitine supplementation (20 mg/kg per dialysis session) may also be beneficial.[34] An intradialytic blood volume biofeedback control system has been shown to reduce the incidence of muscle cramps.[35]

Restless Legs Syndrome

Restless legs syndrome is common in dialysis patients. The typical complaint is of crawling sensations in the legs that occur with inactivity, and symptoms may worsen during dialysis. The etiology, prevention, and management of restless legs syndrome are discussed in Chapter 86.

Dialysis Disequilibrium Syndrome

Despite a decline in its incidence, dialysis disequilibrium syndrome (DDS) is still observed sporadically in patients who are initiated on HD on high-flux dialyzers with large surface areas and short dialysis time. Risk factors include young age, severe uremia, rapid and marked intradialytic falls in urea at dialysis initiation, low dialysate sodium concentration, and preexisting neurologic disorders (see Chapter 86).

Dialysis disequilibrium syndrome commonly presents with restlessness, headache, nausea, vomiting, blurred vision, muscle twitching, disorientation, tremor, and hypertension. More severe manifestations include obtundation, seizures, and coma. DDS usually develops toward the end of dialysis but may be delayed for up to 24 hours. Although cerebral edema is a consistent finding on computed tomographic scanning, DDS remains a clinical diagnosis because laboratory tests, including electroencephalography, are nonspecific. It is usually self-limited, but full recovery may take several days.

The pathogenesis of DDS is still a subject of debate. The reverse urea effect theory, which proposes that a transient osmotic disequilibrium occurs during dialysis as a result of a more rapid removal of urea from blood than from cerebrospinal fluid, has been disputed.[36] In animals undergoing rapid dialysis, despite the correction of systemic acidosis, a paradoxical cerebrospinal fluid acidosis develops that is aborted by slower dialysis. An additional mechanism is the intracerebral accumulation of idiogenic osmoles, such as inositol, glutamine, and glutamate.

In high-risk patients, preventive measures include the use of volumetric-controlled machines, bicarbonate dialysate, sodium modeling, earlier recognition of uremic states, and stepped initiation of dialysis (short initial treatment times with lower blood pump speeds). In addition, short and more frequent dialysis treatments are recommended with use of small surface area dialyzers and reduced blood flow rates. The target reduction in blood urea should initially be limited to 30%. The prophylactic use of mannitol or anticonvulsants is not recommended.

An extension of this syndrome may be one that mimics osmotic demyelination syndrome—similar to that seen with rapid correction of hyponatremia. Several cases have been reported in association with dialysis initiation, with clinical manifestations similar to the locked-in pontine picture of central demyelination. The difference is that with the dialysis-related condition, the patients appear to recover over the ensuing 5 to 7 days and the condition seems to be related to edema rather than demyelination.[37]

Seizures

Intradialytic seizures occur in less than 10% of patients and tend to be generalized but easily controlled. However, focal or refractory seizures warrant evaluation for focal neurologic disease, particularly intracranial hemorrhage. Causes of seizures are summarized in Figure 95-2 and are discussed further in Chapter 86.

Treatment of established seizures requires cessation of dialysis, maintenance of airway patency, and investigation for metabolic abnormalities. Intravenous diazepam, alprazolam or clonazepam, and phenytoin may be required. Intravenous 50% dextrose in water should be administered promptly if hypoglycemia is suspected.

Headache

Dialysis headache is common and consists of a bifrontal discomfort that develops during dialysis and may become intense and

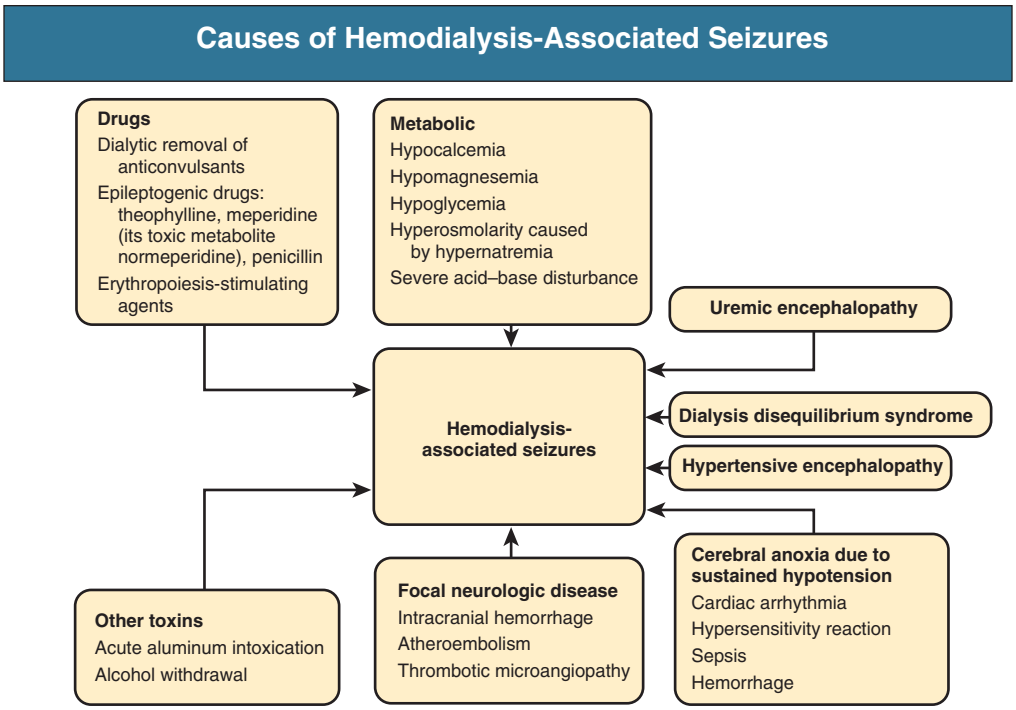

Figure 95-2 Causes of hemodialysis-associated seizures.

throbbing, accompanied by nausea and vomiting. It is usually aggravated by the supine position, but there are no visual disturbances.

Although its cause has not been elucidated, dialysis headache may be a subtle manifestation of DDS or may be related to the use of acetate, which is present in low concentrations (3 to 4 mmol/l) in almost all dialysate fluid. A role for nitric oxide has also been postulated.[38] Alternatively, it may be a manifestation of caffeine withdrawal caused by dialytic removal of caffeine.

Management consists of oral analgesics (e.g., acetaminophen [paracetamol]). Preventive measures include slow dialysis with reduced blood flow rates, change to bicarbonate dialysate, sodium and ultrafiltration modeling, coffee ingestion during dialysis, and use of reprocessed dialyzers. Attention should also be paid to adequate flushing of the lines and dialyzer before commencement of dialysis. Changing the dialysis membrane, especially to a synthetic membrane or an alternative synthetic membrane, sometimes is useful in patients with refractory cases.

HEMATOLOGIC COMPLICATIONS

Complement Activation and Dialysis-Associated Neutropenia

During dialysis with unsubstituted cellulose dialyzers, which are infrequently used, the free hydroxyl groups present on the membrane cause activation of the alternative pathway of complement.[39] This results in activation and increased adherence of circulating neutrophils to the endothelial capillary pulmonary vasculature, leading to transient neutropenia that reaches a nadir after 15 minutes of dialysis, followed by a rebound leukocytosis 1 hour later. Complement activation and neutropenia have also been detected with other more widely used dialyzer membranes, including cellulose acetate and polysulfone, but to a lesser degree. Although the long-term clinical relevance of this phenomenon remains speculative, its contribution to acute intradialytic morbidity is discussed later.

Intradialytic Hemolysis

Acute hemolysis can be caused by faulty dialysis equipment, chemicals, drugs, toxins, or patient-related factors (Fig. 95-3).[40] With the advent of better dialysis equipment and the widespread use of reverse osmosis and/or deionization systems and carbon filters, traumatic red blood cell fragmentation caused by poorly designed blood pumps and methemoglobinemia caused by water contamination with chloramine or copper are rarely seen today. However, nitrate or nitrite intoxication causing methemoglobinemia still occurs sporadically in patients on home HD who use well water that is contaminated with urine from domesticated animals. Furthermore, during dialyzer reprocessing, formaldehyde retention can result in hemolysis by inducing formation of cold agglutinins or inhibiting red cell metabolism.

The diagnosis of acute hemolysis is evident when grossly translucent hemolyzed blood is observed in the tubing. Patients with methemoglobinemia have nausea, vomiting, hypotension, and cyanosis, and oxygen therapy does not improve the black blood present in the extracorporeal circuit. Copper contamination should be suspected in the presence of skin flushing and abdominal pain or diarrhea.

Evaluation should include reticulocyte count, haptoglobin, lactate dehydrogenase, blood smear, Coombs test, and measurement of methemoglobin. Chromium 51 (^{51}Cr)–labeled red blood cell survival and bone marrow examination may occasionally be indicated if there is recurrent hemolysis. More important, analysis of tap water for chloramines and metal contaminants and thorough analysis of the dialysis equipment for clues of increased blood turbulence are recommended.

Hemorrhage

Bleeding complications are commonly related to the use of intradialytic anticoagulation, which further confounds the uremic bleeding diathesis (see Chapter 84).[41] In addition, dialysis patients are prone to spontaneous bleeding at specific sites, such as gastrointestinal

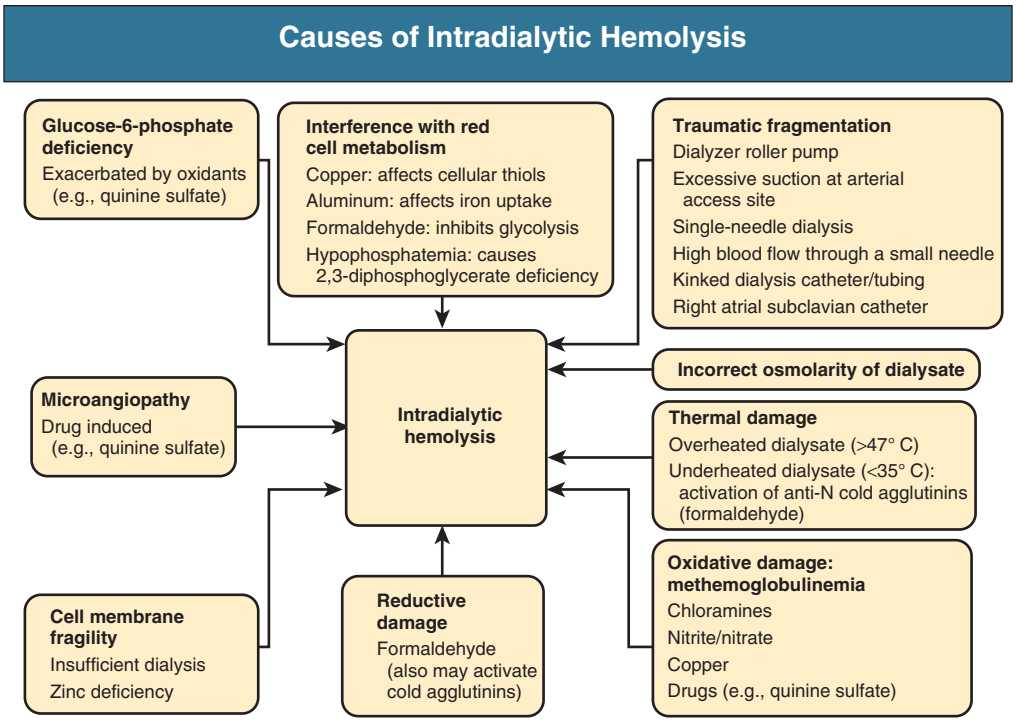

Figure 95-3 Causes of intradialytic hemolysis.

arteriovenous malformations; subdural, pericardial, pleural, retroperitoneal, and hepatic subcapsular spaces; and the ocular anterior chamber. Despite its limitations, the bleeding time remains the best indicator of hemorrhagic tendency.

In addition to specific measures directed to the site of hemorrhage, reversal of uremic platelet dysfunction is imperative. Strategies include the use of erythropoiesis-stimulating agents or red blood cell transfusions to achieve a hematocrit above 30% to improve rheologic platelet–vessel wall interactions, intravenous conjugated estrogens at 0.6 mg/kg per day for 5 consecutive days, intravenous or subcutaneous 1-deamino-8-D-arginine vasopressin (DDAVP) at 0.3 μg/kg administered over 15 to 30 minutes, and intravenous infusion of cryoprecipitate (see Box 84-2). For patients experiencing severe bleeding, it is advisable to consider heparin-free dialysis with use of normal saline flushes every 15 to 30 minutes with ultrafiltration adjustments. Other alternatives may include regional heparin or citrate anticoagulation, and in the long term the use of low-molecular-weight heparin, heparin modeling, or prostacyclin may be considered. More recently, the use of heparin-bound dialyzers (such as Hemophan or AN69ST) has been advocated in patients at risk of bleeding.[42] In patients scheduled for elective surgery or invasive procedures, cessation of aspirin should be considered a week earlier depending on the local protocols, the dose of anticoagulant reduced to a minimum, and the hematocrit maintained above 30%. In some patients, intravenous DDAVP to reverse the uremic platelet defect may also be required. Tranexamic acid, a potent fibrinolytic inhibitor, has occasionally been used as an adjuvant treatment to control hemorrhage in dialysis patients.[43]

Thrombocytopenia

An increasingly important cause of thrombocytopenia in dialysis patients is heparin-induced thrombocytopenia. The diagnosis and management, including alternative strategies for anticoagulation strategies for HD, are discussed in Chapter 84.

PULMONARY COMPLICATIONS

Dialysis-Associated Hypoxemia

In most patients, the arterial Pa_{O_2} decreases by 5 to 20 mm Hg (0.6 to 4 kPa) during dialysis, reaching a nadir at 30 to 60 minutes, and resolves within 60 to 120 minutes after discontinuation of dialysis. This decrease is usually of no clinical significance to patients unless there is preexisting chronic cardiopulmonary disease.

Hypoventilation is the main implicated factor and is primarily central in origin as a result of a decrease in carbon dioxide production after acetate metabolism (specific to acetate dialysate), loss of carbon dioxide in the dialyzer (with both acetate and bicarbonate dialysate), and rapid alkalinization of body fluids (particularly with large surface area dialyzers).[44] In addition, acetate-induced respiratory muscle fatigue can lead to hypoventilation, especially in acutely ill patients. Furthermore, a commonly observed ventilation-perfusion mismatch may be caused by pulmonary leukocyte agglutination (in part resulting from complement activation) or impaired cardiac output (resulting from acetate-induced myocardial depression).

In high-risk patients with fluid overload, preventive measures consist of using intradialytic oxygen supplementation, conventional bicarbonate dialysate, and biocompatible membranes. Optimizing hematocrit values and performing sequential ultrafiltration followed by HD may further reduce the likelihood of hypoxemia.

TECHNICAL MALFUNCTIONS

Air Embolism

The most vulnerable source of air entry into the extracorporeal circuit is the prepump tubing segment, where significant subatmospheric pressures prevail. However, other sources need to be considered, including intravenous infusion circuits especially with glass bottles, air bubbles from the dialysate, and (especially uncuffed)

dialysis catheters. High blood flow rates may allow rapid entry of large volumes of air despite small leaks.

Clinical manifestations depend on the volume of air introduced, the site of introduction, the patient's position, and the speed at which air is introduced.[45] In the sitting position, air entry through a peripheral vein bypasses the heart and causes venous emboli in the cerebral circulation. The acute onset of seizures and coma in the absence of precedent symptoms such as chest pain and dyspnea is highly suggestive of air embolism. In the supine position, air introduced through a central venous line will be trapped in the right ventricle, where it forms foam, interferes with cardiac output, and, if it is large enough, leads to obstructive shock. Dissemination of microemboli to the pulmonary vasculature results in dyspnea, dry cough, chest tightness, or respiratory arrest. Furthermore, passage of air across the pulmonary capillary bed can lead to cerebral or coronary artery embolism. In the left Trendelenburg position, air emboli migrate to the lower extremity venous circulation, resulting in ischemia as a result of increased outflow resistance. Foam may be visible in the extracorporeal tubing, and cardiac auscultation may reveal a peculiar churning sound.

The immediate management of clinically suspected air embolism is summarized in Figure 95-4. Prevention depends primarily on dialysis machines that are equipped with venous air bubble traps and foam detectors located just distal to the dialyzer and a venous pressure monitor at the venous end. The detector is attached to a relay switch that simultaneously activates an alarm, shuts off the blood pump, and clamps the venous blood line if air is detected. Therefore, dialysis should never be performed in the presence of an inoperative air detection alarm system. Glass bottles should be avoided because they create vacuum effects that can permit air entry into the extracorporeal system. Dialysis catheters should be aspirated and flushed with saline before connection. Dialyzer rinsing, before use, should expand all compartments to remove residual air bubbles.

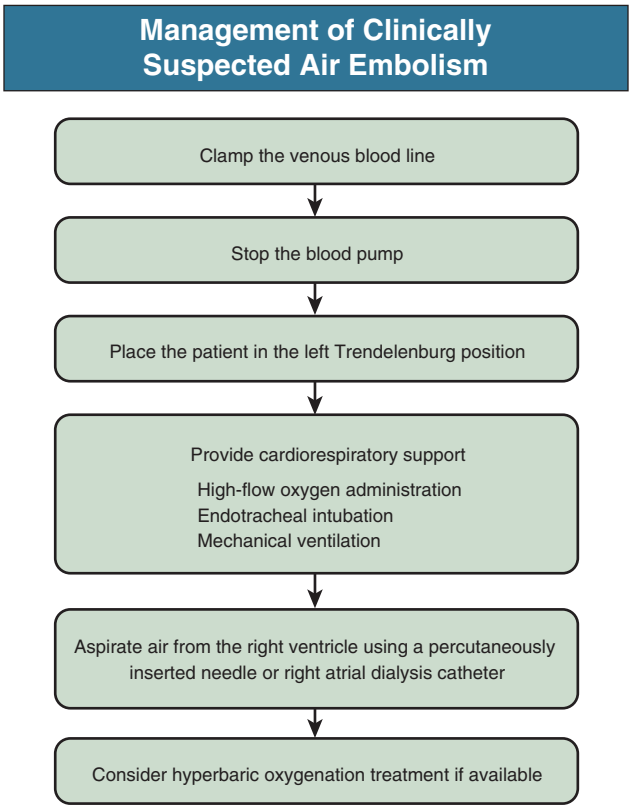

Figure 95-4 **Management of clinically suspected air embolism.**

Incorrect Dialysate Composition

Incorrect dialysate composition results from technical or human errors. Because the primary solutes constituting the dialysate are electrolytes, the dialysate concentration will be reflected by its electrical conductivity. Therefore, proper proportioning of concentrate to water can be achieved by the use of a meter that continuously measures the conductivity of the dialysate solution as it is being fed to the dialyzer. Life-threatening electrolyte and acid-base abnormalities are avoidable if the conductivity alarm is functioning properly and the alarm limits are set correctly. However, in dialysis machines that are equipped with conductivity-controlled mixing systems, the system automatically changes the mixing ratio of the concentrates until the dialysate solution conductivity falls within the set limits. This may inadvertently lead to dialysate without any bicarbonate, with apparently acceptable conductivity. Therefore, if conductivity-controlled systems are used, it is safer to also check the dialysate pH before dialysis. Conductivity monitors can fail or can be improperly adjusted by human error. Therefore, it is important to add human monitoring of dialysate composition before every treatment, whenever a machine has been sterilized or moved about, or whenever a new concentrate is used. Furthermore, many nonstandardized solutions are available, some of which may be used with an inappropriate proportioning system. Therefore, it is also essential that the supplies match the machine-proportioning ratio for which they were prepared for the appropriate final dialysate composition to be obtained. Double checking of concentrate variations (e.g., potassium and calcium concentration) should be practiced, as it is for intravenous drug administration.

Hypernatremia

Hypernatremia occurs when concentrate or the ratio of concentrate to water is incorrect and the conductivity monitors or the alarms are not functioning properly. Hyperosmolality results in intracellular water depletion. Clinical manifestations include thirst, headache, nausea, vomiting, seizures, coma, and death. Aggressive treatment is mandatory and includes cessation of dialysis, hospitalization, and infusion of 5% dextrose in water. Dialysis should be resumed with a different machine; the dialysate sodium level should be 2 mmol/l lower than the plasma level, and isotonic saline should be concurrently infused. Dialysis against a sodium level 3 to 5 mmol/l lower than the serum level may increase the risk of disequilibrium. Ultrafiltration with equal volume replacement with normal saline is another option.

Hyponatremia

Failure to add concentrate, inadequate concentrate-water ratio, or conductivity monitor or alarm malfunction can cause hyponatremia. Hyponatremia can also occur during the course of dialysis with a proportioning system if the concentrate container runs dry and the conductivity set limits are inappropriate. Acute hypo-osmolality causes hemolysis with hyperkalemia and hemodilution of all plasma constituents. Symptoms include restlessness, anxiety, pain in the vein injected with the hypotonic hemolyzed blood, chest pain, headache, nausea, and occasional severe abdominal or lumbar cramps. Pallor, vomiting, and seizures may be observed. Treatment consists of clamping the blood lines and discarding the hemolyzed blood in the extracorporeal circuit. High-flow oxygen and cardiac monitoring are

imperative because of hyperkalemia and potential myocardial injury. Dialysis should be restarted with a new dialysate batch containing low potassium, and high transmembrane pressure should be applied to remove excess water. Correction of serum sodium concentration should be achieved by no more than 1 to 2 mmol/l/h. Anticonvulsants are indicated for seizures and blood transfusions for severe anemia. Successful correction of severe hyponatremia has been reported in a single 3-hour HD session with a dialysate sodium concentration of 135 mmol/l without any adverse neurologic consequences despite a serum sodium correction rate of 3 mmol/l/h.[46] This suggests that elevated blood urea levels might protect uremic patients from the development of demyelinating syndromes when hyponatremia is rapidly corrected.

Metabolic Acidosis

Although acute intradialytic metabolic acidosis can be a manifestation of improper mixing of concentrates or failure of pH monitors, other causes need to be ruled out, including diabetic or alcoholic ketoacidosis, lactic acidosis, toxic ingestions, and dilutional acidosis.[47] The diagnosis is usually suggested by the acute onset of hyperventilation during HD and confirmed by laboratory evaluation. In most circumstances, correction of the underlying cause and use of bicarbonate dialysate at the appropriate concentration (32 to 35 mmol/l) are adequate measures.

Metabolic Alkalosis

Severe intradialytic metabolic alkalosis is rare and may be caused by error in dialysate concentrates, reversed connection of bicarbonate and acid concentrate containers to the entry ports of the dialysis machine, pH monitor malfunction, or use of regional citrate anticoagulation. The most common cause, however, is hydrochloric acid loss as a result of vomiting or nasogastric suction. Attention should also be directed to identification of sources of added alkali.[48] Furthermore, the combination of sodium polystyrene sulfonate and aluminum hydroxide can lead to absorption of alkali that is normally neutralized in the small intestine.

Acute treatment is rarely necessary unless a technical error has occurred. Removal of the alkali source is usually sufficient, and H_2 antagonists or proton pump inhibitors may be successful if there is gastric acid loss. The administration of sodium chloride to anephric patients with chloride-sensitive alkalosis will not repair the alkalosis. If a more rapid reduction in serum bicarbonate is desired, modification of the dialysate bath by replacement of alkali with chloride, substitution of bicarbonate with acetate dialysate, use of acid dialysate, and infusion of hydrochloric acid are effective but cumbersome measures. The use of conventional or low-bicarbonate (25 to 30 mmol/l) dialysate is probably as effective.

Temperature Monitor Malfunction

Malfunction of the thermostat in the dialysis machine can result in the production of excessively cool or hot dialysate. Whereas cool dialysate is not dangerous and may have beneficial hemodynamic effects (see discussion regarding intradialytic hypotension), overheated dialysate can cause immediate hemolysis and life-threatening hyperkalemia, particularly if the dialysate temperature increases to more than 51°C. In such an event, dialysis must be stopped immediately and blood in the system discarded. The patient should be monitored for hemolysis and hyperkalemia. Dialysis should be resumed to cool the patient by use of a dialysate temperature of 34°C to treat hyperkalemia and to allow blood transfusions if necessary. Visual and audible alarms are mandatory to prevent this complication.

Blood Loss

Intradialytic blood loss can result from arterial or venous needle disengagement from the access, separation of the venous or arterial line connections, femoral or central line dialysis catheter perforation or dislodgment, or rupture of a dialysis membrane with or without malfunction of the blood leak detector. Clinical findings include hypotension, loss of consciousness, and cardiac arrest. In addition, after traumatic insertion of a dialysis catheter, blood loss can result in pain or mass from a rapidly expanding hematoma; chest, shoulder, or neck pain from intrapericardial blood loss; back, flank, groin, or lower abdominal pain or distention from retroperitoneal bleeding; or hemoptysis from pulmonary bleeding. Acute management includes the discontinuation of HD, pressure application for local hemostasis, reversal of anticoagulation (e.g., protamine sulfate for heparin), hemodynamic support, oxygen administration, and surgical intervention if needed.

Clotting of Dialysis Circuit

Clotting of the extracorporeal circuit during dialysis is a common practical problem, has many underlying causes, and warrants a thorough investigation. Technical factors include an inadequate or poor priming technique, resulting in retention of air in the dialyzer, and lack of or inadequate priming of the heparin infusion line. Such operator-induced errors are corrected through ongoing staff education and competency assessment. Incorrect heparin loading dose, insufficient time lapse after loading dose of heparin for systemic anticoagulation to occur, incorrect pump setting for constant heparin infusion, delayed start of the heparin pump, and failure to release the heparin line clamp are important correctible causes of clotting that should also be considered. Low-molecular-weight heparin is often used as a single bolus at the commencement of dialysis but may not maintain anticoagulation for extended hours of treatment (e.g., nocturnal dialysis). Vascular access–related problems from inadequate blood flow caused by needle or catheter positioning or clotting, excessive access recirculation, and frequent interruption of blood flow resulting from inadequate delivery or machine alarm situations are additional causes that can result in clotting. Immediate management requires prompt recognition of the underlying cause and implementation of corrective actions, including ongoing heparin dose adjustment and, if indicated, vascular access revision.

DIALYSIS REACTIONS

During HD, blood is exposed to surface components of the extracorporeal circuit, including the dialyzer, tubing, sterilization processes, and other foreign substances related to the manufacturing and reprocessing procedures. This interaction between the patient's blood and the extracorporeal system can lead to various adverse reactions (Fig. 95-5).[49]

Anaphylactic and Anaphylactoid Reactions

Clinical Presentation

Anaphylaxis is the result of an IgE-mediated acute allergic reaction in a sensitized patient, whereas anaphylactoid reactions result from the direct release of mediators by host cells. The onset of symptoms usually occurs within the first 5 minutes of initiation of dialysis,

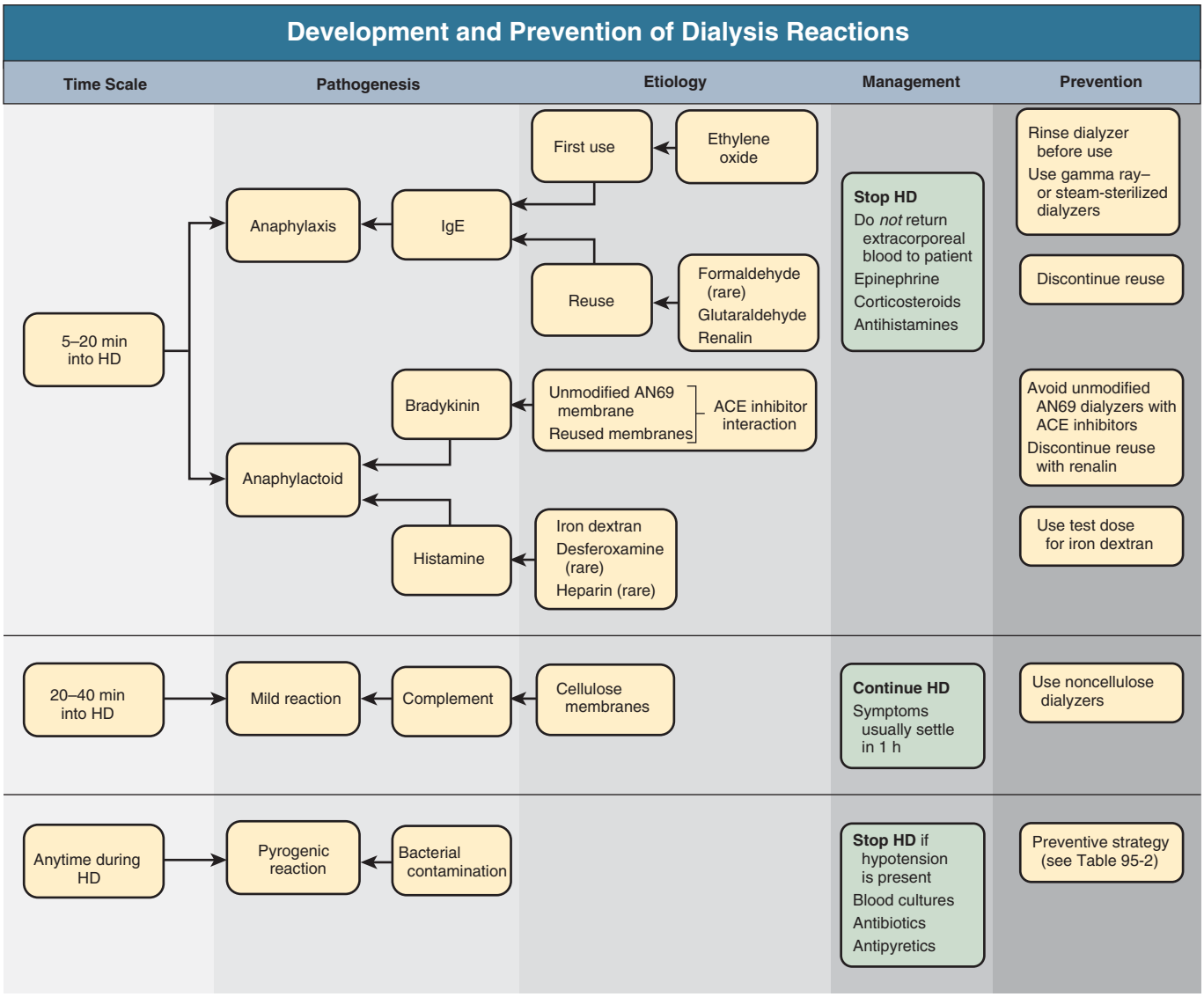

Figure 95-5 Development and prevention of dialysis reactions. *ACE,* Angiotensin-converting enzyme; *HD,* hemodialysis.

although a delay of up to 20 minutes is possible. Symptoms vary from subtle to severe and include burning or heat throughout the body or at the access site; dyspnea, chest tightness, and angioedema or laryngeal edema; paresthesias involving the fingers, toes, lips, or tongue; rhinorrhea, lacrimation, sneezing, or coughing; skin flushing; pruritus; nausea or vomiting; abdominal cramps; and diarrhea. Predisposing factors include a history of atopy, elevated total serum IgE, eosinophilia, and the use of ACE inhibitors. The etiology of dialysis reactions is diverse, and a thorough investigation is required.

First-Use Reactions

The majority of first-use reactions were ascribed to the manufacturer's dialyzer sterilant ethylene oxide (ETO), which is now rarely used. The potting compound that anchors the hollow fibers in the dialyzer housing acts as a reservoir for ETO and may impede its washout from the dialyzer, leading to sensitization. When it is conjugated to human serum albumin (HSA), ETO acts as an allergen. By use of a radioallergosorbent test (RAST), specific IgE antibodies against ETO-HSA are detected in two thirds of patients with such reactions. However, 10% of patients with no history of dialysis reactions have a positive RAST result.

Reuse Reactions

Because most residual ETO is washed out of the dialyzer during first use, reuse reactions are likely to be a result of the disinfectants used for dialyzer reprocessing. These agents include formaldehyde, glutaraldehyde, and peracetic acid–hydrogen peroxide (Renalin); in allergic patients, specific IgE antibodies against formaldehyde are occasionally detectable.

Bradykinin-Mediated Reactions

In the early 1990s, anaphylactoid reactions appeared in Europe among patients dialyzed with modified acrylonitrile (AN69) dialyzers who were also taking ACE inhibitors. Investigation of these incidents revealed that binding of factor XII to this sulfonate-containing, negatively charged membrane resulted in the formation of kallikrein and release of bradykinin, which in turn led to the production of prostaglandin and histamine, with subsequent vasodilation and

increased vascular permeability. ACE inactivates bradykinin, and therefore ACE inhibitors can prolong the biologic activities of bradykinin.[50] These membranes have since been chemically modified, thereby reducing this risk.

Anaphylactoid reactions have also been observed in patients taking ACE inhibitors who were dialyzed with membranes that had been reprocessed. Renalin was the sterilant used, and the reactions abated once reprocessing was discontinued, despite continued use of ACE inhibitors. It has been speculated that Renalin may oxidize cysteine-containing proteins that are adsorbed on the dialyzer membrane, leading to the formation of cysteine sulfonate and contact activation of factor XII.

Drug-Induced Reactions

Anaphylactoid reactions to parenteral iron dextran occur in 0.6% to 1% of HD patients. Significantly higher rates of anaphylactoid reactions have been observed among users of higher molecular weight compared with lower molecular weight iron dextran.[51] *In vitro,* dextran produces a dose-dependent basophil histamine release. In light of hypersensitivity reactions, the National Kidney Foundation's Clinical Practice Guidelines recommend that resuscitative medication and personnel trained to evaluate and to resuscitate anaphylaxis should be available whenever a dose of iron dextran is administered.[52] There are now alternative preparations of iron that provoke fewer anaphylactoid reactions than iron dextran. These are discussed further in Chapter 83.

Hypersensitivity to heparin formulations is rare and usually responds to substitution of beef with pork heparin, or vice versa. An alternative is to substitute low-molecular-weight heparin. A recent nationwide outbreak in the United States of severe adverse reactions in HD patients was attributed to vials of heparin contaminated with oversulfated chondroitin sulfate.[56]

Treatment and Prevention

Treatment of anaphylactic and anaphylactoid reaction requires the immediate cessation of HD without returning the extracorporeal blood to the patient. Epinephrine, antihistamines, corticosteroids, and respiratory support should be provided, if needed. Specific preventive measures include rinsing the dialyzer immediately before first use, substituting ETO- with gamma ray– or steam-sterilized dialyzers, avoiding unmodified AN69 membranes in patients taking ACE inhibitors, and discontinuing reprocessing procedures in selected patients.

Mild Reactions

Mild reactions particularly occur 20 to 40 minutes after initiation of dialysis, predominantly with unsubstituted cellulosic dialyzers, and consist of chest or back pain. Dialysis can be continued because symptoms usually abate after the first hour, suggesting a relation to the degree of complement activation. Indeed, these reactions decrease with the use of substituted and reprocessed unsubstituted cellulose membranes. Oxygen therapy and analgesics are usually sufficient. Preventive measures include automated cleansing of new dialyzers and use of noncellulose dialyzers.

Fever and Pyrogenic Reactions

Fever during dialysis can be the result of either a localized or a systemic infection or excessive microbial contamination of the dialysis apparatus. The latter, known as *pyrogenic reaction,* is usually a diagnosis of exclusion. Several factors during dialysis place patients at risk of exposure to bacterial products, including contaminated water or bicarbonate dialysate, improperly sterilized dialyzers, use of central venous dialysis catheters, and cannulation of infected arteriovenous grafts or fistulas.[49] Soluble bacterial products such as endotoxin fragments can diffuse across the dialyzer into the blood, resulting in cytokine production and, consequently, pyrogenic reactions. Whereas high-flux dialyzers have larger pores that may potentially allow larger fragments to cross from the dialysate to the patient, the synthetic high-flux membranes have a thick wall that tends to be very adsorptive for endotoxin fragments, thus mostly preventing this phenomenon.[57] Strategies for the prevention of pyrogenic reactions are summarized in Table 95-2.[58]

When fever develops during HD, the first step is to address hemodynamic stability. If the patient is hypotensive, administration of fluids, cessation of ultrafiltration, and discontinuation of dialysis are often required, and refractory hypotension suggesting severe sepsis should trigger hospitalization.

The next step is to identify a potential source of infection. The dialysis vascular access should be carefully examined. If a non–vascular access–related infectious source is identified, specific therapy should be instituted on the basis of the working diagnosis. Nontunneled and tunneled central venous dialysis catheters should always be suspected as a likely cause of infection, even in the absence

Strategies to Prevent Bacterial Contamination

Strict Adherence to AAMI Standards		
Type of Fluid	**Microbial Count**	**Endotoxin**
Water products	<200 cfu/ml	<2 EU
Dialysate	<200 cfu/ml	No standard
Reprocessed dialyzers	No growth	—
Use appropriate germicide: 4% formaldehyde* 1% formaldehyde heated to 40°C*† Glutaraldehyde† Hydrogen peroxide–peracetic acid mixture (Renalin)*† Heat sterilization (105°C for 20 hours) for reprocessing of polysulfone membranes†		
Wash and rinse the vascular access arm with soap and water.		
Before cannulation, inspect vascular access for local signs of inflammation.		
Scrub the skin with povidone-iodine or chlorhexidine and allow to dry for 5 minutes before cannulation.		
Record temperature before and after dialysis.		
When central delivery system is used: Clean and disinfect connecting pipes regularly. Remove residual bacteria or endotoxin by additional filtration.		
When single-patient proportioning dialysis machine is used: Freshly prepare bicarbonate dialysate on a daily basis. Discard unused solutions at the end of each day. Rinse and disinfect containers with fluids that meet AAMI standards. Air dry containers before dialysate preparation.		
Follow manufacturer's guidelines for use of preservative-free medications.		

Table 95-2 Strategies to prevent bacterial contamination. *AAMI,* Association for the Advancement of Medical Instrumentation; *cfu,* colony-forming units; *EU,* endotoxin units. *A minimum of 11- or 24-hour exposure to peracetic acid or formaldehyde is required, respectively. †These germicides are equivalent or superior to 4% formaldehyde. The action level for the total viable microbial count in the product water and conventional dialysate is 50 cfu/ml, and the action level for the endotoxin concentration is 50% of the relevant standard.

of local signs of infection such as erythema and exit site drainage. Catheters with evident signs of infection at the insertion site should be removed and the tip cultured.

Antipyretics should be administered and blood culture specimens should be obtained before initiation of antibiotic therapy; this should include cultures from temporary access devices. The initial choice of antibiotics should include gram-positive and gram-negative bacterial coverage, and the regimen should be adjusted according to the culture results.[59]

In the presence of a dialysis catheter, paired blood culture specimens should be obtained from both a peripheral vein and the catheter lumen, and the aforementioned broad-spectrum antibiotic regimen should be initiated. Catheter lock solutions that use either antibiotics or sterilants such as calcium citrate have been demonstrated to significantly reduce the rate of catheter-related bacteremia.[60-62] In the case of catheter-related bacteremia, removal of the dialysis catheter is strongly indicated, as is transesophageal echocardiography to rule out endocarditis, particularly with staphylococcal sepsis. A regimen of at least 14 days of antibiotic therapy is also recommended.[59]

An outbreak of bacteremia among several dialysis patients involving a similar organism should prompt a thorough search for bacterial contaminants in the dialysis equipment.[49] Attention should also be paid to single-use vials that are punctured several times, such as vials of EPO, which has been linked to an outbreak of bloodstream infection.[63]

Investigation of a Dialysis Outbreak

Although causes of dialysis outbreaks are usually easily identifiable, often the reason for the outbreak is less clear, such as water contamination with bacterial toxins,[64] medication chemical impurities,[56] bacterial contaminants,[63] systemic embolization of degraded dialyzer membrane polymer after prolonged or improper storage,[65] and hemolysis from faulty blood tube sets.[66] Investigation of a dialysis outbreak requires a methodical approach including a critical review of the medical records and the various steps of the dialysis procedure (Box 95-2).

Investigation of Dialysis Outbreak

Review of Medical Records
Demographics
Underlying diseases
Dialysis schedule
Dialysis machine
Dialyzer used
- Membrane
- Type
- Manufacturer's sterilization method
- Reuse germicide (if applicable)

Medication history
Signs and symptoms of illness
Laboratory tests
Interview of medical staff caring for patient during incident

Procedural Review
Water treatment systems and practices
- Disinfection
- Distribution
- Storage procedures

Disinfection and maintenance of reprocessed dialyzers
Disinfection and maintenance of dialysis machines
Review of patient's dialysis sessions

Box 95-2 Investigation of a dialysis outbreak.

MISCELLANEOUS COMPLICATIONS

Postdialysis Fatigue

An ill-defined "washed out" feeling or malaise during or after HD is a common nonspecific symptom that is observed in about one third of patients[67] and has multifactorial origins. Reduced cardiac output, peripheral vascular disease, depression, poor conditioning, postdialysis hypotension, hypokalemia or hypoglycemia, mild uremic encephalopathy, myopathy caused by carnitine deficiency, and membrane bioincompatibility through cytokine production have all been incriminated. The use of bicarbonate dialysate with or without additional glucose (5 to 10 mmol/l) and L-carnitine supplementation (20 mg/kg/day) have been shown to improve postdialysis well-being. A trial of thrice-weekly L-carnitine at 20 mg/kg for 6 months resulted in a marked decrease in C-reactive protein level, which was paralleled by an increase in body mass index.[68] To date, however, there are insufficient data to support the use of L-carnitine to improve quality of life in unselected dialysis patients.[52]

Compared with thrice-weekly HD, more frequent dialysis, including short daily and nocturnal HD, has been associated with a marked shortening in the time it takes for patients to recover from a dialysis session and to resume their daily activities, which is a surrogate for postdialysis fatigue.[69]

Pruritus

Pruritus is common. The etiology is often multifactorial, including xerosis, hyperparathyroidism, neuropathy, derangements in the immune system, and inadequate dialysis. In many patients, pruritus is more severe during or after dialysis and may be a manifestation of an allergic reaction to heparin, ETO, formaldehyde, acetate, or the dialysis membrane. In this subgroup of patients, use of gamma ray–sterilized dialyzers, discontinuation of formaldehyde use, switching to bicarbonate dialysate, and use of low dialysate calcium and magnesium might result in cessation of itching. Eczematous reactions to antiseptic solutions, rubber gloves or puncture needle components, puncture needles, or adhesive tapes used to secure dialysis needles should also be considered.[70]

The management of uremic pruritus is discussed further in Chapter 88 (see Fig. 88-3).

Genitourinary Problems

Priapism occurs in less than 0.5% of male HD patients. It is not related to sexual activity and occurs while the patient is on dialysis. The patient is usually awakened from sleep by a painful erection. Although the majority of cases are idiopathic, secondary causes include heparin-induced hyperviscosity; high hematocrit from androgen or epoetin therapy; dialysis-induced hypoxemia and hypovolemia from excessive ultrafiltration, particularly in African American men with sickle cell disease; and use of α-blockers, such as prazosin, or an antidepressant, such as trazodone.[71]

Urgent urologic referral is mandatory. Acute treatment consists of corporal aspiration and irrigation. Although surgical bypass provides venous egress from the corpora cavernosa, secondary impotence commonly develops but may be effectively treated by a penile prosthesis.

An unusual case of testicular angina occurring during excessive ultrafiltration has also been described. The patient was diabetic and had extensive vascular calcification evident on imaging. He eventually required orchidectomy.[72] A similar mechanism for this type of "angina" has also been described for the mesentery and right colon.

Hearing and Visual Loss

Intradialytic hearing loss may be caused by bleeding in the inner ear as a consequence of anticoagulation or cochlear hair cell injury from edema.

Intradialytic visual loss is rare but can be caused by central retinal vein occlusion, retinal hemorrhage secondary to heparin exposure in diabetics, precipitation of acute glaucoma, ischemic optic neuropathy secondary to hypotension, or Purtscher-like retinopathy secondary to leukocyte embolization.

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CHAPTER 96

Peritoneal Dialysis: Principles, Techniques, and Adequacy

Bengt Rippe

Peritoneal dialysis (PD) is presently used by approximately 180,000 end-stage renal disease (ESRD) patients worldwide, representing approximately 7% of the total dialysis population.[1] In PD the peritoneal cavity, which is the largest serosal space in the body, is used as a container for 2 to 2.5 L of sterile, usually glucose-containing dialysis fluid, which is exchanged four to five times daily via a permanently indwelling catheter. The dialysis fluid is provided in plastic bags. The peritoneal membrane, via the peritoneal capillaries, acts as an endogenous dialyzing membrane. Across this membrane waste products diffuse to the dialysate, and excess body fluid is removed by osmosis induced by the glucose or another osmotic agent in the dialysis fluid, usually denoted *ultrafiltration* (UF). PD is usually provided 24 h/day and 7 days/wk in the form of continuous ambulatory peritoneal dialysis (CAPD). Approximately one third of the patients in most centers are on automated peritoneal dialysis (APD; sometimes also referred to as continuous cycling peritoneal dialysis [CCPD]), in which nightly exchanges are delivered via an automatic PD-cycler. The use of PD as a modality for ESRD treatment varies widely among countries, mostly because of nonmedical factors such as the reimbursement policy. One study reported that 81% of all dialysis patients in Hong Kong were treated with CAPD or APD in 2006, followed by Mexico (71%) and New Zealand (39%), whereas in the United States, PD was used by only 7.5%, and in Germany by 4.8%.

ADVANTAGES AND LIMITATIONS OF PERITONEAL DIALYSIS

If patients or their care givers are competent to undertake PD, the only absolute contraindications are large diaphragmatic defects, excessive peritoneal adhesions, surgically uncorrectable abdominal hernias, or acute ischemic or infectious bowel disease. These and other relative contraindications are discussed further in Chapter 97. PD is best used for patients with some residual renal function, although anuric patients may also do very well. Most patients who start PD will eventually, after several years, transfer to other modalities of renal replacement therapy (RRT), such as hemodialysis (HD), if adequacy cannot be maintained or as a result of other complications, such as recurrent peritonitis or exit site or catheter problems. Only rarely do HD patients transfer to PD, most commonly because of failure to maintain adequate vascular access for HD.

Peritoneal dialysis offers a number of advantages over HD, at least during the first 2 or 3 years of treatment. First, PD represents a slow, continuous, physiologic mode of removal of small solutes and of excess body water, associated with relatively stable blood chemistry and body hydration status. Second, there is no need for vascular access. The absence of vascular access and the absence of the blood-membrane contact of HD make catabolic stimuli less prominent in PD than in HD. Furthermore, residual renal function is somewhat better preserved in PD patients than in HD patients. Because of its continuous nature, PD provides a standardized weekly *Kt/V* similar to that of thrice-weekly HD despite less efficient small-solute clearance.

Peritoneal dialysis is a home-based therapy, and most patients are trained to do the bag exchanges themselves. In general, home dialysis patients have a better quality of life than those on other types of dialysis. The number of hospital visits is reduced, and the ability to travel is increased. There is also some evidence that PD patients may be better candidates for transplantation than HD patients; several studies have shown a lower incidence and severity of delayed graft function in PD patients after transplantation.[2] In children, PD (usually APD) is the preferred dialysis modality because it is noninvasive and socially acceptable, reducing hospital visits and allowing the child to attend school. Advocates of PD often recommend that RRT should ideally begin with PD according to the patient's choice and then proceed, as required when residual renal function declines, to HD or transplantation. PD should thus be regarded as part of an integrated RRT program, together with HD and transplantation.[3] Factors influencing the choice of dialysis modality between PD and HD as well as global variations in the use of PD are discussed further in Chapter 90.

PRINCIPLES OF PERITONEAL DIALYSIS

Three-Pore Model

The major principles governing solute and fluid transport across the peritoneal membrane are diffusion, driven by concentration gradients, and convection (filtration or UF), driven by osmotic or hydrostatic pressure gradients. The barrier separating the plasma in the peritoneal capillaries from the fluid in the peritoneal cavity is represented by the capillary wall and the interstitium. The interstitium can be regarded as a barrier coupled in series with that of the capillary wall; the mesothelium lining the peritoneal cavity is of much less significance as a transport hindrance. For the transport of fluid (UF) and of large solutes, the capillary wall is by far the dominating transport barrier. However, for small-solute diffusion the interstitium accounts for approximately one third of the transport (diffusion) resistance. The permeability of the capillary wall can be described by a three-pore model of membrane transport (Fig. 96-1).[4,5] In the capillary wall the major route for small-solute and fluid exchange between the plasma and the peritoneal cavity is the space between individual endothelial cells, the so-called interendothelial clefts. The functional radius of the permeable pathways in these clefts, denoted *small pores,* is 40 to 50 Å, slightly larger than the radius of albumin (36 Å). The size of these pores markedly impedes the transit of albumin and completely prevents the passage of larger molecules

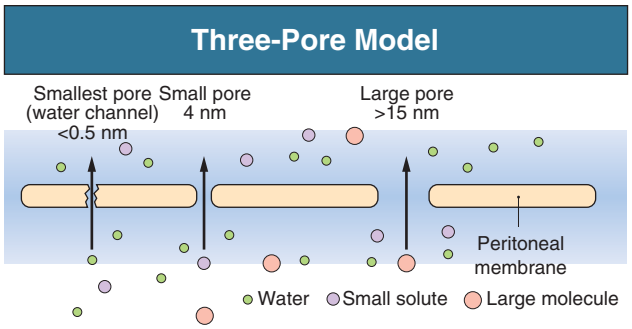


Figure 96-1 Three-pore model. The small pores in the middle represent the major pathway across the peritoneum through which small solutes move by diffusion and water by convection driven by hydrostatic, colloid osmotic, and crystalloid osmotic pressure differences. Across large pores *(to the right),* macromolecules move out slowly by convection from plasma to the peritoneal cavity. The smallest pores *(to the left)* are represented by aquaporins permeable to water, but impermeable to solutes. Water moves here exclusively by crystalloid osmotic pressure.

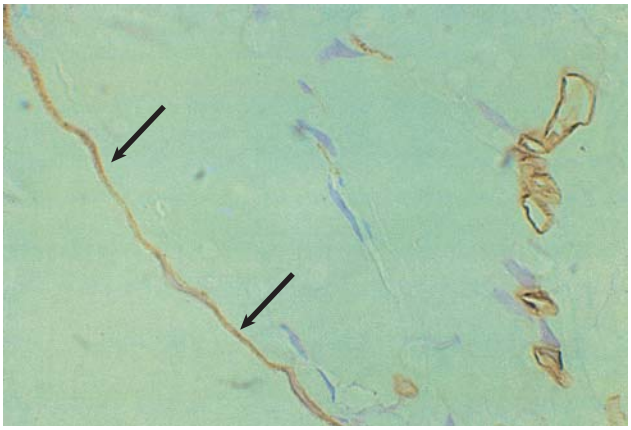
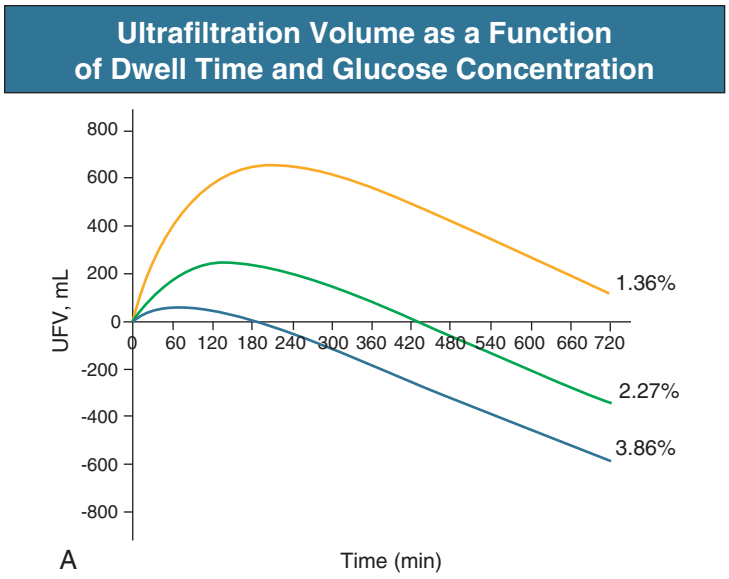


Figure 96-2 Light microscopic section of a peritoneal membrane with capillaries and venules *(to the right)* in an "amorphous" interstitium. The peritoneum is lined by a thin layer of mesothelium *(to the left).* Capillaries and venules, as well as the mesothelium, are immunocytochemically stained for aquaporin-1 (AQP-1) *(brownish in color). (From reference 55.)*

(e.g., immunoglobulins and α_2-macroglobulin). However, larger proteins can transit via very rare large pores (radius approximately 250 Å) in capillaries and postcapillary venules. The large pores constitute only 0.01% of the total number of capillary pores, and the transport across them occurs by hydrostatic pressure–driven unidirectional filtration from the plasma to the peritoneal cavity. In addition, the capillary wall has a high permeability to osmotic water transport via aquaporin-1 (AQP-1) channels in the endothelial cell membranes (Fig. 96-2).[6]

Fluid Kinetics

Under normal (non-PD) conditions most transport occurs via the small pores. Only 2% of peritoneal water transport occurs via AQP-1. In PD, fluid removal is markedly enhanced by infusion of a hyperosmolar dialysate into the peritoneal cavity. The type of osmotic agent used markedly affects the mechanism of osmosis. Glucose will induce fluid flow through both AQP-1 (approximately 45%) and small pores (approximately 55%), whereas large molecules, such as polyglucose (icodextrin) will remove fluid mainly via small pores (approximately 90%). Thus glucose osmosis will result in a rapid



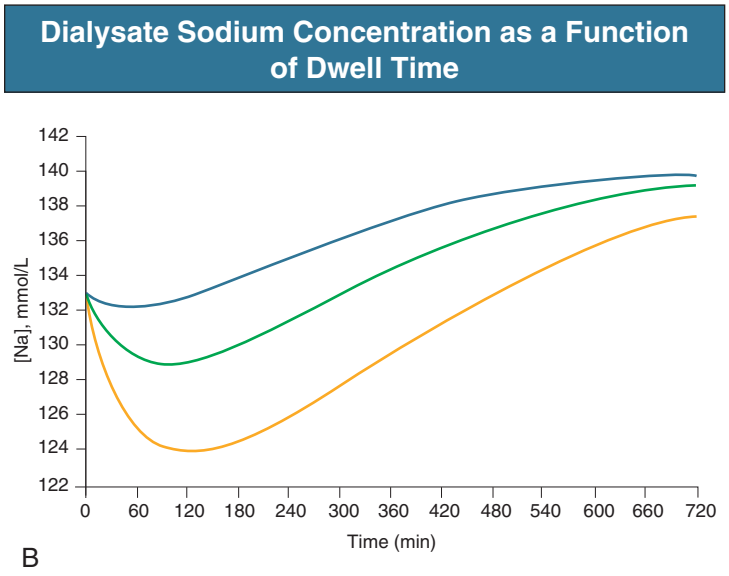


Figure 96-3 A, Ultrafiltration as a function of dwell time. Net ultrafiltration volume *(UFV)* as a function of dwell time for 3.86% *(yellow line),* 2.27% *(green line),* and 1.36% *(blue line)* glucose, computer simulated using the three-pore model of peritoneal transport. **B, Dialysate sodium as a function of dwell time.** Dialysate sodium as a function of dwell time for 3.86% *(yellow line),* 2.27% *(green line),* and 1.36% *(blue line)* glucose, computer simulated according using the three-pore model of peritoneal transport.

dilution of the peritoneal dialysate, as reflected by a fall in sodium concentration *(sodium sieving)* during the first 2 hours of the dialysate dwell, caused by relatively large transport via the water-only AQP-1 channels; this tends to correct later as diffusion across the small pores eventually increases the sodium concentration to that in the plasma.

Glucose, the commonly used osmotic agent, is usually available at three concentrations: 1.36%, 2.27%, and 3.86%. Figure 96-3, *A*, demonstrates the intraperitoneal fluid kinetics, computer simulated using the three-pore model, over 12 hours of dwell time with these three solutions. Glucose is an intermediate-size osmolyte with a low osmotic efficiency (osmotic reflection coefficient [σ] = 0.03) across small pores, whereas glucose is 100% efficient as an osmotic agent across AQP-1 (σ = 1). For that reason, glucose will markedly (30-fold) boost the transport of fluid through AQPs and thus redistribute

fluid transport away from the small pores toward AQP-1, resulting in significant sodium sieving. For example, for 3.86% glucose in the PD solution, the dialysate Na^+ concentration will drop from 132 mmol/l to 123 mmol/l in 60 to 100 min, which later increases toward serum Na^+ concentration (Fig. 96-3, *B*). On the other hand, icodextrin, with an average molecular weight of 17 kd, has a high osmotic efficiency (σ approximately 0.5) across small pores and in relative terms is rather inefficient across AQPs. Hence, during icodextrin-induced osmosis only a very minor fraction of the UF will occur through AQP-1, producing insignificant sodium sieving (see Fig. 96-7, *B*).

In addition to the size of the osmotic agent, the degree of sodium sieving is dependent on the presence and quantity of AQP-1, and also on the total rate of net UF (which is mainly determined by the glucose concentration), and the diffusion capacity of Na^+. A high rate of small-solute transport, and thereby of sodium diffusion, in so-called fast transporters will manifest as rapid equilibration of small solutes (creatinine and glucose) in the peritoneal equilibration test (PET; see later) and will also reduce sodium sieving.

In the absence of an osmotic agent in the PD fluid, the dialysate would be reabsorbed into the plasma within a few hours, mainly driven by the difference in colloid osmotic pressure between plasma and the peritoneum. This absorption will to a major extent occur via small pores, whereas approximately 30% of the peritoneal fluid will be removed by lymphatic absorption. The partial fluid flows in the peritoneal membrane modeled across different fluid conductive pathways in the three-pore model (for 3.86% glucose) are shown in Figure 96-4. It is the presence of relatively high concentrations of glucose in the peritoneal fluid that prevents the reabsorption of fluid into the plasma during the first few hours of the dwell.

Patients who have a high rate of sodium diffusion (fast transporters) also have rapid transport of glucose out of the peritoneal cavity. Therefore the glucose gradient favoring UF dissipates more rapidly, and it is harder to achieve effective fluid removal compared with "slow transporters." In fast transporters the maximum UF volume is reduced and UF occurs earlier. There is usually also a more rapid reabsorption of fluid in the late phase of the dwell. The issue of fluid loss from the peritoneum is, however, very controversial, because some authors claim that the peritoneal fluid loss occurring in the late phase of the PD dwell is dominated by lymphatic absorption.[7]

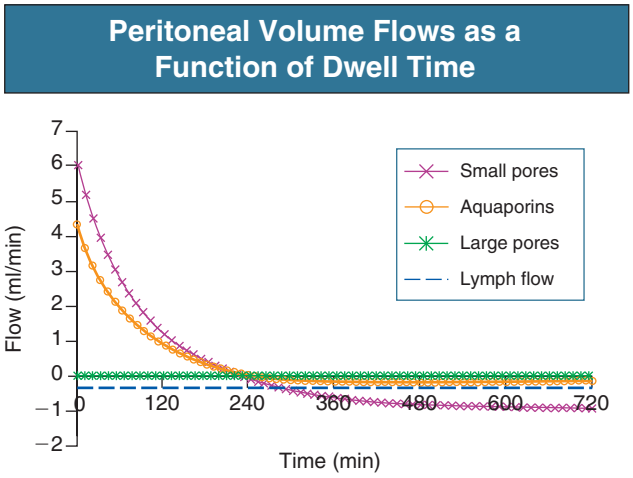


Figure 96-4 Peritoneal volume flows as a function of dwell time. Peritoneal volume flows as a function of dwell time for 3.86% glucose partitioned among aquaporins, small pores, large pores, and lymphatic absorption. The small-pore volume flow is initially approximately 60% of total volume flow and becomes negative after peak time (220 min). The aquaporin-mediated water flow becomes slightly negative after approximately 250 min. The large-pore volume flow is negligible and remains constant throughout the dwell, as does lymphatic absorption (0.3 ml/min). *(Modified from reference 56.)*

Effective Peritoneal (Vascular) Surface Area

The functional surface area of the peritoneum reflects the effective surface area of the peritoneal capillaries.[8] The transport of small solutes, such as urea, creatinine and glucose, is partly limited by the degree of perfusion of these capillaries—the effective peritoneal membrane blood flow. Furthermore, as mentioned earlier, some of the diffusion resistance for the smallest solutes (urea and creatinine) is located in the interstitium. The number of effectively perfused capillaries is increased by arteriolar vasodilation and reduced by vasoconstriction. These alterations often occur without large changes in the fluid permeability (hydraulic conductance [L_pS]) of the peritoneum. Thus, during vasodilation or vasoconstriction there is usually a dissociation between changes in the permeability–surface area product (PS) for small solutes and in the L_pS of the membrane. Vasodilation, with recruitment of capillary surface area, occurs early in the dwell when glucose is used as the osmotic agent, causing early, transient increases in PS.[9]

Peritonitis is also associated with marked vasodilation, again leading to increases in small-solute PS, in the absence of large changes in L_pS, during the first 60 to 100 minutes of the dwell. However, in some patients with peritonitis, an increase in L_pS will result in relative increased fluid transport across the small pores. Furthermore, there is usually an opening of large pores in the capillaries (and postcapillary venules), resulting in enhanced leakage of macromolecules (e.g., albumin and immunoglobulins) from plasma to peritoneum. Peritonitis may thus result in relative difficulty in removing fluid (because of rapid dissipation of intraperitoneal glucose), a reduced sodium sieving (because of the reduced UF and increased Na^+ diffusion), and a markedly increased leakage of proteins to the dialysate.

The contact area between the dialysate and the peritoneal tissue varies as a result of posture and fill volume. Adult patients usually tolerate 2 to 2.5 liters of instilled volume. An intraperitoneal hydrostatic pressure (IPP) of less than 18 cm H_2O (supine position) is usually tolerated.[10] At higher pressures (>18 cm H_2O) the patient usually feels some discomfort. At intraperitoneal volumes of less than 2 liters there is a reduction in small-solute PS, whereas PS is only moderately increased at high fill volumes. Overall, an increased fill volume implies a more efficient exchange with regard to both small-solute exchange and UF, the latter being much more pronounced for hypertonic solutions.[11] For a long time it was thought that increased fill volumes would directly affect peritoneal fluid reabsorption by the hydrostatic pressure effect (increases in IPP). However, because 80% of any increase in IPP is transmitted via vein compression back to the capillaries, the actual changes in the transcapillary hydrostatic pressure gradient, which governs UF, will be rather small.[12] Thus the impact of IPP on fluid absorption is moderate.[13]

PERITONEAL ACCESS

The key to successful chronic PD is a safe and permanent access to the peritoneal cavity (Fig. 96-5). Despite improvements in catheter survival over the past few years, catheter-related complications still occur, causing significant morbidity and sometimes forcing the removal of the catheter. Catheter-related problems are a cause of permanent transfer to HD in up to 20% of all patients. Most catheters

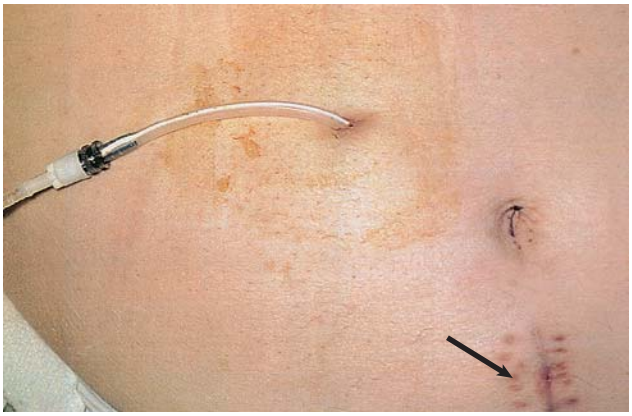


Figure 96-5 A recently implanted peritoneal dialysis catheter *in situ*. Note the subumbilical midline scar where the catheter enters the peritoneal cavity *(arrow)*.

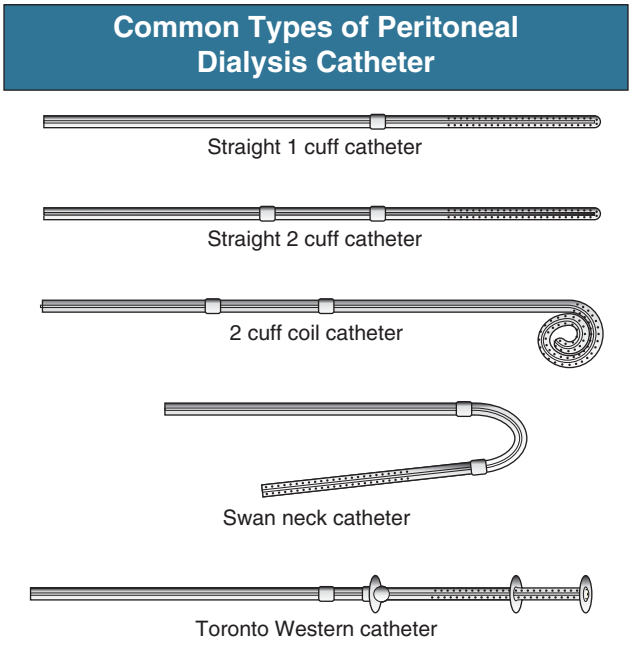


Figure 96-6 Common types of peritoneal dialysis catheter.

are derived from that originally devised by Tenckhoff and Schechter.[14] The Tenckhoff catheter is a Silastic tube with side holes along its intraperitoneal portion. There are usually one or two Dacron cuffs, allowing tissue ingrowth, which secures the catheter in place and prevents pericatheter leakage and infection. The Tenckhoff catheter is straight, having one cuff lying on the peritoneum with the catheter tip pointing in the caudal direction; the outer cuff is close to the skin exit. Several centimeters of the catheter is thus located transcutaneously. Intraperitoneal and transcutaneous catheter modifications continue to appear, indicating that no single design is perfect (Fig. 96-6). Although a number of studies report less frequent catheter drainage failures with use of the arcuate "swan neck" catheter (see Fig. 96-6) compared with straight catheters, there is no hard evidence that any of the modified catheters on the market are actually superior to the original (one- or two-cuff) Tenckhoff catheter.[15]

Ideally, catheter insertion should be undertaken under operating room sterile conditions by an experienced operator, either a surgeon or a nephrologist trained in interventional nephrology techniques. Presurgical assessment for the presence of herniation or any weakness of the abdominal wall is essential. If present, it may be possible to correct these at the time of catheter insertion. Before the operation, eradication of nasal carriage of *Staphylococcus aureus* with locally applied antibacterials (such as mupirocin) significantly reduces exit site infection rates. A single preoperative intravenous dose of a first- or second-generation cephalosporin is also recommended. To avoid development of vancomycin-resistant enterococcus, vancomycin should not be used as a prophylactic agent. Several placement techniques have been described and practiced: surgical mini-laparotomy and dissection, blind placement using the Tenckhoff trocar, blind placement using a guidewire (Seldinger technique), mini-trocar peritoneoscopy placement, and laparoscopy. These techniques are discussed further in Chapter 92.

TECHNIQUES OF PERITONEAL DIALYSIS

In CAPD, 2 to 2.5 liters of dialysis fluid is instilled into the peritoneal cavity four or five times daily. In 4 to 5 hours there is 95% equilibration of urea and approximately 65% equilibration of creatinine, whereas the glucose gradient has dissipated to approximately 40% of the initial value. For glucose as an osmotic agent, 4 to 5 hours is a suitable dwell time. For night dwell exchanges, longer dwell times can be accepted (8 to 10 hours), although this increases the quantity of glucose and therefore calorie absorption. Furthermore, there is room for individual exchange schedules that can be adjusted to suit individual patient convenience. Dwell times shorter than 4 to 5 hours can be performed with use of a machine (cycler). This technique can be used to maintain adequate dialysis when more frequent lower-volume exchanges are needed—for example, to minimize leakage in conjunction with catheter insertion, hernia repair, or abdominal operations. Rapid exchanges may also be required during treatment for peritonitis, or in patients with fluid overload when the patient's hydration status needs to be corrected rapidly.

Today, double-bag systems (so-called Y systems) are in general use according to the principle "flush before fill." The double-bag system contains the unused dialysis fluid connected to an empty sterile drain bag via a Y-set tubing system. After the patient has connected the system and flushed the connection (for 2 to 3 seconds), a frangible (breakable) pin to the drain bag is opened, and the peritoneal cavity is drained over 10 to 15 minutes to fill the drain bag. Then this bag is clamped and the fresh bag opened, so as to fill the peritoneal cavity over another 10 to 15 minutes. The time for exchange (instillation and drainage), if the catheter is in good order, should not exceed a total of 30 minutes. Usually the first 1.6 to 1.8 liters will drain rapidly (at ≥200 ml/min), whereas the last 200 to 300 ml will drain much more slowly. The breakpoint between the rapid and the slow phase may vary markedly from individual to individual.

Automated peritoneal dialysis is usually performed with use of a cycler overnight (8 to 10 hours), during which large volumes (10 to 20 liters) can be exchanged. During the daytime the APD patient usually has a so-called wet day—that is, a long dwell, usually with icodextrin as the osmotic agent in the dialysis fluid. Some patients with nightly APD perform one daily exchange so that there are two long (6- to 8-hour) daily dwells. Most cyclers can be programmed to vary inflow volume, inflow time, dwell time, and drain time. Cyclers usually warm the fluid before inflow, and they also monitor outflow volume and the excess drainage (UF volume). Current APD machines have alarms for inflow failure, overheating, and poor drainage. Some cyclers interrupt drainage at the breakpoint between the fast and slow phases to make the exchange more efficient. Another way to

accelerate exchanges is to allow a considerable sump volume in the peritoneal cavity by not letting all the fluid drain; subsequent inflow volumes are proportionally reduced, and after a number of cycles complete drainage occurs. This technique is called *tidal peritoneal dialysis* (TPD).

The exchange volume should be adjusted according to the patient's size. Adult patients weighing less than 60 kg should start with 1.5-liter bags. The average patient (60 to 80 kg) should receive 2-liter exchanges, and for patients weighing more than 80 kg, 2.5 liters should be used. If pressure monitoring systems are available, the IPP may inform the choice of exchange volume. In the supine position most patients have an IPP of 12 cm H_2O.

PERITONEAL DIALYSIS FLUIDS

The majority of PD fluids used today have the composition of a lactate-buffered, balanced salt solution devoid of potassium, with glucose (1.36%, 2.27%, or 3.86%) as the osmotic agent. The K^+ concentration in current PD fluids is zero to aid control of potassium balance.

Lactate is used as a buffer instead of bicarbonate, because bicarbonate and Ca^{2+} may precipitate (to form calcium carbonate) during storage. With the advent of newer multichambered PD delivery systems, it is possible to replace lactate with bicarbonate and to make a number of other solution modifications that previously were not feasible. However, the higher cost of a number of the newer more physiologic fluid formulations should be borne in mind.

Electrolyte Concentration

In current PD fluids the concentrations of Na^+, Cl^-, Ca^{2+}, and Mg^{2+} are selected to be close to the serum concentration. The removal of these ions across the peritoneum is therefore a result of the low diffusion gradient, more or less completely dependent on convection. For every deciliter of fluid removed in a 4-hour dwell, approximately 10 mmol of Na^+[16] and 0.1 mmol of Ca^{2+} are removed, provided that serum Na^+ and Ca^{2+} are within the reference ranges.[12]

The frequent use of calcium-containing phosphate binders requires an understanding of Ca^{2+} kinetics for various types of dialysis fluids to avoid hypercalcemia. The calcium concentration of current PD solutions is usually 1.25 to 1.75 mmol/l. However, because Ca^{2+}, like Na^+ and Mg^{2+}, has a UF-dominated transport, 1.25 mmol/l may be considered appropriate only for 1.36% glucose, to achieve a zero (neutral) peritoneal calcium removal. To reach the same objective for 3.86% glucose, the dialysis fluid Ca^{2+} would have to be increased to 2.3 mmol/l to prevent (UF-driven) Ca^{2+} loss during a 4-hour dwell. With use of a three-compartment system for the PD bags, it would be possible to adapt the dialysis fluid Ca^{2+} concentration to obtain net zero peritoneal Ca^{2+} transport across the peritoneum, or to reach a preset calcium removal target, for each PD fluid glucose concentration used.[17] However, in currently available PD solutions, Ca^{2+} concentration is not variable as a function of glucose concentration; therefore 1.25 mmol/l Ca^{2+} is recommended when patients use calcium-containing phosphate binders. However, it should be noted that net peritoneal calcium removal with 1.25 mmol/l Ca^{2+} level can be achieved only by PD fluids containing 2.27% or 3.86% glucose.

The Mg^{2+} concentration commonly used in current PD solutions is 0.25 to 0.75 mmol/l. For 1.36% glucose, 0.25 mmol/l would be appropriate for zero Mg^{2+} transport during the dwell, whereas for higher dialysis fluid glucose concentrations there will be net Mg^{2+} losses.

Osmotic Agents

Glucose is the principal osmotic agent used for fluid removal (UF) in PD. Alternative commercially available osmotic agents are amino acids and icodextrin. Icodextrin is a polydisperse glucose polymer with an average molecular weight of 17 kd.[18] However, because of the polydispersity of icodextrin, approximately 70% of the molecules have a molecular weight of 3 kd or less.[11] Icodextrin is available as a 7.5% solution with essentially the same electrolyte composition as glucose-based dialysates. The osmolality of the glucose polymer solution, unlike that of 1.36% glucose (osmolality 350 mOsm/kg) dialysis fluid, is within the same range, or actually slightly lower, than that of normal serum. The presence of larger molecules in the icodextrin solution, compared with those in glucose-based solutions, improves the osmotic efficiency markedly across the small pores ($\sigma = 0.5$) and also reduces the dissipation of the osmotic gradient over time. This yields a sustained UF over 8 to 12 hours (Fig. 96-7, *A*). Therefore, icodextrin is preferably used for long dwell exchanges, for example, overnight, and particularly for patients who tend to absorb glucose rapidly (fast transporters, see later). Icodextrin is slowly absorbed into serum and degraded (circulating α-amylase) to oligosaccharides, such as maltose, which may give false-positive results for glucose, leading to erroneous measures of hyperglycemia and to inappropriate use of glucose-lowering agents.[19]

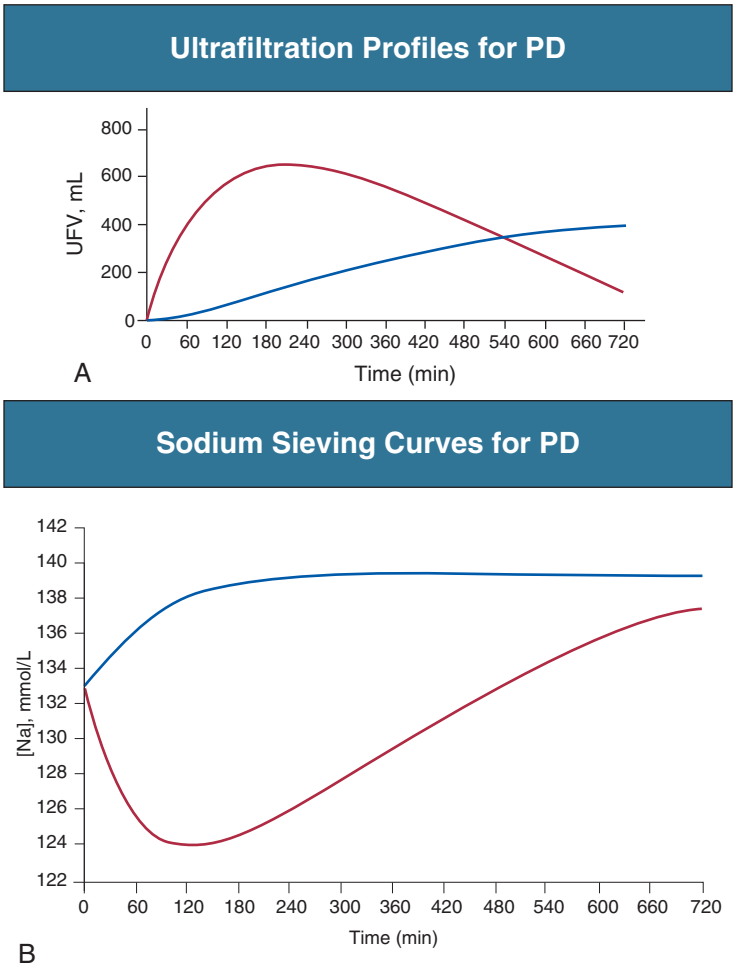


Figure 96-7 A, Ultrafiltration (UF) profiles for peritoneal dialysis *(PD).* Ultrafiltration profile for 7.5% icodextrin *(blue line),* computer simulated according to the three-pore model in an average patient who is not naive to icodextrin, in comparison with the computer simulated UF curve for 3.86% glucose *(red line). UFV,* ultrafiltration volume. **B, Sodium sieving curves for PD.** Sodium-sieving curves for 7.5% icodextrin *(blue line)* and 3.86% glucose *(red line)* (see Fig. 96-3). *Na,* sodium. *(A from reference 11.)*

Another alternative osmotic agent that is commercially available is a 1.1% amino acid mixture having the same osmolality as 1.36% glucose.[20] According to some studies, regular use of this dialysate may increase certain nutritional indices, although there is also some evidence that amino acid solutions increase acidosis and raise plasma urea. Both icodextrin-based and amino acid–based solutions may be used to reduce the glucose exposure of the peritoneal membrane and the total glucose load to the patient.

Until recently, conventional PD solutions have had a low pH and a high concentration of glucose degradation products (GDPs). GDPs are reactive carbonyl compounds that form during heat sterilization and/or storage of glucose-based solutions. GDPs are toxic to a variety of cells *in vitro* and also potentially toxic *in vivo*.[21] By the use of multicompartment systems it has been possible to compose new solutions with much lower concentrations of GDPs and a neutral pH, and also to use bicarbonate or bicarbonate-lactate mixtures as buffers.[22-24] Solutions using bicarbonate or bicarbonate-lactate mixtures result in significantly less infusion pain and are as effective as lactate at correcting acidosis, when used at the same total buffer ion concentration.[25] In prospective, randomized studies these fluids have been associated with improvement in dialysate effluent markers of peritoneal membrane integrity, particularly cancer antigen 125 (CA-125), a measure of peritoneal mesothelial cell mass.[22-24] There have also been some indications of improved residual renal function in patients with PD solutions low in GDPs,[24] although this was not confirmed in recent prospective, randomized studies.[26,27] One of those studies, however, the balANZ study,[27] suggested that biocompatible PD solutions may delay the onset of anuria and reduce the incidence of peritonitis compared with conventional solutions.

Pyruvate is an alternative buffer to lactate (or bicarbonate) but is not yet clinically available. Finally, certain additives may help to preserve the peritoneal membrane, such as *N*-acetylglucosamine (NAG), hyaluronic acid (HA), citrate, and low-molecular-weight heparin (LMWH). LMWH, 4500 IU in every morning bag daily for 3 months, increased UF as a result of reduced glucose reabsorption during the dwell.[28] This effect was, however, not found in a subsequent randomized open multicenter study of the addition of daily self-administration of LMVH (3500 IU) to the long daily icodextrin-based dwell.[29] Conceivably, if LMVH actually increases UF, this action may be a result of reduction of the initial vasodilation that regularly occurs with intraperitoneal instillation of glucose-based PD solutions.[28] HA seems to reduce the reabsorption of fluid that occurs in the late phase of the dwell, possibly by producing a "filter cake" at the peritoneal surface.[30] None of the mentioned additives (NAG, HA, or LMWH) or buffers (pyruvate, citrate) can yet be recommended in routine clinical practice, and further trial data are awaited.

ASSESSMENTS OF PERITONEAL SOLUTE TRANSPORT AND ULTRAFILTRATION

Small-Solute Removal

The net removal of solutes and fluid during PD, in excess of residual renal excretion, can be measured by evaluating the drained dialysate. For this purpose the concentrations of urea and creatinine are measured in dialysate and plasma. The dialysate-plasma concentration ratios (D/P) of either of these solutes multiplied by the daily drain volume gives the 24-hour clearance. Weekly creatinine and urea clearances are obtained by multiplying these figures by 7. For comparison between patients, creatinine clearance is conventionally related to body standard surface area (1.73 m^2), and urea clearance (mostly for comparison with HD) is expressed as *Kt/V* (where *Kt* is the weekly clearance and *V* the volume of distribution of urea). In PD, routine assessment of *V* is imprecise, in contrast to the situation in HD, in which *V* can be mathematically derived directly from urea kinetics. *V* should preferably be determined by direct techniques, such as from the dilution of isotopic water (total body water); in practice, however, *V* is usually approximated from standard tables using BW and height as anthropometric parameters together with gender.[31] Criticism of the *Kt/V* concept in PD is based on the uncertainty of determining a correct value for *V*. In those who are markedly underweight or overweight the ideal body weight should be used for calculating *V*.[32]

Large-Solute Removal

For more insight into peritoneal transport, the clearance of larger solutes such as β_2-microglobulin, as well as markers for transport across the large pores, such as albumin, immunoglobulins and α_2-macroglobulin, can be measured. Although many centers assess the daily peritoneal removal of total protein and/or albumin, measurements of most other solutes are not made in routine clinical practice.

Ultrafiltration

Ultrafiltration can be assessed with a 24-hour collection. Even if done accurately, there is a considerable dwell-to-dwell and day-to-day variability in UF depending on drainage conditions, posture, and varying levels of residual (sump) intraperitoneal volume. Reasonably accurate estimations of daily UF volume can be obtained by averaging collections of all fluid during a period of several days. In clinical practice, the patient's own daily dialysis records should also be examined with respect to dwell-to-dwell UF volumes and the number of hypertonic bags used per day. For a 3.86% glucose dwell a UF volume less than 400 ml will indicate insufficient UF—that is, ultrafiltration failure (UFF). UF volume can also be determined by the PET as described later. In a routine 2.27% glucose PET, less than 200 mL of UF in 4 hours signals UFF. More accurate determination of intraperitoneal volume can be achieved as a function of time with use of a marker, such as iodine 125 (^{125}I)–human serum albumin or dextran 70. This is not required in routine clinical practice but as a research tool allows more precise UF volume estimations.

Peritoneal Membrane Function

Peritoneal Equilibration Test

The PET yields approximate estimations of the rate of peritoneal transport of small solutes and of UF capacity.[33] The rate of small-solute transport is dependent on the effective peritoneal surface area, which is essentially dependent on the number of effectively perfused capillaries available for exchange (and the blood flow). The volume ultrafiltrated in 4 hours is a function of the so-called osmotic conductance to glucose (OCg; the peritoneal UF coefficient times the reflection coefficient for glucose) as well as the rate of dissipation of the glucose osmotic gradient (the rate of small-solute transport). In general, when the rate of glucose disappearance is high, UF volume is low.

The PET procedure is summarized in Box 96-1. After an overnight dwell (8 to 12 hours) the dialysate fluid is drained, and a 2-liter 2.27% glucose bag is infused for 10 minutes with the patient in supine position (rolling from side to side every 2 minutes). After 10 minutes—that is, at completion of the infusion—200 ml is drained into the drainage bag and mixed, and a zero time dialysate sample taken. At the end of the 4-hour dwell period, dialysate is drained out

and measured. The net volume is noted. Concentrations of glucose and creatinine in the outflow and plasma are measured, as well as the concentration of glucose in the zero sample. The results are expressed as the dialysate-plasma (D/P) solute concentration ratio and as the dialysate glucose at 4 hours–dialysate glucose at time zero (D/D_0) concentration ratio. The higher the D/P ratio for creatinine, the faster the rate of transport for small solutes. According to D/P ratios for creatinine or D/D_0 for glucose, patients can be divided into slow, slow average, fast average, or fast transporters (Fig. 96-8).

It should, however, be emphasized that D/P measurements give only an approximate estimation of small-solute transport rate. Additional information can be obtained by variations including the modified PET (instilling a 3.86% solution and draining after 4 hours),[34] the mini-PET (instilling a 3.86% solution and draining after 1 hour), and the double-mini-PET (instilling sequentially a 1.36% solution and a 3.86% solution, draining each after 1 hour).

Mini–Peritoneal Equilibration Test

In the mini-PET, a 3.86% glucose solution is instilled and completely drained after 1 hour. The Na^+ concentration in the drained dialysate assesses the degree of sodium sieving and hence gives a measure of AQP-mediated ("free") water flow.[35,36] The fraction of "free" water transport can be evaluated in the early phase of the dwell from the 1-hour drained volume minus the 1-hour peritoneal Na^+ clearance (i.e., the drained Na^+ minus the instilled Na^+ divided by the serum Na^+ concentration). In the first hour when Na^+ diffusion is negligible, the peritoneal clearance of sodium (across small pores) will directly reflect the peritoneal small-pore fluid clearance (UF). This value is then subtracted from the total (1-hour) UF volume to yield an estimate of the free (AQP-mediated) water transport. Reductions in this parameter usually occur over time on PD, and marked reductions in free water transport are assumed to reflect peritoneal fibrosis.[37,38]

Double–Mini–Peritoneal Equilibration Test

The OCg can be measured with a double-mini-PET—that is, a 1-hour dwell with 1.36% glucose and also a 1-hour dwell with 3.86% glucose solution. The calculation of OCg is based on the difference in the 1-hour drained volume between the 3.86% and 1.36% glucose solutions.[39] In long-term PD, increases in D/P-creatinine and reductions in D/D_0-glucose are usually seen, eventually resulting in UFF. These changes are often combined with moderate reductions in OCg, the latter perhaps coupled with peritoneal fibrosis.[40] Marked reductions in OCg may signal imminent development of peritoneal sclerosis.

An overview of current techniques to clinically assess peritoneal membrane function has recently been published.[41]

Peritoneal Equilibration Test

1. The night bag (8 to 12 hours) must be 1.36% or 2.27% glucose, drained for 20 minutes with patient sitting.
2. Two liters (warm) 2.27% fluid instilled for 10 minutes with the patient supine and rolling from side to side every 2 minutes.
3. Exactly at 10 minutes after start of the infusion, 200 ml is drained into the bag. Draw 5 ml (discard); the next 5 ml taken for creatinine and glucose determination.
4. After 2 hours, new samples collected as in 3.
5. After 4 hours (exactly), drainage for 20 minutes. Note total bag weight. Subtract empty bag weight. Take samples (after mixing) for creatinine and glucose.
6. Glucose D/D_0 (the ratio of dialysate glucose at 4 hours and at time zero) and creatinine D/P (the ration of dialysate and serum creatinine at 4 hours) are plotted versus time (as shown in Figure 96-8). The drain volume is noted.

Box 96-1 **Peritoneal equilibration test.**

Residual Renal Function

In PD, residual renal function is of considerable importance for patient and technique survival. Residual renal function is somewhat better preserved over treatment time in PD than in HD.[42] Residual renal function can be assessed by collecting all urine during a day and by assessing the urine concentrations of urea and creatinine and total urine volume. Because renal creatinine clearance, as a result of tubular secretion, yields an overestimate of the glomerular filtration rate (GFR) (by 1 to 2 ml/min) when the GFR is 10 ml/min or lower, and renal urea clearance yields an underestimate of GFR (by 1 to 2 ml/min) in the same interval of (reduced) GFR, a good estimate of actual GFR can be calculated as the average of renal creatinine clearance and urea clearance. However, if the daily urine volume is

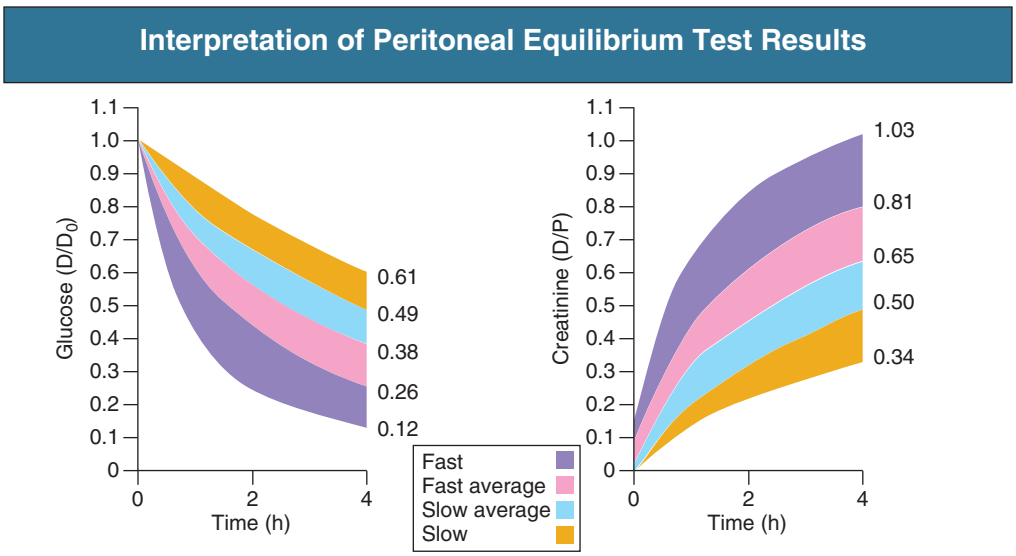


Figure 96-8 **Interpretation of the peritoneal equilibration test (PET) results.** Changes in solute concentration during a PET allow classification into different transport types. *(Modified from reference 33.)*

less than 200 ml, residual renal function will be too small to be measured accurately.

ADEQUACY

The most important measure of dialysis adequacy is the general clinical state of the patient, as manifested by a good nutritional status (maintained muscle mass) and the absence of anemia, edema, hypertension, electrolyte and acid-base disturbances, neurologic symptoms, pruritus, and insomnia. Management of anemia and bone disease in ESRD patients is discussed in Chapters 83 and 85 respectively. Some criteria for PD adequacy are given in Table 96-1.

Small-Solute Clearance

Few prospective randomized studies define adequate PD. From a clinical point of view it has been suggested that a weekly *Kt/V* above 1.7 and a weekly creatinine clearance above 50 l/1.73 m^2 would be (minimally) adequate for patients on CAPD. In a large prospective study in the United States and Canada, the CANUSA study, the outcome for a cohort of 680 patients starting CAPD was studied with an average follow-up of 2 years.[43] In this study, patients who maintained a high *Kt/V* or creatinine clearance over time did better than those who did not. An increase of 0.1 unit of *Kt/V* (peritoneal + renal) per week was associated with a 5% decrease in relative risk of death, and an increase of 5 l/1.73 m^2 of creatinine clearance per week (peritoneal + renal) was associated with a 7% decrease in the relative risk of death. Further analysis of the CANUSA study findings indicated that the survival advantage of patients with higher total small-solute clearance was entirely attributed to the residual renal function. For each increase of 250 ml of urine output per day, there was a 36% decrease in the relative risk of death. In the Adequacy of Peritoneal Dialysis in Mexico (ADEMEX) study,[44] a large randomized controlled clinical trial (RCT) designed to test the value of increasing peritoneal small-solute clearance in a Mexican PD cohort, there was no survival advantage of increasing the peritoneal clearance to obtain a total weekly creatinine clearance above 60 l/1.73 m^2 at an average peritoneal *Kt/V* of 2.12 (intervention group) compared with a clearance above 50 l/1.73 m^2 at an average peritoneal *Kt/V* of 1.56 (control group). However, although overall mortality, hospitalization, withdrawal, and technique survival were similar in the two groups, the causes of withdrawal were different. Relatively more patients in the control group withdrew because of uremia, hyperkalemia, and acidosis and died from congestive heart failure than in the intervention group.

From these studies it seems that renal and peritoneal clearance are not mutually comparable. High residual renal function is of greater survival advantage than high peritoneal solute transport capacity. The fact that the survival of PD patients is equal to or supersedes that of HD patients during the first 2 to 3 years of dialysis (see later), despite the fact that PD provides approximately 50% of the total *Kt/V* of HD, indicates that the benefit of PD goes beyond the clearance of small solutes. In a European multicenter study of APD, the European Automated Peritoneal Dialysis Outcomes Study (EAPOS), small-solute clearance did not correlate with survival in anuric patients.[45] On the contrary, total volume removal and hydration state were important factors. Still, there is reasonably good evidence that a weekly *Kt/V* above 1.7 and a weekly creatinine clearance above 50 l/1.73 m^2 are adequacy targets that should be reached and maintained in a majority of patients. Lower values of *Kt/V* and creatinine clearance have been found to be associated with more clinical problems and higher consumption of erythropoiesis-stimulating agents in a large RCT.[46]

Commercially available computer programs* can predict urea and creatinine clearances and peritoneal UF performance and provide suggestions for treatment options, based on drained volumes and on plasma and dialysate creatinine and urea values. These parameters are often obtained by PET or standardized schedules for specified dwell exchanges. Some of the programs yield an estimate of peritoneal albumin clearance, which to a great extent is dependent on the filtration occurring across large pores, being increased in "inflammation." Recommended dialysis schedules based on the categorization of the PET are given in Table 96-2.

Criteria for Peritoneal Dialysis Adequacy	
Clinical	Patient feels well and has stable lean body mass No symptoms of anorexia, asthenia, nausea, emesis, insomnia Stable nerve conductance velocity
Small-solute clearance	Weekly *Kt/V* urea >1.7 (renal + peritoneal) Weekly creatinine clearance >50 l/1.73 m^2
Large-solute clearance	Albumin clearance <0.15 ml/min
Fluid balance	No edema No hypertension No postural hypotension
Electrolyte balance	Serum potassium <5 mmol/l
Acid-base balance	Serum bicarbonate >24 mmol/l
Nutrition	Daily protein intake ≥1.2 g/kg Daily calorie intake >35 kcal/kg/day Serum albumin >3.5 g/l BMI 20-30 kg/m^2 Stable midarm muscle circumference

Table 96-1 Criteria for peritoneal dialysis adequacy. *BMI,* Body mass index.

Fluid Balance

As in all types of RRT, long-term maintenance of adequate fluid and electrolyte balance is of crucial importance for the survival of patients on PD. As already mentioned, the outcome of PD is directly related to residual renal function, particularly a high urine output. Furthermore, patients with fast transport in the PET (a more rapid absorption of glucose and a more rapid loss of the osmotic gradient) have a reduced technique survival. It seems evident that after 2 or 3 years of PD, when residual renal function is low, most patients in PD are fluid overloaded.[47,48] It is likely that volume overload not only aggravates hypertension but also leads to progression of left ventricular hypertrophy, often already present at the start of PD. However, during the first year of PD there is often a fall in blood pressure and a reduced need for antihypertensive agents. Unfortunately, with time on PD, blood pressure usually rises and the number of antihypertensive drugs needed usually again increases.[49] Therefore it is advisable to regularly assess fluid removal in the patients over time, at least every 6 months, with a modified PET (4-hour 3.86% glucose dwell, in conjunction with a standard 2.27% 4-hour PET.

Management of Fluid Overload

As total urinary water (and sodium) excretion and peritoneal UF volume decline, it is advisable to instruct patients to restrict salt and

*www.baxter.com/products/renal/software/pdadequest/index.htmlwww.gambro.com/int/2713/Peritoneal-Dialysis/Products/Synergy/www.fmc-ag.com/internet/fmc/fmcag/neu/fmcpub.nsf/Content/Software_%28Peritoneal_Dialysis%29

Typical Peritoneal Dialysis Regimens Required for Achievement of Adequate Solute Clearances

Patient Body Surface Area (m^2)	Peritoneal Solute Transport Characteristics—D/P Creatinine at 4 Hours: Slow (<0.5)	Slow Average (0.5 to <0.65)	Fast Average (0.65-0.82)	Fast (>0.83)
<1.7	CAPD/APD 10-12.5 l	CAPD/APD+ 10-12.5 l	APD+* 10-12.5 l	APD* 10-12.5 l
1.7-2.0	CAPD+/APD 12.5-15 l	APD+ 12.5-15 l	APD+* 12.5-15 l	APD+* 12.5-15 l
>2.0	CAPD+, HD	APD+ 15-20 l	APD+* 15-20 l	APD+* 15-20 l

Table 96-2 Peritoneal dialysis regimens. Typical peritoneal dialysis regimens required to achieve adequate solute clearance according to patient size and membrane characteristics in anuric patients. The total volume of dialysate fluid required increases with body size, with use of 2.5- or even 3.0-liter exchanges. As solute transport increases, the use of automated peritoneal dialysis (APD) with shorter overnight exchanges is favored over continuous ambulatory peritoneal dialysis (CAPD). Both CAPD and APD may have to be augmented by the use of an additional exchange (denoted by +); this is given by way of an additional afternoon exchange in CAPD patients or by use of an exchange device that delivers a single additional exchange at night. *D/P,* Dialysate-plasma concentration ratios; *HD,* hemodialysis. *The use of glucose polymer (icodextrin) solution for the long exchange will enhance both solute clearance and ultrafiltration.

water intake. In view of the difficulty in compliance with salt restriction, the use of PD solutions with lower sodium concentration has been advocated. Preliminary studies of low-sodium PD solutions have been very promising with regard to reducing the need for blood pressure–lowering drugs to control hypertension[50]; however, low-sodium solutions are not yet commercially available. Loop diuretics such as furosemide 250 to 500 mg daily can be used to maintain urine volumes but do not maintain renal clearance. If salt and water restriction and diuretics are not effective in maintaining UF, it can be enhanced by increasing the dialysis glucose concentration. Patients with alterations in peritoneal membrane function, appearing over the first few years of PD, usually have an increased small-solute transport combined with only a moderate change in peritoneal UF capacity,[40] and there is an increased reabsorption of fluid in the late phase of the dwell. These patients can benefit from switching to APD and to the use of icodextrin for one of the (daily) exchanges. Randomized controlled trials using icodextrin for the long daytime dwell in APD have demonstrated an improved UF and a reduced extracellular fluid (ECF) volume.[51] Patients who have been on PD for several years may have a reduced UF capacity (reduced OCg).[39,40] These patients would (theoretically) benefit less from switching to icodextrin because of the reduced UF capacity.[11]

Nutrition

During their first year of treatment, CAPD patients typically have evidence of net anabolism; the average weight gain may exceed 5 kg without any clinical signs of fluid overload. Contributing to this weight gain is the peritoneal glucose reabsorption (on average 100 to 150 g daily), which adds 400 to 600 kcal of energy intake daily and results in metabolic syndrome in approximately 50% of prevalent PD patients.[52] As residual renal function declines, the nutritional and metabolic abnormalities in CAPD become increasingly manifest, with reductions in lean body mass. The main cause of protein-energy malnutrition and wasting, apart from poor food intake, is the impaired metabolism of protein and energy in uremia. Despite glucose absorption, many patients on long-term CAPD have signs of energy malnutrition, a major component of the uremic wasting syndrome. Contributing factors are (low-grade) inflammation associated with carbonyl and oxidative stress and with accelerated atherosclerosis, the so-called malnutrition inflammation atherosclerosis (MIA) syndrome.[53] It is important that CAPD patients be prescribed an adequate amount of protein (>1.2 g protein/kg/day) and energy (total energy intake >35 kcal/kg/day) and a sufficient dose of dialysis, enabling the patient to ingest this diet. It should be noted that the daily losses of protein to the dialysate are not negligible, but approximately 5 to 7 g daily, of which approximately 4 to 5 g is albumin. This actually compares with the losses occurring in nephrotic range proteinuria. The nutritional management of PD patients should include frequent assessments of their nutritional status, and if inadequate, referral for HD (or transplantation) should be considered. Nutrition in PD patients is discussed further in Chapter 87.

OUTCOME OF PERITONEAL DIALYSIS

Registry data have indicated a lower risk of death in patients treated with PD during the first 3 years of treatment compared with those treated with HD, although overall the mortality of patients on PD compared with HD is not significantly different.[1] Survival differences seem to vary substantially according to the underlying cause of ESRD, age, and baseline comorbidity. In a study based on U.S. Medicare registry data,[54] HD was associated with a higher risk of death among diabetic patients with no comorbidity and among younger patients (age 18 to 44), whereas PD was associated with a higher risk of death among older patients (age 45 to 64). In patients with mortality rates adjusted for comorbidity at start of dialysis, there were no differences between HD and PD among nondiabetic patients and among younger diabetic patients (age 18 to 44), but mortality was higher on PD for older diabetic patients with baseline comorbidity.

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CHAPTER 97

Complications of Peritoneal Dialysis

Simon J. Davies and Martin E. Wilkie

Peritoneal dialysis (PD) is associated with a number of potential complications that affect technique and patient survival. Understanding their etiology, presentation, and management frequently enables their prevention, correction, or amelioration. These complications can be separated into mechanical aspects relating to the PD technique and the catheter itself, infections either at the exit site of the catheter or peritonitis, changes affecting the peritoneal membrane, and metabolic consequences that arise from components of the dialysis solutions—predominantly the glucose content. Mechanical or catheter-related problems are more likely to occur at the start or early in the treatment course, or when there is an increase made to the volume of the dialysate; infectious complications can occur at any stage during the course of treatment, whereas membrane and metabolic problems are more prominent after the patient has been on treatment for months or years.

CATHETER MALFUNCTION

Optimal Timing and Placement of the Peritoneal Dialysis Catheter

Catheter dysfunction adversely affects patient outcome by preventing commencement of the chosen dialysis modality, as well as by being disruptive to training schedules and increasing health care costs. Published literature does not give a strong indication that one insertion technique is better than another, although a recent meta-analysis suggested an advantage of the laparoscopic compared with the open surgical insertion technique[1] (techniques of catheter insertion are further discussed in Chapters 92 and 96). It is clear that the enthusiasm and experience of the operator are key determinants of catheter outcome,[2] and international guidelines describe the optimal conditions for catheter insertion.[3] Timing is also important: Patients randomized to the late start limb of the Initiating Dialysis Early and Late (IDEAL) study (estimated glomerular filtration rate [eGFR] 5 to 7 ml/min), as opposed to patients starting dialysis early (eGFR 10 to 14 ml/min), were less likely to start on PD despite it being their treatment of choice, probably because of delayed planning.[4] Early catheter problems are more difficult to manage in the absence of residual kidney function. For optimized catheter function it is necessary that each center audit its success with catheter placement against internationally agreed-on standards as part of local quality improvement cycles.[2,3]

Catheter Function: Inflow

A 2-liter bag of dialysate should take 15 minutes or less to run into the peritoneal cavity. If inflow is significantly slowed or even stopped completely, mechanical causes should be suspected. After a check to ensure that the tubing and catheter are not kinked, that all clamps or rollers are open to the inflow position, and that any frangible seal is fully broken, the catheter should be flushed vigorously with 20 ml of heparinized saline. If the catheter is cleared, then heparin should be added (500 U/l) to the next few cycles because the cause of the blockage is often a fibrin plug. Should the catheter remain blocked, a plain abdominal radiograph is required. If this shows that the catheter is in a satisfactory position in the pelvis, an attempt to restore patency should be made with a thrombolytic agent (urokinase, 100,000 U or tissue plasminogen activator [tPA], 2 mg in 40 ml of normal saline, either instilled for at least 1 hour)[5] diluted in normal saline, which can be instilled into the PD catheter for approximately 1 hour before being withdrawn. If inflow is restored, heparin should be added to the dialysate for the next few cycles. We would no longer recommend the use of an endoscopic brush because of safety concerns.

If the radiograph shows the catheter to be malpositioned, an attempt should be made to reposition the catheter tip into the pelvis (Fig. 97-1). This can be done under radiologic screening with a sterile catheter guide although this is not widely practiced. Alternatively, the catheter can be repositioned at laparotomy or with the laparoscope. Sometimes the catheter becomes wrapped in omentum, suggested usually by complete inflow and outflow failure. This requires a partial omentectomy or an omental hitch, a surgical procedure in which the omentum is temporarily held away from the catheter by a dissolvable suture. The value of laparoscopy in this context is that it can provide a diagnosis as to the cause of catheter flow failure and provide a solution—for example, by repositioning the catheter, removing an omental wrap, or performing a limited omentectomy.

Catheter Function: Outflow

The most common reason for outflow failure is constipation, although causes of inflow failure discussed previously should also be considered. Loading of the bowel with fecal material is often obvious on a plain radiograph, but treatment for constipation should be initiated without recourse to this investigation because it is so common. Constipation should be treated with oral laxatives or an enema. Subsequently, bowel action should be kept regular by increasing the fiber in the diet and, if necessary, adding a mild laxative. Slow outflow can be a problem in patients using automated peritoneal dialysis (APD), resulting in excessive machine alarms. This is can be managed by switching to tidal APD and using a relatively large residual volume, for example 25% to 50% of the fill volume.

Fibrin in the Dialysate

The mesothelial cells of the peritoneal membrane have a range of physiologic functions including the production of fibrinolytic agents such as tPA. This process is disrupted during peritonitis when the appearance of fibrin in the dialysate is common. If fibrin causes restriction of dialysate flow, heparin (500 U/l) should be added to each bag. A small number of patients have fibrin formation in the absence of peritonitis. Immediately on drainage the bag may appear

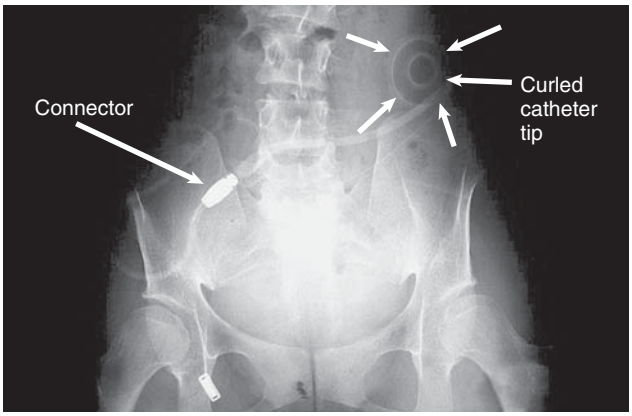

Figure 97-1 Catheter malposition. Plain radiograph of the abdomen with curled catheter *(arrows)* misplaced in the upper left abdomen.

cloudy, but on standing the fibrin will aggregate and the fluid becomes clear. The first time this happens, a sample must be sent to the microbiology laboratory to exclude infection. If the results of this testing prove negative, the patient can be reassured.

FLUID LEAKS

Fluid leaks occur whereby dialysate leaks out of the peritoneal cavity—which can be either visible externally or not. It is recommended that after PD catheter surgery, patients be allowed to heal sufficiently before use (2 weeks) to minimize this risk. If the catheter has to be used early, then low volumes should be used (start with 1 liter) in the supine position (e.g., APD with a dry day), with the patient instructed not to mobilize while dialysate is in the peritoneal cavity during the first 2 weeks after catheter insertion. Although PD catheters can be used as the primary approach to manage late-presenting patients or for acute kidney injury, the incidence of leaks is higher under these conditions.[6]

External Leaks

On occasion, fluid may leak from the exit site or even the incision used to insert the catheter into the peritoneal cavity. A leak of dialysate, which is confirmed by measuring glucose concentration in the leaking fluid, is a risk factor for infection. It is important that PD catheters be adequately immobilized if used for early start PD to reduce the risk of tugging and leak.

Internal Leaks

Isolated edema of the abdominal wall suggests an internal leak from the peritoneal cavity, either spontaneously or in association with a surgical hernia. In contrast, genital edema suggests an inguinal hernia or patent processus vaginalis. On occasion, both can be present. The site of the leak can be visualized on computed tomography (CT) scanning after intraperitoneal instillation of contrast material or on magnetic resonance imaging (MRI) without the use of contrast. It may be necessary for the patient to stand or to perform other maneuvers to increase intra-abdominal pressure before the leak is demonstrated (Fig. 97-2, *A*). An alternative diagnostic test is to perform scintigraphy after injection of a compound such as technetium Tc 99m–labeled diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA; Fig. 97-2, *B*). A surgical repair will be required if a major leak is visualized and should always be considered when there is a hernia.

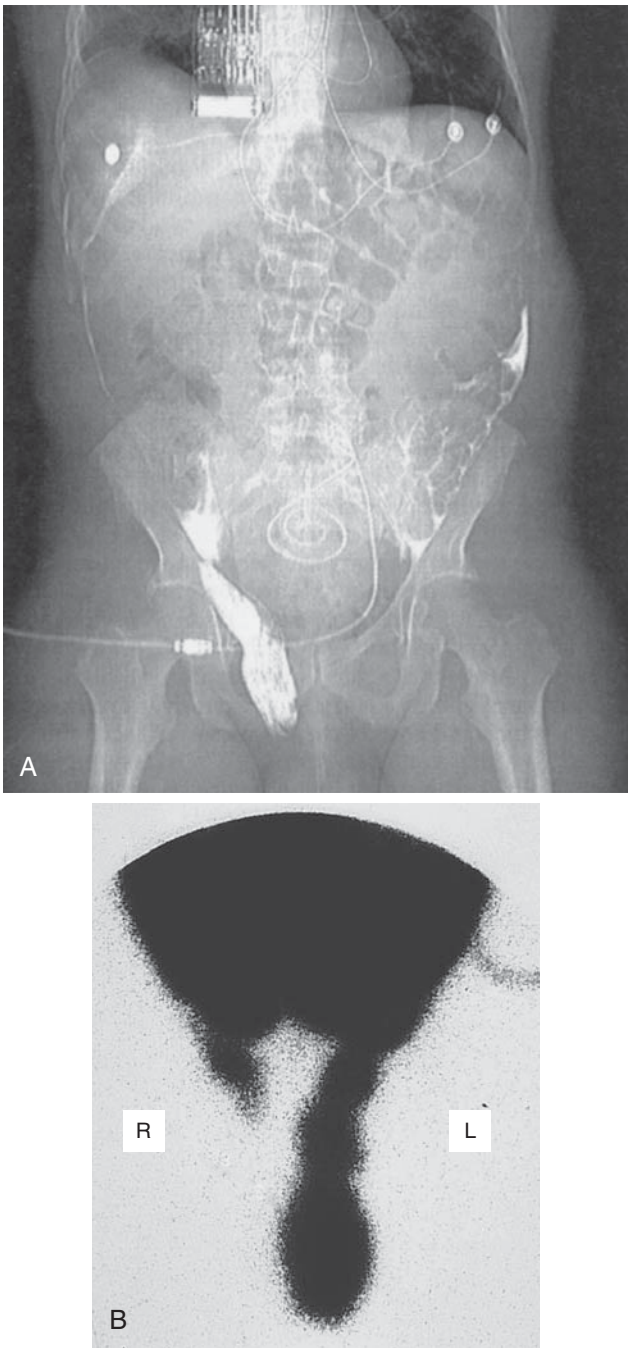

Figure 97-2 Inguinal hernia during peritoneal dialysis. A, CT scan after intraperitoneal injection of contrast material in a male patient showing dialysate flowing into a right inguinal hernia. **B,** Peritoneal scintigram of a male patient on peritoneal dialysis showing bilateral inguinal hernias. The left hernia extends into the scrotum; the right hernia is less extensive. (***A*** *from reference 34.*)

Most leaks, however, will heal after resting or with APD, using dry days, or temporary HD.

Hydrothorax

A pleural effusion can occur with generalized fluid overload or local lung disease, but it is occasionally caused by a leakage of dialysate through the diaphragm (Fig. 97-3, *A*). This occurs more commonly on the right side. A leak is most simply indicated by aspirating a sample of the effusion and demonstrating that its

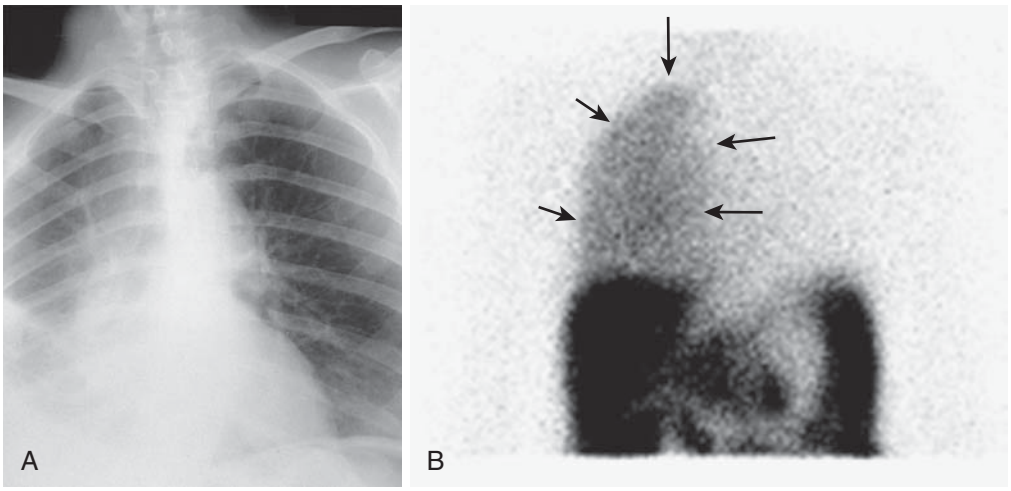

Figure 97-3 Hydrothorax in peritoneal dialysis. A, Chest radiograph showing a right-sided pleural effusion with partial collapse of the right lung caused by a diaphragmatic leak. **B,** Scintigram in a peritoneal dialysis patient showing isotope in the right hemithorax *(arrows)* confirming a right pleural effusion.

glucose concentration is higher than the patient's blood glucose concentration, and this can be confirmed by scintigraphy after intraperitoneal instillation of isotope, usually ^{99m}Tc-DTPA (Fig. 97-3, *B*). If one can be confident that the pleural effusion is not caused by the PD, then PD can be continued while the effusion is investigated and managed. Although there are reports that repairing pleural leaks allows subsequent PD, the best advice is to transfer the patient to HD unless there are very strong reasons not to.

PAIN RELATED TO PERITONEAL DIALYSIS

Inflow Pain

Soon after starting PD, patients may experience pain during fluid inflow, and occasionally pain affects the shoulders and is pleuritic in nature, possibly because of diaphragmatic irritation, which usually resolves over the following days. Slowing the rate of fluid inflow will often reduce the symptoms, and peritonitis should be excluded and treated. A small number of individuals have persistent inflow pain, and the use of bicarbonate-lactate–buffered dialysate at physiologic pH improves symptoms in such patients.[7]

Outflow Pain

Some patients have discomfort or even pain when the fluid is drained out, which can be experienced in the genital area or rectum, and is commonly a result of pelvic irritation related to the catheter tip. This emptying sensation is abolished when the next cycle runs in and is best treated by leaving a small residual volume of fluid in the peritoneal cavity at the end of the drain, for example by using tidal APD.

Blood-Stained Dialysate

Blood-stained dialysate is uncommon. It is rarely serious but causes considerable alarm to the patient. There is sometimes a clear history of trauma to the abdomen or of unexpected strain. A range of rare conditions are associated with this complication[8]; a few female patients relate the episode to their time of ovulation or menstruation. The treatment is to flush the abdomen with a few cycles of dialysate containing heparin (500 U/l) to minimize the chances of clotting in the catheter. The problem usually resolves spontaneously and often is visible only in one outflow. It is unusual for the blood-stained dialysate to be associated with infection, although it is wise to have the fluid cultured. Routine use of antibiotics is not necessary.

INFECTIOUS COMPLICATIONS

Peritonitis

There are wide variations in peritonitis rates both between and within countries. Reducing peritonitis rates requires a multifaceted, multidisciplinary approach based on the use of preventative measures around the time of catheter insertion, the use of modern disconnect systems, exit site management, and education of patients and health care professionals.[9] This should be supported by regular local audit of peritonitis rates including causative organisms and local sensitivities, which is increasingly important because of the emergence of resistant organisms, and the requirement to use antibiotics effectively. Root cause analysis should be performed after each episode of PD peritonitis, with retraining as appropriate. Guidelines for the diagnosis and management of PD peritonitis are published by the International Society for Peritoneal Dialysis (ISPD; www.ispd.org).[10] The spectrum of peritonitis and its management in children have also recently been described in detail.[11] The reader is directed to a detailed review on reducing peritonitis risk.[9]

Diagnosis of Peritonitis

The diagnosis of peritonitis should be suspected in any patient who develops a cloudy bag when PD fluid is drained or abdominal pain. Fever may also be present but is not a universal feature. Patients should be advised to contact their dialysis unit immediately if they observe a cloudy bag or develop persistent abdominal pain. Samples of the dialysate should be taken for cell count and microbiologic examination. The diagnosis is confirmed by finding more than 100 white blood cells/mm^3 (1×10^7 cells/l). A Gram stain of the spun deposit should also be performed to help identify the type of causative organism, although initial treatment will usually be empiric pending culture and sensitivity results. Various culture techniques have been proposed, but white cell lysis and inoculation into blood culture media is often helpful in increasing the yield of a positive growth.

The dialysate leukocyte count will be affected by dwell length, and this needs to be taken into account in APD patients. In short dwells, the count will be lower, and under these circumstances, if the proportion of cells that are neutrophils exceeds 50%, empiric treatment of peritonitis should be commenced. Conversely, if the patient has had a dry abdomen during the day, the initial drain on connection may be cloudy. This will clear within one or two cycles, and the majority of the cells found will be mononuclear leukocytes.

Treatment of Peritonitis

The empiric treatment of peritonitis will vary according to center and should be developed in close collaboration with the local microbiology service, taking into account sensitivity patterns and infection control policy. Initial regimens must cover both gram-positive and gram-negative organisms; the latest ISPD guidelines (www.ispd.org) give examples of appropriate antibiotics including vancomycin, cephalosporins, and aminoglycosides.[10,11] Dosage regimens will depend on whether the patient is on CAPD or APD. For CAPD, the antibiotic is administered as a loading dose in the first bag and then as a maintenance dose in subsequent bags. Although it was customary to transfer APD patients to CAPD for the purpose of treating peritonitis, this is no longer necessary. APD patients are now given large loading doses in dialysis fluid with a minimum 6-hour dwell (e.g., vancomycin 30 mg/kg) and then are given additional doses every 3 to 5 days according to checked blood levels. Once the culture result is available, the regimen should be modified accordingly (Table 97-1). If the organism is methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin will be continued as part of the regimen.

If the culture is negative, empiric therapy should be continued for 2 weeks, assuming there is a clinical response. If a gram-negative organism is identified, the subsequent management will depend on the sensitivity (Fig. 97-4). The isolation of multiple organisms including anaerobes strongly suggests perforation of the small or large intestine or biliary system. Metronidazole should be added to the regimen to cover anaerobic organisms, and consideration given to surgical intervention.

A wide variety of antibiotics other than those cited have been used with success. In particular, a commonly used strategy is to include an oral quinolone, such as ciprofloxacin. There is debate surrounding the role of aminoglycosides—advantages being simplicity of use and good gram-negative organisms coverage; however, there are concerns regarding ototoxicity and nephrotoxicity, the former of which is irreversible. Reports regarding the impact of these agents on residual renal function are not consistent, and it is clear that serious episodes of peritonitis in themselves have an adverse

Antibiotic Regimens for Bacterial PD Peritonitis

Culture	Antibiotic
Enterococci (including vancomycin-resistant enterococci)	Ampicillin
*Staphylococcus aureus** Methicillin resistant*	Cephalosporin-floxacillin (flucloxacillin) Vancomycin
Other gram-positive organism†	Cephalosporin-floxacillin
Gram-negative organisms (including *Pseudomonas* species)*	Cefazolin, quinolone, or aminoglycoside‡, depending on sensitivities and residual renal function
Multiple or anaerobic organisms*	Metronidazole ± laparotomy
Culture negative	Continue empiric treatment

Table 97-1 Antibiotic regimens for bacterial PD peritonitis. Suggested antibiotic regimens when dialysate fluid culture is available. Except for culture-negative episodes, empiric treatment is stopped once the sensitivities are known. All antibiotic regimens should be developed in consultation with local microbiology practices. *Three-week treatment. †Two-week treatment. ‡Avoid unnecessary use if there is residual function.

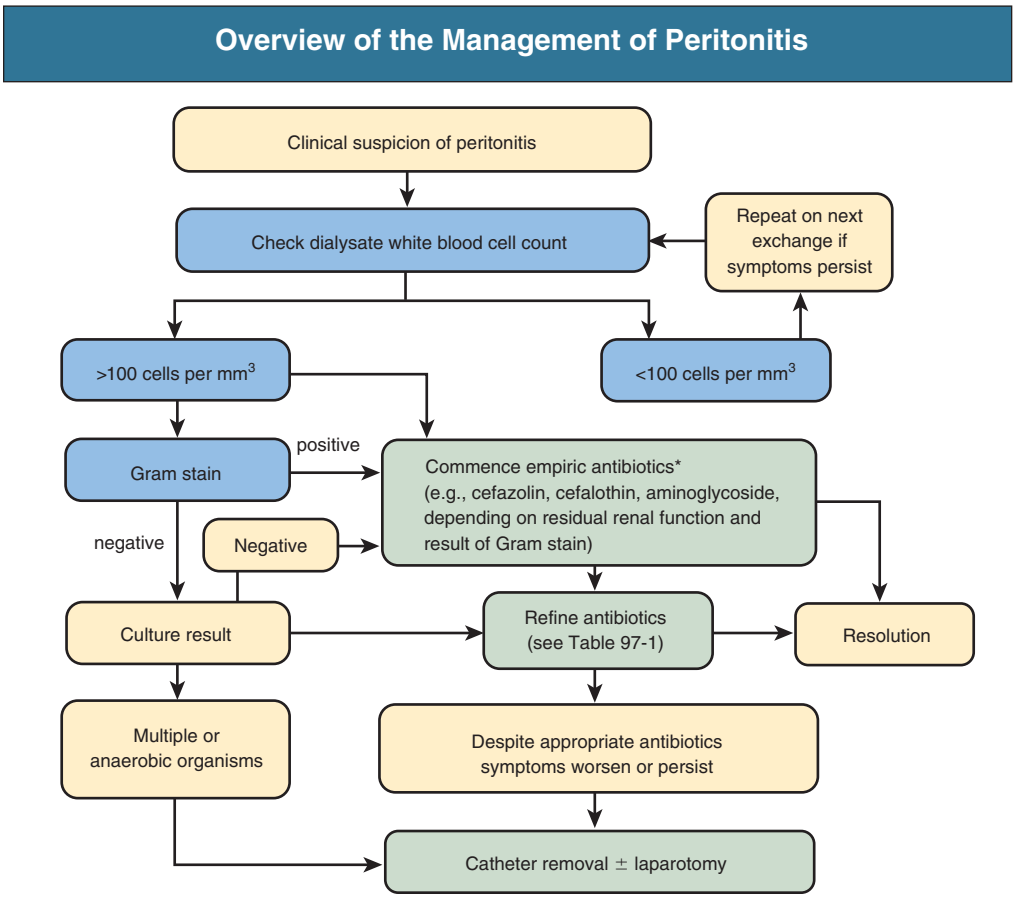

Figure 97-4 Overview of the management of peritonitis.

effect on residual renal function. It is, however, advisable to avoid recurrent courses of aminoglycosides; and if they are used, concomitant *N*-acetylcysteine should be considered to block the ototoxicity. Current recommendations are that for gram-positive organisms, therapy should be for 14 days except in the case of *S. aureus,* for which 21 days is suggested. For culture-negative episodes, 14 days of therapy should suffice. The same is true in the case of single-organism gram-negative peritonitis. For *Pseudomonas* species, *Xanthomonas* species, or multiple organisms, 21 days is recommended.

Many patients can be treated successfully as outpatients. It is extremely important, however, that they be followed up either in the clinic or by telephone. In most patients, clinical resolution, as judged by the clearing of the bags, starts within 48 hours. If there is no improvement within 96 hours despite use of the correct antibiotic, as judged by sensitivity tests, the fluid must be retested by cell count, Gram stain, and culture. The ISPD recommends that the catheter be removed if there is no improvement in 5 days; however, in a severe infection this should be done earlier, and in a more indolent case the period of observation can be longer. In addition, the possibility of intra-abdominal or gynecologic disease or the presence of unusual organisms such as mycobacteria should be considered. Under these circumstances, a mini-laparotomy should be performed to exclude intra-abdominal disease, and if mycobacterial infection is suspected, a peritoneal biopsy specimen should be obtained for culture.

Fungal Peritonitis

If peritonitis is caused by yeasts or fungi, the peritoneal catheter should always be removed. This should be combined with antifungal treatment with fluconazole, combined with intraperitoneal flucytosine until sensitivities are known, with care taken in view of its toxicity in renal failure. Oral antifungals should be continued for at least 10 days and up to 4 weeks after catheter removal, at which point catheter replacement can be considered.[10,11]

Relapsing Peritonitis

Relapsing peritonitis is defined as infection caused by the same organism as the original infection occurring within 4 weeks, whereas *recurrent peritonitis* is defined as a different organism within 4 weeks of completion of an appropriate course of antibiotics. In general, the advice is to treat as for a primary infection but to try to establish an underlying cause. For example, recurrence of *S. aureus* infection should trigger the search for pericatheter infection. If enterococci or gram-negative organisms are the cause of a relapse, the possibility of intra-abdominal disease or an abscess should be considered (although these organisms are frequently water-borne). If a patient has other gastrointestinal symptoms, such as change in bowel habit, appropriate investigation should be conducted. Some organisms (including coagulase-negative staphylococci) produce biofilm that can lead to a relapse of the infection. Consideration should be given to changing the PD catheter once the infection has been treated; of course, the catheter will need to be removed if the infection does not respond to treatment. Current practice in most units is to allow a period of up to 3 weeks before a new catheter is inserted.

Culture-Negative Peritonitis

The importance of culture-negative peritonitis is that it is associated with increased treatment failure. Commonly the cause relates to the sampling technique or the microbiologic approach; alternatively, concurrent antibiotic use may be responsible. It is important to be aware of the possibility of fastidious organisms (e.g., atypical mycobacteria or yeasts). In addition, other causes of peritoneal inflammation may responsible; these include the presence of an intra-abdominal malignancy or surgical pathology or eosinophilic reactions—for example, in the case of vancomycin allergy or some fungal infections. Chylous effluent is a rare finding in PD; the cause is often unclear, but if recurrent; conditions affecting lymphatic drainage should be considered.

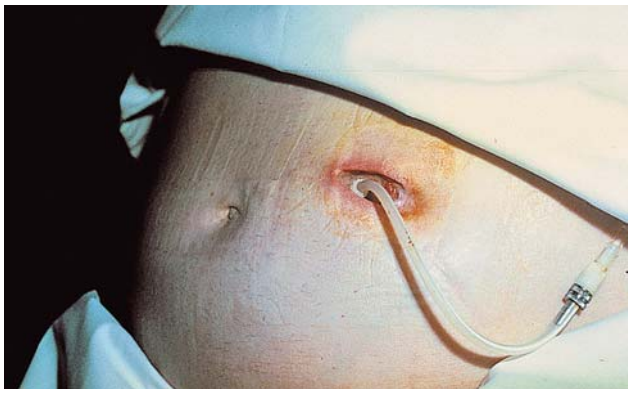

Figure 97-5 Exit site infection. A severe exit site infection that has exposed the outer cuff of the catheter.

Exit Site Infection

Exit site infection is an important complication of long-term PD. The diagnosis is suspected on clinical grounds, usually by the presence of marked erythema or discharge from the exit site (Fig. 97-5). A scoring system for exit sites has been developed to determine the likelihood of infection and to grade its severity, with points assigned for crusting, swelling, pain, and discharge according to severity; if the discharge is purulent, this mandates treatment.[10] Extension of the infection into the tunnel may be assessed either clinically or by ultrasound. The most common infecting organism is *S. aureus.* There is evidence for the use of prophylactic topical antibiotics at the exit site, the strongest being for mupirocin; a systematic review concluded that mupirocin prophylaxis was effective in prevention of exit site infection and peritonitis caused by *S. aureus.*[12] There is also evidence for the use of topical gentamicin; however, a number of case reports of gentamicin resistance following regular topical application has raised concerns regarding its use as a routine prophylactic agent.

All suspected infected exit sites should be swabbed; routine swabbing of healthy exit sites should be avoided, and incidental bacterial growths do not require treatment. Unless there is prior evidence that the patient carries MRSA or *Pseudomonas,* initial treatment should be with an antibiotic effective against *S. aureus*—for example, flucloxacillin (500 mg four times a day) or a cephalosporin if the patient is allergic to penicillin. In most patients, the drug can be given orally; but if the individual is systemically ill, the antibiotics should be administered intravenously until clinical improvement occurs. Hospitalization, parenteral antibiotics, and often urgent catheter removal are required if there is evidence of spread into the tunnel. If the infection is with MRSA, eradication therapy should be attempted with systemic vancomycin, as for peritonitis. Should the culture grow a gram-negative organism, ciprofloxacin (500 mg twice a day orally) will be effective empiric treatment in most patients.

Treatment is recommended for a minimum of 2 weeks. In gram-positive infections, if there is no improvement within 7 days, ultrasound of the catheter tunnel should be performed because a collection of fluid around the catheter signifies a tunnel infection. If complete healing does not take place after 4 weeks of therapy, further measures should be considered, such as exteriorizing and shaving the outer

cuff because it may be involved in the infection. If the infection persists or relapses, catheter removal must be considered because there is a high risk that the exit site infection will lead to peritonitis. It is important that the new exit site be formed in a different part of the anterior abdominal wall.

REDUCED ULTRAFILTRATION AND ULTRAFILTRATION FAILURE

Definition and Significance of Ultrafiltration Failure

There are two complementary approaches to defining ultrafiltration failure. The first is absolute and membrane based: With use of a standard 4-hour peritoneal equilibration test (PET), net ultrafiltration capacity below 400 ml with a hypertonic glucose exchange (3.86%) is indicative of an inadequate membrane,[13] bearing in mind that this may not be clinically relevant in a patient with well preserved residual renal function. If a middle-strength glucose solution is used (2.27%), then the equivalent value is 0 ml (excluding overfill). In both cases, in measuring the ultrafiltration capacity it is important that overfill of dialysis bags by the manufacturers, which can be as much as 200 ml, be taken into account. Although this definition is clear enough, the main limitation is that it relies on a single measurement of ultrafiltration capacity, which is subject to significant error (coefficient of variation is up to 25%). The second approach to defining ultrafiltration failure is more holistic in that it considers patient factors that affect fluid status (such as comorbid conditions) and an acceptable glucose exposure required to maintain adequate hydration. Many clinicians now take the view that regular the use of hypertonic solutions is not acceptable unless the life expectancy is shorter than the development of severe membrane failure and its complications.

Ultrafiltration failure is a significant cause of technique failure[14]; it results in low ultrafiltration, which in turn increases the risk of mortality in anuric patients[15,16]; and is also a risk factor for encapsulating peritoneal sclerosis (EPS).[17] Although it is impossible to set a precise overall fluid removal goal that applies to all patients, the European Automated Peritoneal Dialysis Outcomes Study (EAPOS), which preset an ultrafiltration target of more than 750 ml/day in anuric patients on PD, found that those who failed to reach this goal had higher mortality and less efficient membranes.[15] Patients who achieve less than a total fluid removal of 1 liter per day should have their membrane function assessed.

Establishing the Causes of Ultrafiltration Failure

Failure of the membrane to ultrafiltrate needs to be distinguished from other causes of inadequate peritoneal fluid removal such as catheter dysfunction, leak, or excessive fluid reabsorption.[18] The latter can occur if the intraperitoneal cavity pressure is too high, suspected if the ultrafiltration falls after an increase the dialysate volume. If doubt is present, a dialysate sodium concentration below 125 mmol/l 1 hour into a PET using 3.86% glucose suggests that ultrafiltration is preserved.

There are two main causes of ultrafiltration failure: fast peritoneal solute transport rate (fPSTR) and low membrane ultrafiltration efficiency caused by reduced osmotic conductance. Both can exist at the start of PD or can be acquired with time on therapy, although it is rare for a patient to develop reduced osmotic conductance without also having rapid transport.

Fast Peritoneal Solute Transport Rate–Related Ultrafiltration Failure: Diagnosis and Management

With the 4-hour PET, a dialysate–plasma creatinine ratio greater than average (0.64) could contribute to poor ultrafiltration. This is because the more rapid the diffusion of small solute across the membrane, the earlier the dissipation of the osmotic gradient driving ultrafiltration. Furthermore, once the gradient is lost, membranes with a larger diffusive area will reabsorb fluid more rapidly. In continuous ambulatory PD patients, fPSTR is associated with increased mortality,[19] whereas the converse is true when APD is used.[20] Thus both theoretically and empirically the short exchanges used in APD prescription are associated with better outcomes in fPSTR-associated poor ultrafiltration. Prevention of fluid reabsorption during the long day or night exchange is also required in these patients, and this can be achieved by use of icodextrin (polyglucose solution), which also improves the fluid status.[21] It is now known that the main determinant of fPSTR is increased intraperitoneal inflammation, which is independent of systemic inflammation. Only the latter is an independent predictor of mortality.

Low Osmotic Conductance–Related Ultrafiltration Failure: Diagnosis and Management

This problem should be suspected if despite adjustment of the prescription to accommodate the peritoneal solute transport rate (PSTR), ultrafiltration failure persists. Osmotic conductance is a measure of the efficiency of the peritoneal membrane to ultrafiltrate for a given osmotic agent—typically glucose. Osmotic conductance can be measured quite easily in the clinic with the double-mini-PET,[18] which requires back-to-back 1-hour exchanges using low (1.36%) and high (3.86%) glucose concentrations; a difference of less than 200 ml net ultrafiltration between the two exchanges indicates poor osmotic conductance. The two causes so far identified are reduced aquaporin function, possibly constitutive and thus present at the start of treatment, and progressive fibrosis of the membrane as a consequence of acquired membrane injury. There is no specific treatment, so clinical effort should focus on prevention (next section).

CHANGES IN PERITONEAL STRUCTURE AND FUNCTION

It is widely assumed that alterations in peritoneal function, a combination of an increased PSTR and loss of osmotic conductance, are related to structural changes in the peritoneal membrane.[22] There is accumulating evidence that continuous exposure to dialysis solution components and repeated episodes of bacterial peritonitis are the main drivers of this process (Fig. 97-6). Although the relationship between structure and function has not been fully defined, increased PSTR is likely to reflect a greater vascular surface area, whereas loss of osmotic conductance requires an additional mechanism that could be explained by the progressive fibrotic changes.

Studies that have quantified these changes within the submesothelial collagenous zone suggest a progressive increase in thickness with time on PD (Figs. 97-7 and 97-8). Changes within the peritoneal vascular bed have also been identified. These include progressive changes to the structure of small venules ranging from subtle thickening of the subendothelial matrix to complete obliteration of vessels (Fig. 97-9).[23] In one study the extent of these changes in a small group of patients correlated with the loss of ultrafiltration.[24] Thus there is accumulating evidence that changes occur in both the

interstitial and vascular compartments of the dialyzed peritoneal membrane.

Preventing Membrane Injury

The main clinical factors associated with more rapid and severe membrane injury are early loss of residual renal function, recurrent or severe peritonitis, and the earlier use of higher glucose-containing solutions (often associated with loss of diuresis but an independent risk factor).[25] Hypertonic solutions may induce injury because of direct glucose toxicity, glucose degradation products (GDPs) present as a result of the sterilization process, or both. The prevention of membrane injury should focus on all of these drivers and include the following: preservation of residual renal function by avoiding volume depletion and using angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs); use of loop diuretics to maintain urine volume and delay use of hypertonic exchanges; use of icodextrin in the long exchange; avoidance of peritonitis; and use of low-GDP neutral pH solutions.[25] The balANZ study shows that the increase in PSTR over the first 2 years of PD is

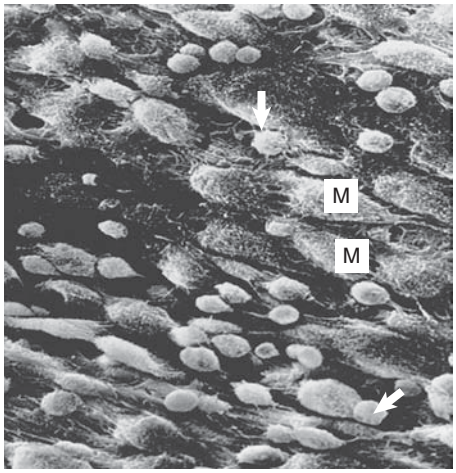

Figure 97-6 Peritonitis. Scanning electron micrograph of the peritoneum from a patient receiving peritoneal dialysis who has peritonitis. The small round cells *(arrows)* are phagocytes, which are widely distributed among the mesothelial cells *(M).* (Magnification ×1800.)

Peritoneal Membrane Thickening in Peritoneal Dialysis

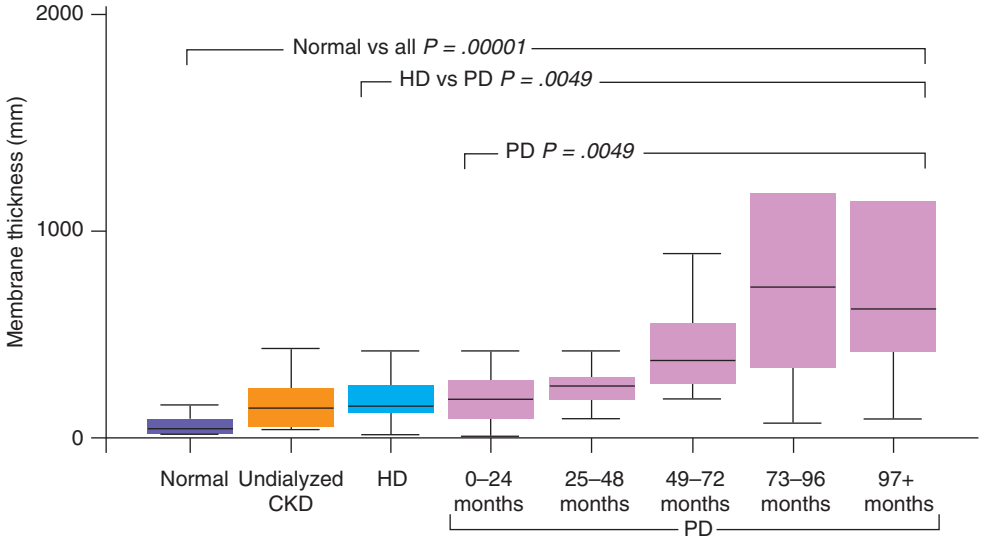

Figure 97-7 Peritoneal membrane thickening in peritoneal dialysis *(PD).* The thickness of the submesothelial collagenous zone of the peritoneal membrane in normal individuals, in undialyzed patients with advanced CKD, patients with uremia, in patients receiving hemodialysis *(HD),* and in those who have received PD for different periods. Membrane thickness is significantly increased in all uremic and dialysis patients compared with normal individuals. Membrane thickness increases significantly with duration of PD and is increased in PD patients as a group compared with HD patients.

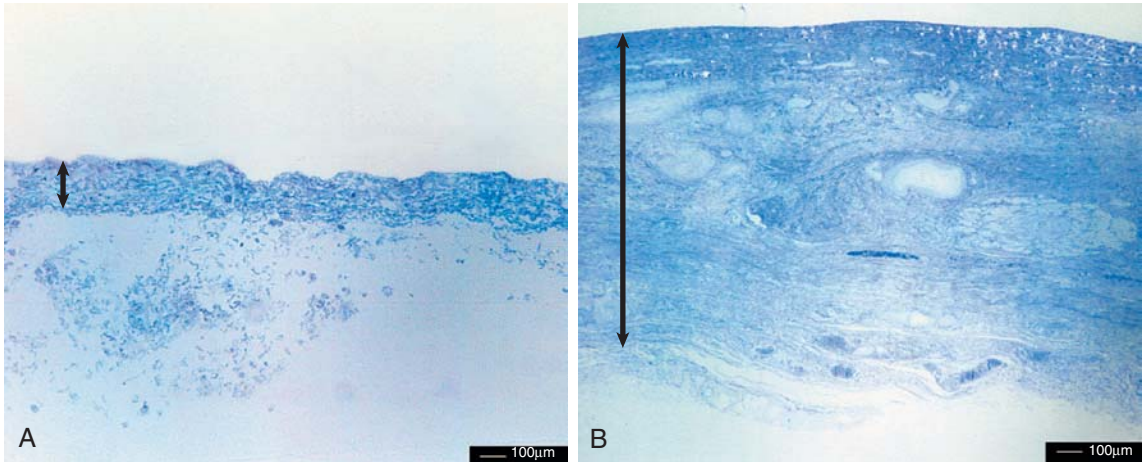

Figure 97-8 Morphologic changes in the parietal peritoneal membrane. A, Normal. **B,** A patient who has been on peritoneal dialysis (PD) for 10 years. Note the marked thickening of the submesothelial compact zone *(arrows)* (toludine blue).

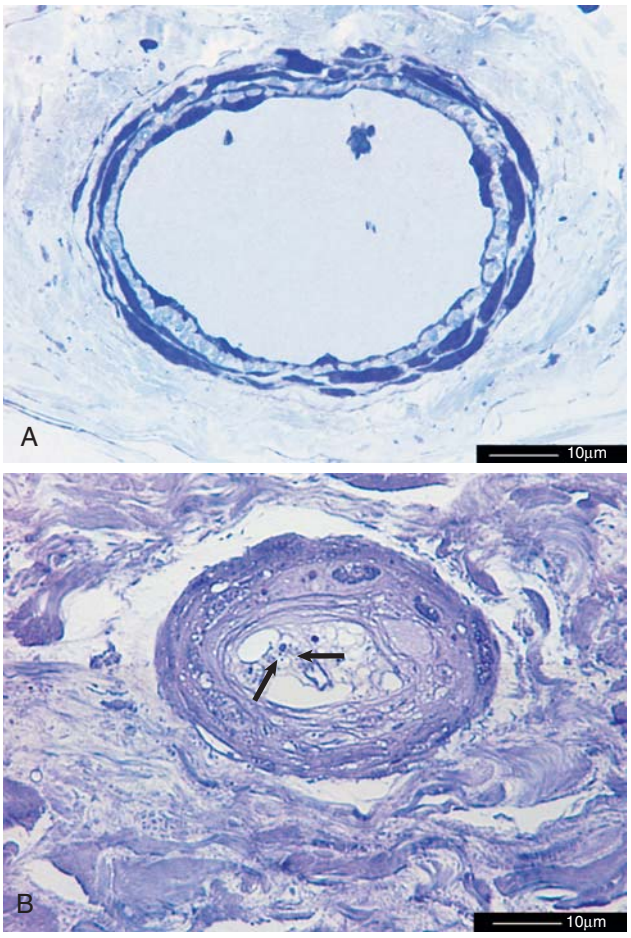

Figure 97-9 Blood vessels in the parietal peritoneum: transverse sections of peritoneal arterioles. A, Normal. **B,** Vasculopathy in a patient on peritoneal dialysis; the vascular lumen *(arrows)* is occluded by connective tissue containing fine calcific stippling.

prevented by use of ultralow-GDP dialysis fluid. Equally important, this study showed that achievement of less ultrafiltration early in the course of PD is associated with preservation of residual kidney function.[26] This supports the main strategy clinicians should adopt in preserving the membrane—prescribing to maintain adequate but not excessive ultrafiltration, which will only drive thirst and increase the risk of volume depletion.

Encapsulating Peritoneal Sclerosis

A minority of patients on PD develop EPS, in which the bowel is enveloped in a thick cocoon of fibrous tissue, causing intestinal obstruction (Fig. 97-10).[17] It is variable in severity but may be life-threatening, causing death from malnutrition or intra-abdominal catastrophe; but with experienced management by a multidisciplinary team, overall survival compares well with that of matched controls. The current definition of this syndrome requires both clinical signs and symptoms of bowel obstruction leading to weight loss and malnutrition (with or without features of systemic inflammation) combined with either typical features on imaging (CT scanning) or confirmation of fibrous cocooning at laparotomy. Although ultrafiltration failure, especially when it is associated with loss of osmotic conductance, is a risk factor, there are important differences, suggesting that this is at least in part a different pathologic process. It is predominantly a disease of visceral as opposed to parietal membrane, is usually associated with another risk factor or trigger (such

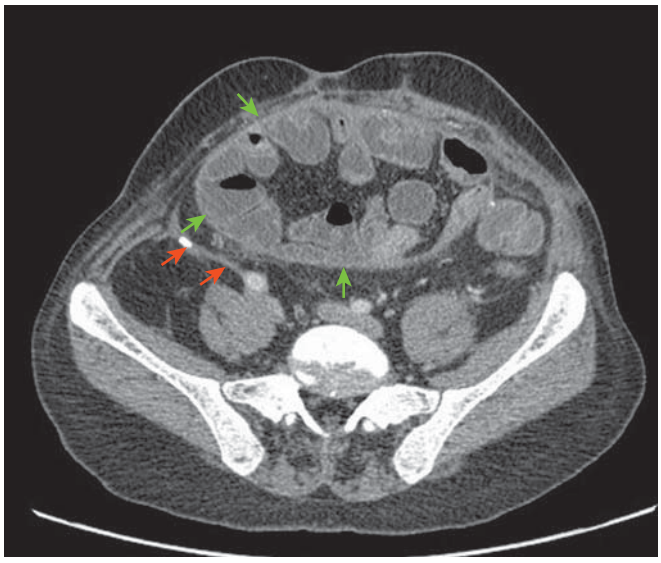

Figure 97-10 Encapsulating peritoneal sclerosis. Abdominal CT scan from a patient with encapsulating peritoneal sclerosis. *Red arrows* indicate thickened parietal peritoneum with calcification; *green arrows* indicate thickened visceral peritoneum forming a cocoon containing loops of bowel.

as severe peritonitis or stopping of PD, including for transplantation), and frequently has a systemic inflammatory phase; biopsy material more often shows inflammation and fibrinous exudates.

The single most important risk factor for EPS is time on PD; at 5 years the incidence is 2% to 3%, whereas by 10 years, this rises to 6% to 20%.[17] There is increasing evidence that the most successful treatment is surgery in the form of extensive adhesion lysis and excision of the peritoneum while avoiding enterotomy, especially when there are obstructive symptoms.[19] This should be undertaken by an experienced surgical team, which can achieve cure rates of 70% to 80%. Parenteral nutrition can be used, mainly as a preparation for surgery but occasionally as a long-term solution. In about 50% of patients, symptoms are less severe and gradually resolve. There appears to be little role for preemptive screening by CT scanning, but this is helpful in diagnosis. Most commonly, the condition develops after transfer from PD to either HD or transplantation; but if it develops in a patient on PD, the consensus is that PD should be stopped to avoid continued exposure to nonphysiologic dialysis solutions. Other strategies, such as continued irrigation, dual-modality treatment with PD and HD, and use of antifibrotic drugs such as tamoxifen, are practiced, but an evidence base for such management is lacking.

NUTRITIONAL AND METABOLIC COMPLICATIONS

Undernutrition

Cross-sectional surveys of patients receiving PD show that about 40% have evidence of mild and 8% severe protein-calorie depletion as judged by the subjective global assessment of nutritional state. Malnutrition is an adverse risk factor for morbidity and mortality of patients on PD and often associated with inflammation. The assessment and management of malnutrition are discussed further in Chapter 87. It has been recommended that ideally, PD patients should consume daily at least 1.2 to 1.3 g of protein per kilogram of body weight. In practice, many patients take only about 0.8 g/kg/day and seem to be nutritionally stable. It is likely that they have achieved a steady state but with a lower total body nitrogen or lean body mass.

Peritoneal dialysis patients have abnormal eating behavior with smaller meals, slow eating, and impaired gastric emptying compared

with normal individuals. The full peritoneal cavity may produce easy satiety, and some patients complain of feeling bloated. However, studies have shown that there is no actual difference in food consumption with or without dialysate in the abdomen. Amino acid–based dialysate improves nitrogen balance in malnourished patients, but the long-term nutritional benefit is marginal.[27]

One obvious contributing factor is protein loss through the peritoneum, which averages 8 g/day. It is proportional to effective membrane area and so is most marked during peritonitis and in patients with fPSTR. The ensuing hypoalbuminemia exacerbates the extravascular extracellular fluid (ECF) expansion in these patients.[28]

Acid-Base Status

Correction of acidosis is best achieved by use of dialysate with higher levels of potential buffer,[29] but if necessary, oral bicarbonate may be added. There is evidence that correction of acidosis, by whatever means, to within the upper half of the normal range for serum bicarbonate reduces protein catabolism, resulting in weight gain and increased midarm muscle circumference.[30] The use of amino acid–containing dialysate fluid can worsen acid-base status, requiring close monitoring.

Lipids and Obesity

Peritoneal dialysis results in a significant daily glucose absorption, which may range from 80 to 200 g/day, producing 300 to 800 kcal. The resultant effect is a tendency for patients on CAPD to develop features of metabolic syndrome: central obesity, hyperglycemia, dyslipidemia, and hyperinsulinemia; they may even develop frank diabetes, although there is no evidence that this is more common than in hemodialysis patients. These problems can be reduced by use of icodextrin and amino acid solutions in place of glucose with better glycemic control in diabetics.[31] Blood glucose monitoring in diabetic patients using icodextrin must not use glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ) test strips as this will lead to falsely high estimates and risk of severe hypoglycemia. The benefits of using lipid-lowering agents (e.g., simvastatin and ezetimibe) seen in chronic kidney disease to prevent cardiovascular events extend to PD patients.[32]

Despite these concerns, there is no evidence to suggest that PD should be avoided in obese patients. The survival advantage seen in HD associated with a higher body mass index is not seen with PD.[33]

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CHAPTER 98

Dialytic Therapies for Drug Overdose and Poisoning

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Poisoning and drug overdose, whether intentional or accidental, remains a common medical emergency, accounting for around 140,000 hospital admissions per year in the United Kingdom (nearly 1% of all admissions).[1] Most human exposures, however, do not require hospital admission; around 70% of the approximately 2.3 million cases in the United States in 2011 were managed at the site of the incident, in a non–health care facility.[2] The spectrum of agents ingested is wide, ranging from overdose of prescription or proprietary drugs to poisoning with nonpharmacologic substances and recreational drugs.

The pattern of toxin ingestion has changed over the years but also varies according to geographic location. Frequently implicated agents in industrialized societies include analgesics (acetaminophen, opioids, salicylates), antidepressants, sedatives, and antipsychotics. Barbiturate poisoning is now less common but was in the past a major contributor. Pesticides remain a frequent cause of poisoning in areas of the developing world.[3]

Changes in legislation have been instituted in attempts to affect availability of potential toxins; in the United Kingdom, for instance, paraquat was withdrawn from sale in July 2008, although occasional exposures continue as a result of residual stored product.[4] U.K. legislation limiting pack size of paracetamol (acetaminophen) in 1998 has been followed by a significant reduction in the number of deaths from paracetamol overdose.[5]

Data in the United States indicate a low mortality rate—1995 fatalities for 2.3 million episodes in 2011.[2] However, poisoning remains a major cause of death in young people.[3]

The mainstays of management include hemodynamic, respiratory, and other supportive care, prevention of further drug absorption (oral activated charcoal in specific patients), neutralization of drug toxicity (e.g., intravenous *N*-acetylcysteine after significant acetaminophen overdose or digoxin immune Fab [Digibind] for digitoxicity), and enhancement of drug elimination.

Extracorporeal therapy is one method of achieving poison removal, either by dialysis or by a nondialytic technique such as hemoperfusion. These enhanced elimination techniques are only occasionally needed, with around 2300 patients recorded as requiring extracorporeal therapy in the United States in 2011.[2] In that report the treatment was predominantly hemodialysis (HD) with only 14 patients recorded as receiving hemoperfusion, the decline of which is perhaps explained by the increasing rarity of theophylline and barbiturate overdose—historically, the main indications for this technique.

Aspects of the management of poisoning beyond those related to extracorporeal therapies are well covered through resources such as Toxbase in the United Kingdom (www.toxbase.org) and the American Association of Poison Control Centers (www.aapcc.org). Other local and regional poison information services are linked through the website of the European Association of Poisons Centres and Clinical Toxicologists (www.eapcct.org).

TREATMENT MODALITIES

Intermittent Hemodialysis and Hemofiltration

Diffusion against a steep concentration gradient, the physical process used in intermittent HD, encourages the rapid removal of the smaller solutes that are the usual agents of overdose. Clearances can be enhanced by increasing dialyzer efficiency (indicated by the K_oA, the urea mass transfer area coefficient) or membrane surface area. Larger-solute removal can be enhanced by increasing dialyzer flux when intermittent HD is used (for toxins >500 d and up to 10,000 d, e.g., desferrioxamine [deferoxamine] aminoglycosides) or by switching to hemofiltration (usually applied continuously; see later), in which the physical process of higher volume convection and larger membrane pore size can allow removal of toxins up to approximately 40,000 d.

A range of physical and biologic factors determines whether a given toxin can be eliminated by HD and whether that elimination is actually therapeutic (Box 98-1). In addition to molecular weight, other important physical characteristics relevant to dialyzability are water solubility and the degree of protein binding.

For each individual patient, it should be determined whether HD is expected to contribute significantly to total toxin removal. Dialysis will have a limited impact if the rate of drug removal is significantly faster by endogenous routes. The risks of therapy (e.g., acute transfer to a specialist center, vascular access, anticoagulation) also have to be balanced against the clinical relevance of any gain in drug elimination. If endogenous elimination is minimal—either because these routes are naturally limited or because of toxin-associated attenuation of elimination (e.g., liver or renal failure)—HD can be effective. It is generally accepted that if at least 30% can be added to total body clearance by extracorporeal treatment, its use is justified. This is not a threshold that is readily calculated at the bedside without knowledge of endogenous clearance rates and the expected contribution from exogenous therapy. The summary of product characteristics may help determine the endogenous clearance rates (at least for pharmaceuticals; available from, for instance, www.medicines.org.uk/emc/) but may not account for the impact of disease on specific endogenous routes of elimination. An estimate of the clearances of a variety of solutes of different molecular weights by a dialyzer can be obtained from its product insert. For hemofiltration (see the later discussion of continuous renal replacement therapy [CRRT]), an estimate of clearance can be provided by the ultrafiltration rate.

The efficacy of toxin removal is also influenced by its theoretical volume of distribution (V_D). Substances confined to the bloodstream

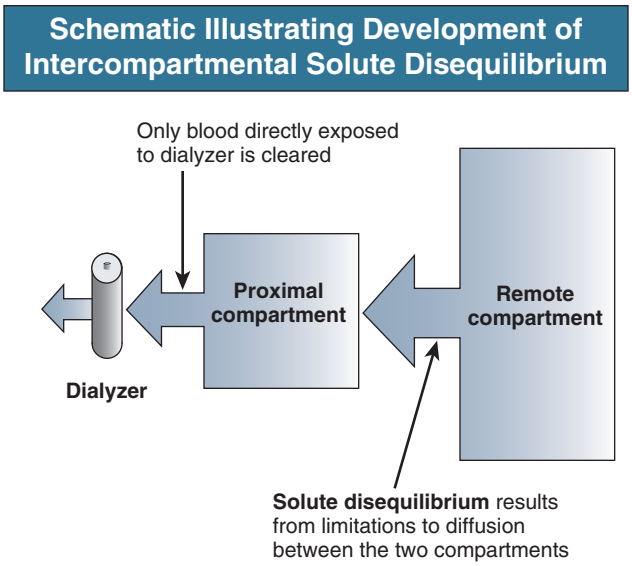

Figure 98-1 Intercompartmental solute disequilibrium. Access of dialyzer to toxin is limited by disequilibrium, which retains toxin in remote compartment.

Factors Affecting Toxin Removal by Hemodialysis
Molecular weight
Water solubility
Degree of protein binding
Significance of dialytic toxin removal relative to endogenous routes of clearance
Theoretical volume of distribution
Degree of solute compartmentalization

Box 98-1 Factors affecting toxin removal by hemodialysis. See text for explanation.

will have a low V_D (approximately 0.07 l/kg body weight); those distributed in the extracellular space, a V_D of approximately 0.2 l/kg; and those confined to total body water, approximately 0.6 l/kg. Higher distribution volumes are, however, not uncommonly found in those substances with avid tissue binding or sequestration. As V_D increases, more solute must be removed for achievement of a particular blood level. The ideal solute would therefore have a low distribution volume, which would also be a single, well-mixed compartment that was directly accessible by the dialysis process. However, as shown in Figure 98-1, solute is often distributed across at least one remote body compartment that is not directly accessible during HD. If there is any resistance to solute movement between the accessible proximal and the remote compartments, disequilibrium will develop over the course of the dialysis session, reducing the overall efficiency of toxin removal. This may be significant, as in the case of lithium, and will manifest as a large postdialysis rebound in blood levels as solute re-equilibrates from the remote compartment. A significant solute rebound to a potentially toxic level may be missed if the immediate postdialysis blood level is relied on as a measure of elimination (Fig. 98-2).

Extending the HD session beyond 4 hours can to some extent ameliorate rebound, but intermittent HD is an inherently inefficient process that depends on the solute concentration presented to the dialyzer. Most solute removal occurs at the start of dialysis. Any gains in solute removal will be disproportionately low in comparison to

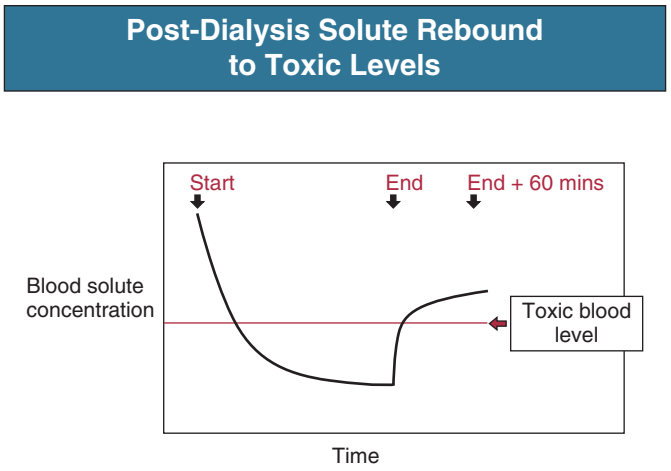

Figure 98-2 Postdialysis rebound. Falling solute concentration during dialysis with rapid postdialysis rebound to toxic levels.

the increases in dialysis time. An alternative or adjunctive solution is to increase dialysis session frequency.

Compartmentalization need not preclude HD-related toxin removal, but the closer its distribution is to a single compartment, the easier that removal becomes.

In summary, intermittent HD is usually the first-choice extracorporeal modality because of its common availability, the rapidity of toxin removal, and the low molecular weight of the common agents of poisoning. The role of other renal replacement modalities is less clear because of a lack of published data.

Peritoneal Dialysis

Peritoneal dialysis is rarely used in the treatment of poisoning because of the comparatively slow rate of clearance, the risks associated with acute peritoneal dialysis catheter insertion, and the widespread availability of extracorporeal techniques (at least in the industrialized world). It may have a role in the treatment of poisoning in children because the lower clearance may be sufficient for their smaller solute distribution volumes. There may, in addition, be technical challenges making HD less satisfactory, especially in the very young.

Continuous Renal Replacement Therapy

Continuous renal replacement therapy may be used when intermittent HD is not immediately available or when more rapid solute removal would be compromised by significant intercompartmental disequilibrium. For small-solute clearances, continuous hemofiltration and continuous HD have near kinetic equivalence. Full saturation of dialysate effluent in continuous HD, because of its slow flow rates, gives it a small-solute concentration similar to both the ultrafiltrate from hemofiltration and plasma water as it leaves the hollow-fiber device. CRRT gives better longer-term solute clearances (over the course of several days) but does not provide the rapidity of elimination afforded by intermittent HD when minimizing toxin exposure is a high priority. Delivered small-solute clearances of CRRT can be maximized by combining techniques in the form of continuous hemodiafiltration. If it is logistically possible, an ideal combination may be initial use of intermittent HD for rapid reduction of toxin levels, with continuous therapy then being applied to ameliorate any postdialysis rebound when this is predicted. Although combining some of the advantages of both continuous and intermittent

Figure 98-3 A charcoal hemoperfusion cartridge.

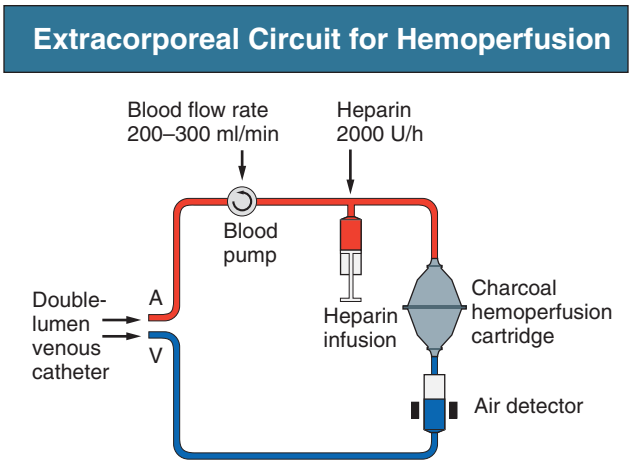

Figure 98-4 Extracorporeal circuit for hemoperfusion.

techniques, the role for hybrid modalities, such as sustained low-efficiency dialysis (SLED), requires further evaluation.

Although small-solute clearances are similar in continuous hemofiltration and continuous HD, the former should be used in preference if larger toxins (as described earlier for intermittent HD) require removal.

Renal replacement therapy is also indicated for acute kidney injury (AKI), which can result from ingestion of a variety of different agents (e.g., acetaminophen), and for other complications of poisoning such as pulmonary edema, electrolyte and acid-base disturbances, and hypothermia and hyperthermia.

Because renal replacement therapy modalities are often applied for drug elimination in the absence of any actual renal dysfunction or serious electrolyte disturbance, careful monitoring for evolving biochemical abnormalities is required. Hypokalemia can be corrected by adjusting the dialysate or replacement fluid composition and by supplementation. Hypophosphatemia can be addressed with standard supplements. At least for intermittent HD, the risk of developing a metabolic alkalosis can be attenuated by using a dialysate bicarbonate concentration at the lower end of the physiologic range, provided there is no coexistent renal impairment and no metabolic acidosis or the risk of it. Manipulation of the bicarbonate concentration of premanufactured replacement or dialysate fluid in CRRT is not practical; this is another advantage of intermittent HD in this setting because it affords flexibility of bicarbonate dialysate concentration if a severe metabolic alkalosis is present.

Hemoperfusion

The technique involves the extracorporeal circulation of blood through a hemoperfusion cartridge (Fig. 98-3) containing an adsorbent material such as activated charcoal or a resin. The charcoal sorbent particles are coated with a polymer to increase biocompatibility and reduce the risk of thrombocytopenia. Hemoperfusion removes those substances that can bind to the adsorbent material. It is effective at removing uncharged molecules through competitive binding, especially those that are significantly plasma protein bound and lipophilic. As with HD and hemofiltration, the likely proportional contribution to total toxin elimination should be considered before hemoperfusion is begun.

Other than the cartridge itself and the lack of dialysate and other replacement fluid circuits, the disposables and hardware are those used for standard intermittent HD (Fig. 98-4). Hemoperfusion is much less widely available than HD or hemofiltration but may have its principal usefulness in the removal of protein-bound drugs that are not eliminated effectively by those modalities.[6]

Standard anticoagulation protocols may be insufficient for hemoperfusion because heparin is also adsorbed. A larger unfractionated heparin initial bolus and maintenance dose (e.g., ≥2000 U/h) is usually required, with subsequent adjustments guided by regular monitoring of clotting times during the procedure. The cartridge manufacturer's instructions should be reviewed carefully, because some require specific priming with dextrose solution to prevent hypoglycemia. Other complications include hypocalcemia, charcoal embolization, leukopenia, thrombocytopenia, and adsorption of coagulation factors.

Saturation of the adsorbent material limits the duration of treatment with any individual hemoperfusion cartridge to around 3 hours, although this is usually adequate for a significant lowering of toxin blood levels. Continuous hemoperfusion can help attenuate the postsession rebound that can occur with intermittent treatment, with cartridges being changed every 4 hours.

If a toxin is equally well removed by intermittent HD and hemoperfusion, intermittent HD should be used preferentially, because it also allows fluid, electrolyte, and other metabolic control. Combined hemoperfusion-HD has also been used but only rarely, and its role is not defined.

Other Modalities

There are a few reports of the use of plasma exchange and MARS (molecular adsorbent recirculating system) in poisoning. In principle, both should be useful for those toxins that are strongly protein bound. Plasma exchange can also clear the red cell fragments and free hemoglobin that result from poisoning with sodium chlorate or other agents that can cause hemolysis.

WHEN SHOULD EXTRACORPOREAL REMOVAL BE COMMENCED?

The use of extracorporeal therapy should be considered at an early stage when it is recognized that general supportive therapy including the use of activated charcoal and administration of recognized antidotes will not be effective in removing specific drugs and toxins, particularly in the setting of AKI. The common indications for extracorporeal drug removal are shown in Table 98-1.

Principles guiding the decision to initiate extracorporeal therapy are shown in Box 98-2.

Some Poisonings for Which Extracorporeal Removal May Be Indicated

Hemodialysis	Hemofiltration	Hemoperfusion
Alcohols	Aminoglycosides	*Amanita* mushroom
Ethanol	Desferrioxamine	Barbiturate
Methanol	Sodium edetate	Carbamazepine
Ethylene glycol	Theophylline	Meprobamate
Isopropanol		Theophylline
β-Blockers		
Atenolol		
Sotalol		
Lithium		
Meprobamate		
Metformin		
Salicylates		
Theophylline		

Table 98-1 Some poisonings for which extracorporeal removal may be indicated.

Criteria for Considering Extracorporeal Therapy for a Removable Substance

- Toxic blood levels (if a threshold of toxicity can be defined)
- Serious clinical manifestations despite optimal support
- Delayed action possible (e.g., ethylene glycol, methanol, paraquat)
- Metabolic effects (e.g., acidosis)
- Endogenous routes of clearance, impaired (e.g., liver or renal failure)

Box 98-2 Criteria for considering extracorporeal therapy for poisoning.

EXTRACORPOREAL THERAPY FOR SPECIFIC DRUGS AND POISONS

Alcohols

Ethylene glycol and methanol can be found in antifreeze, de-icing solutions, and windscreen cleaning fluid. The ingestion of as little as 1 g of either methanol or ethylene glycol per kilogram is considered as potentially lethal and results in significant toxicity. Poisoning should be suspected in any patient presenting with nausea, vomiting, abdominal pain, impaired consciousness, severe metabolic acidosis, and AKI. Without prompt treatment there will be resulting optic nerve damage, convulsions, coma, and ultimately death. The urine should be examined for the presence of needle shaped crystals of calcium oxalate monohydrate which are pathognomonic for ethylene glycol toxicity. The toxicity results from metabolism of ethylene glycol and methanol by alcohol dehydrogenase to the toxic metabolites glycolic acid and formic acid respectively. Formic acid causes injury to the basal ganglia and the retina, resulting in blindness. Ethylene glycol is metabolized to glycolic acid and oxalate, resulting in renal tubular injury and obstruction. The associated severe acidosis facilitates the ability of the toxic metabolites to penetrate the cells and cause further injury. Poisoning with ethylene glycol or methanol results in a raised anion gap acidosis and an elevated plasma osmolal gap. However, the raised osmolal gap is not pathognomonic and can also occur with overdoses of excessive alcohol, isopropanol, and diabetic ketoacidosis.

Early recognition of ethylene glycol methanol poisoning is essential, allowing institution of treatment to inhibit hepatic alcohol dehydrogenase with ethanol or fomepizole. Fomepizole has now replaced ethanol as first-line therapy[7,8]; it is safe with minimal side effects, and although it is expensive, this can be offset when compared with the increased cost of HD and intensive care unit admission if fomepizole is not used.

Fomepizole should be prescribed if there is a clear history of ethylene glycol and/or methanol ingestion with an osmolal gap of greater than 10 (indicating significant toxicity) or if the ethylene glycol–methanol blood level is over 20 mg/dl. Fomepizole is administered as a loading dose of 15 mg/kg intravenously. This is followed by 10 mg/kg every 12 hours for four doses and then 15 mg/kg every 12 hours until the metabolic acidosis has resolved and the serum concentration of ethylene glycol and methanol is below 20 mg/dl, or below 10 mg/dl in the presence of end organ damage. If the blood pH is less than 7.3, an infusion of sodium bicarbonate should be commenced at 1 to 2 mEq/kg to maintain the pH above 7.35. Patients who have ingested methanol should also receive folinic acid 50 mg intravenously every 6 hours to enhance the metabolism of formic acid. The administration of thiamine 100 mg intravenously or pyridoxine 50 mg intravenously should be considered in patients with poor nutritional status who have sustained an overdose of ethylene glycol. If fomepizole is not available, intravenous 10% ethanol should be administered as a loading dose of 800 mg/kg followed by an infusion of 80 to 160 mg/kg/h to achieve a serum ethanol concentration of about 1 to 1.5 g/l. Ethanol should be administered until no ethylene glycol or methanol is detectable in the blood.

Immediate HD is recommended if ingestion of ethylene glycol or methanol is confirmed with serum concentration above 50 mg/dL in the setting of severe metabolic acidosis or the presence of end organ damage such as AKI or visual disturbance. It is important to recognize that fomepizole is removed by HD. Therefore if a loading dose of fomepizole has already been administered, a continuous infusion of 1 to 1.5 mg/kg/h should be prescribed for the duration of the HD. Similarly, if ethanol has been used as a competitive inhibitor of alcohol dehydrogenase, its dose will have to be doubled because of its removal by HD.

For optimal clearance the dialyzer should have a large surface area (>1.5 m^2), and the blood flow rate should be greater than 300 ml/min. Bicarbonate buffer should be used and serum concentrations of ethylene glycol and methanol should be measured 2 hours after cessation of treatment to take account of rebound. HD should continue until the pH has normalized and the concentration of ethylene glycol or methanol is below 25 mg/dl.

Patients who have ingested large quantities of ethylene glycol and methanol may require further HD. Continuous extracorporeal treatment is less effective in removing ethylene glycol and methanol but may be used if intermittent HD is not available.

β-Blockers

Symptomatic β-blocker overdose will present within 2 hours of ingestion in the majority of patients, with bradycardia and hypotension. Clinical presentation may also include changes in mental status, seizures, bronchospasm, hypoglycemia and cardiogenic shock in severe overdoses. An increased risk of severe toxicity occurs in patients who have co-ingested other drugs that act on the cardiovascular system. Bradycardia can be treated with intravenous atropine at 0.5 to 1 mg, and bronchospasm can be treated initially with high-dose nebulized salbutamol or albuterol. Intravenous fluids (crystalloid) should be administered to treat hypotension. Symptomatic hypoglycemia requires intravenous dextrose. Activated charcoal should be administered orally to all patients presenting within 1 to 2 hours of β-blocker overdose.

Extracorporeal removal of β-blockers is rarely required and only in those patients who have not improved despite maximal medical therapy. Extracorporeal removal is effective only in hydrophilic, minimally protein-bound drugs such as atenolol, sotalol, nadolol, and acebutolol. Propranolol, timolol, and metoprolol are not removed. Intermittent HD is recommended in hemodynamically stable patients. Continuous venovenous hemodialysis (CVVHD) or continuous venovenous hemodiafiltration (CVVHDF) may be considered in patients who are hemodynamically unstable. There are very few data regarding the effectiveness of β-blocker removal using continuous venovenous hemofiltration (CVVH).

Lithium

Patients with severe lithium poisoning may present with arrhythmias, hypotension, confusion, coma, or seizures. HD is recommended if the serum lithium concentration is above 4 mEq/l or above 2.5 mEq/l in a patient with central nervous system manifestations. Lithium (molecular weight 74 d) is removed easily by HD because of its low molecular weight and negligible protein binding. The clearance of lithium by HD is superior to that achieved by the kidneys, which is limited by significant proximal tubule reabsorption of lithium. Because lithium equilibrates relatively slowly between the extracellular and intracellular compartments, a rebound increase in serum levels of lithium follow HD.[9] Therefore, extended[10] or frequent HD treatment may be needed to minimize the impact of disequilibrium. Serum lithium levels should be checked 6 hours after completion of treatment to guide further therapy. Continuous modalities including CVVHD and CVVH may be advantageous and have been used successfully.[11]

Metformin

Metformin (molecular weight 166 d) is a biguanide hypoglycemic drug used to treat patients with diabetes mellitus. Metformin acts by enhancing the suppression of gluconeogenesis by insulin, reducing glucagon-stimulated gluconeogenesis and increasing the uptake of glucose by muscle and adipose cells. Patients who have taken an overdose of metformin may present with tachypnea, nausea, abdominal pain, tachycardia, hypotension, and, in the setting of AKI, a severe lactic acidosis. Metformin is normally excreted unmetabolized from the kidneys and therefore accumulates if there is reduced kidney function. There is lactic acidosis because metformin inhibits hepatic gluconeogenesis from lactate, and promotes the conversion of glucose to lactate in the small intestine. Medical management will involve the intravenous administration of sodium bicarbonate. In patients who are unresponsive to medical management or who also present with AKI, extracorporeal therapy will be necessary to correct the acidosis. Intermittent HD is effective, and more recently there have been reports of continuous extracorporeal therapy including CVVH being successful.[12]

Salicylates

The clinical manifestations of salicylate overdose include fever, sweating, tinnitus, epigastric pain, nausea, vomiting, diarrhea, vertigo, and blurring of vision. In severe overdoses clinical presentation may progress to depression of mental status, noncardiogenic pulmonary edema, and death. Salicylate intoxication initially results in activation of the respiratory center with hyperventilation and a respiratory alkalosis. This is then followed by a metabolic acidosis caused by the accumulation of lactic acid and ketoacids. Therefore the patient may present with either a respiratory alkalosis or a mixed respiratory alkalosis–metabolic acidosis. Diagnosis is based on the presenting history and clinical examination and confirmed with serum salicylate levels. Moderate toxicity is occurs with salicylate levels greater than 50 mg/dl. Ingestion of enteric-coated salicylate preparations may delay peak levels for up to 36 hours.

Gastric lavage should be attempted up to 12 hours after ingestion if the airway is protected, and activated charcoal should be administered orally. Hypoglycemia should be treated with intravenous dextrose.

Increased salicylate tissue penetration and toxicity can occur with only small decreases in the blood pH as a result of increased concentration of nonionized salicylate. Intravenous sodium bicarbonate should be given to decrease tissue penetration and facilitate the excretion of salicylate through the kidneys. Sodium bicarbonate can be administered as an initial bolus of 1 to 2 mEq of sodium bicarbonate per kilogram and then as an infusion of 100 to 150 mEq of sodium bicarbonate in 1 L of 5% dextrose titrated to maintain a urinary pH above 7.5. Sodium bicarbonate infusion should not be used if the patient has oliguric AKI, pulmonary edema, or cerebral edema because of the risk of precipitating further volume overload and end organ injury.

Extracorporeal therapy is indicated in patients who do not respond to the medical management just described. It is also indicated in patients who have AKI (preventing salicylate excretion), pulmonary edema, or altered mental status or in whom the serum salicylate concentration is greater than 100 mg/dl. Intermittent HD has the advantage over hemoperfusion because of its more rapid correction of associated electrolyte abnormalities and acidemia. There are few data on the use of CVVH for salicylate poisoning.

Theophylline

The clinical presentation of theophylline overdose includes nausea, vomiting, diarrhea, gastrointestinal hemorrhage, hypokalemia, seizures, arrhythmias, and hypotension. Overdose may be acute or chronic in nature. Indications for extracorporeal removal of theophylline after acute intoxication include a serum level above 80 mg/l, or a serum level above 60 mg/l in patients older than 65 years, or a history of epilepsy, recurrent seizure activity, liver disease, cardiac failure, or ischemic heart disease. Indications for extracorporeal removal after chronic intoxication include a theophylline level higher than 40 mg/l in a patient older than 65 years or in any patient who has had seizure activity or an arrhythmia. Theophylline is readily cleared by either HD or hemoperfusion as a result of its low volume of distribution and minimal protein binding.[13] High-efficiency HD is more effective in removing theophylline than hemoperfusion and is associated with fewer side effects. CVVH can be used but requires a more sustained period of treatment.

Valproate

Valproate (molecular weight 144 d) overdose may present with clinical features that include mild confusion, lethargy, nausea, vomiting, tachycardia, hypotension, metabolic acidosis, and electrolyte disturbances (hyponatremia and hypocalcemia). Extracorporeal therapy is rarely indicated for the removal of valproate except in patients with refractory metabolic acidosis or hemodynamic instability. Valproate is poorly cleared despite a low molecular weight and a low volume of distribution as a result of its high degree of protein binding. However, at higher serum levels above 100 mg/dl, the valproate protein binding sites become saturated, resulting in unbound free drug. HD has the advantage over hemoperfusion because it not only readily clears the unbound drug but also reverses associated

metabolic abnormalities.[14] Despite a number of case reports detailing the use of extracorporeal removal of valproate, there is no clear-cut evidence that it improves clinical outcomes.

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CHAPTER 99

Plasma Exchange

Jeremy Levy

The place of plasma exchange (plasmapheresis) in the management of renal disease has become clearer in the last 10 years, with increasing numbers of controlled studies comparing therapeutic plasma exchange with other treatments. Despite this, in many renal diseases the quality of published data still remains poor, and the precise role for plasma exchange unclear. Plasma exchange came into widespread clinical use after early reports of beneficial effects in Goodpasture disease in the mid-1970s. It is used to remove many large-molecular-weight substances from plasma, including pathogenic antibodies, cryoglobulins, and lipoproteins. Newer techniques have also been developed to allow more selective removal of plasma components, such as double-filtration plasma exchange, cryofiltration, and immunoadsorption with or without immobilized ligands.

TECHNIQUES

Plasma exchange can be carried out either by centrifugal cell separators or, more commonly in renal units, with hollow-fiber plasma filters and standard hemodialysis equipment (Figs. 99-1 and 99-2). Centrifugal devices allow withdrawal of plasma from a bowl with either synchronous or intermittent return of blood cells to the patient.[1] There is no upper limit to the molecular weight of proteins removed by this method. The bowls and circuits are single use and disposable and require relatively low blood flow rates (90 to 150 ml/min). Platelet loss can be a particular problem with centrifugal devices, and platelet counts can decrease by as much as 50%. Membrane plasma filtration uses highly permeable hollow fibers with membrane pores 0.2 to 0.5 µm. Plasma readily passes through the membrane while the cells are simultaneously returned to the patient. All immunoglobulins will cross the membrane (IgG more efficiently than IgM); however, some large immune complexes and cryoglobulins may not be adequately cleared, although many membranes allow for clearance of molecules up to 3 million daltons. There is no loss of platelets, but hemolysis can occur if transmembrane pressures are too high (a rare complication). Blood flow rates required are higher (100 to 300 ml/min); there is no increase in rate of plasma filtration at higher blood flows, but an increased risk of hemolysis. Membranes used in plasma filters are polysulfone, polypropylene, cellulose diacetate, polymethylmethacrylate, or polyacrylonitrile.[1] It has been suggested that the adsorptive properties of the membrane for cytokines and other biomolecules may account for some of the beneficial effects of plasma filtration. There have been occasional reports of mild adverse reactions in patients taking angiotensin-converting enzyme (ACE) inhibitors when plasma is filtered with ethylene vinyl alcohol or acrylic copolymer membranes. Reuse of plasma filters is not advised, but performance data do not indicate a major loss of function during routine plasma exchange. For patients with severe renal failure, sequential hemodialysis and plasma exchange can easily be performed with plasmafiltration.

Vascular access is usually achieved using standard central venous catheters, but if a patient already has an arteriovenous (AV) fistula, then of course this can be used. However, sometimes it is also possible to perform plasma exchange using peripheral access through large-bore, short, intravenous cannulas, placed in the antecubital fossa, especially with centrifugal devices because the blood flow rates required are low. Single-needle access using an AV fistula is also relatively easy to accommodate, especially for centrifugal plasma exchange, in which the blood removal and return can be asynchronous, but also for membrane filtration. Anticoagulation is almost always needed and must be carefully managed in patients with a bleeding risk, for example, those with thrombotic microangiopathy (TMA), recent or ongoing pulmonary hemorrhage, or a recent renal biopsy. In general, citrate is used for centrifugal plasma exchange, and heparin for membrane plasma filtration; however, citrate has particular advantages in patients at higher bleeding risk in view of its lack of systemic anticoagulant actions.[1] When heparin is used, higher doses may be needed than in hemodialysis as a result of increased losses during the procedure (heparin is protein bound). Bolus doses of unfractionated heparin of 2000 to 5000 U are given initially, and then 500 to 2000 U/hr. Anticoagulant is administered prefilter.

Both methods of plasma exchange require large volumes of colloid replacement. A single plasma volume exchange will lower plasma macromolecule levels by approximately 60%, and five exchanges over 5 to 10 days will clear 90% of the total body immunoglobulin (Fig. 99-3).[1,2] For most patients, this is achieved by removing 50 ml of plasma per kilogram of body weight at each procedure (approximately 4 liters for a 75-kg person). Daily plasma exchange is likely to be most effective in rapidly depleting total body load in view of redistribution of immunoglobulins from the extravascular compartments, but there is no good evidence that intensity of exchanges has a major effect on outcomes except in patients with hemolytic uremic syndrome (HUS) with poor prognostic markers (see later discussion). Indeed, alternate-day exchanges are of proven efficacy in antineutrophil cytoplasmic antibody (ANCA)–associated diseases. Replacement with crystalloid is contraindicated because of the need to maintain colloid oncotic pressure. Synthetic gelatin–based plasma expanders or hydroxyethyl starch (Hespan) can be used as part of a replacement regimen but have been reported to cause a coagulopathy in patients with sepsis, and have a shorter half-life than human albumin, which is the mainstay replacement fluid. The major disadvantage of albumin solutions is the lack of clotting factors, with the potential development of depletion coagulopathy after plasma exchange. Fresh-frozen plasma (FFP) should be given, usually in addition to human albumin solution, in patients at particular risk of bleeding. If partial replacement is with FFP this should be given late during the exchange so that the constituents are not removed by the ongoing plasma exchange. However, almost all the serious complications of plasma exchange (hypotension,

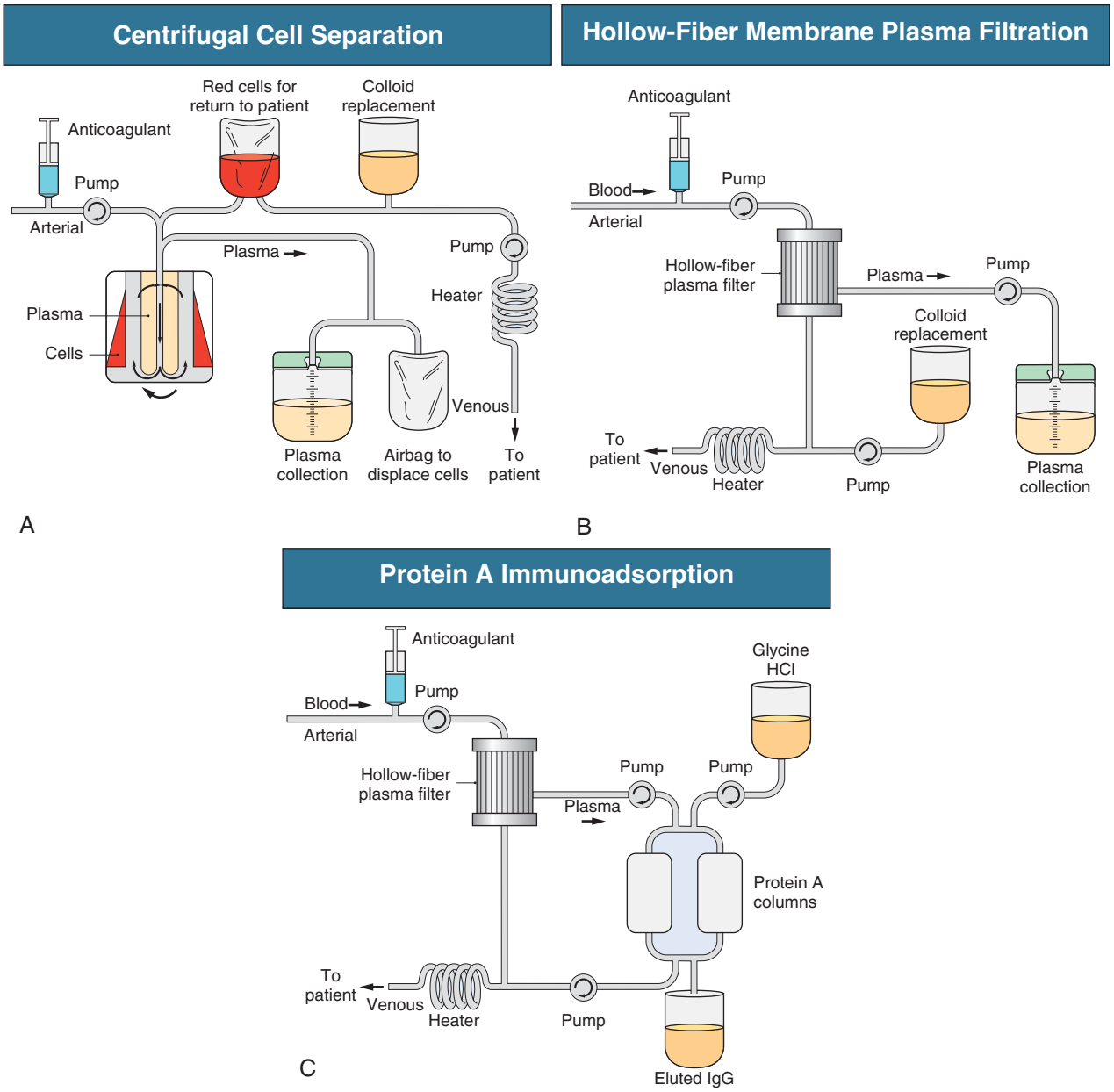

Figure 99-1 Plasma exchange and immunoadsorption techniques. Techniques include centrifugal cell separation **(A),** hollow-fiber membrane plasma filtration **(B),** and protein A immunoadsorption **(C).**

anaphylaxis, citrate-induced paresthesia, urticaria) have been reported in patients receiving FFP rather than albumin (see later discussion).[1,3] Both human products carry a tiny risk of transmission of infectious diseases, especially viral. Standard regimens for plasma exchange are summarized in Table 99-1. Human albumin solution (4% to 5%) should be used for all exchanges except in thrombotic microangiopathies (in which plasma should provide the total exchange), and FFP should form part of the exchange when bleeding risk is high (ongoing pulmonary hemorrhage or within 48 hours of biopsy or surgery). If fibrinogen levels decrease to below 1.25 to 1.5 g/l or prothrombin time is increased 2 to 3 seconds above normal, then FFP should be administered.

Double-filtration plasma exchange (or cascade filtration) uses membrane filtration to separate cells from plasma, and then a secondary plasma filtration (pore size 0.01 to 0.03 μm) to remove plasma solutes based on molecular size. Most albumin is therefore returned to the patient, together with lower-molecular-weight proteins, reducing the need for replacement fluids. Cryofiltration uses a similar principle but exposes the filtrate to 4° C during the procedure, with the aim of precipitating cryoproteins. These techniques are not widely available.

Selective and specific immunoadsorption techniques are increasingly available. Protein A immunoadsorption has been used to remove immunoglobulin alone from plasma, without the need for replacement fluids and without depletion of clotting factors and complement (see Fig. 99-1, *C*). Protein A selectively binds the Fc domains of immunoglobulin molecules, and the immunoadsorption columns can be repeatedly regenerated. Columns have been used for 1 year for a single patient on up to 30 occasions; however, the repeated acid stripping during regeneration does reduce the efficacy of antibody binding. This technique has been used to treat conditions in which autoantibodies are thought to play a key pathogenic role

Figure 99-2 **A centrifugal cell separator in use for plasma exchange.**

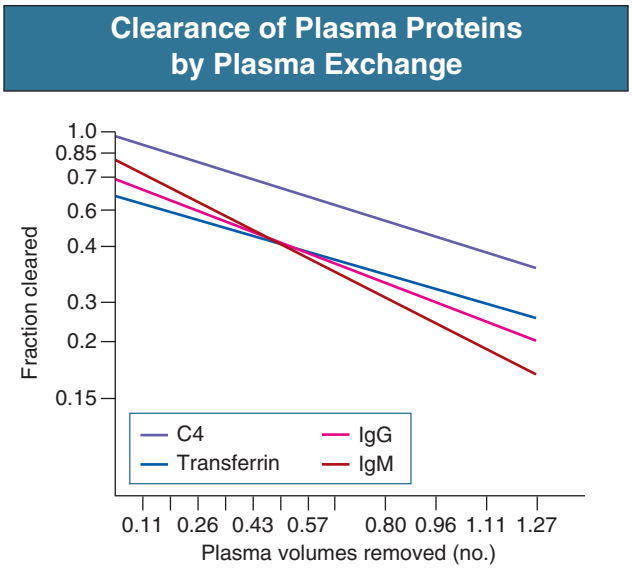

Figure 99-3 **Clearance of plasma proteins by plasma exchange.** Clearance from the intravascular compartment varies with the plasma volume exchanged and among individual proteins. *(Modified from reference 2.)*

Regimens for Plasma Exchange in Renal Disease

Indication	Anti–Glomerular Basement Membrane Antibody (anti-GBM) Disease	Small-Vessel Vasculitis	Cryoglobulinemia	Recurrent FSGS After Transplantation	HUS/TTP
Duration of treatment	Daily, at least 14 days until anti-GBM antibodies 20% of baseline	Daily, 7-10 days depending on clinical response	At least 7-10 days or until clinical response	Daily, at least 10 days initially, then continuing less frequently, often for months	Daily for 7-10 days or until platelet count 80-100 $\times 10^9$/l (sometimes needed twice daily)
Exchange volume	50 ml/kg each treatment	As for anti-GBM disease	As for anti-GBM disease	As for anti-GBM disease	As for anti-GBM disease
Replacement fluid	Human albumin 5% (unless bleeding risk)	As for anti-GBM disease	As for anti-GBM disease	As for anti-GBM disease	Fresh-frozen plasma (FFP) or cryo-poor FFP
Additions to replacement fluid	20 ml 10% calcium gluconate (occasionally more), 3 ml 15% KCl if not dialysis dependent, heparin 5000-10,000 U (unless citrate anticoagulation)	As for anti-GBM disease	As for anti-GBM disease	As for anti-GBM disease	As for anti-GBM disease (may need more calcium because of increased volume of FFP-containing citrate)
Immunosuppression	See Chapter 24	See Chapter 25	See Chapter 21	See Chapter 29	See Chapter 29
Variations	FFP 5-8 ml/kg as part of exchange volume if hemorrhage risk (renal biopsy in last 48 hr, lung hemorrhage, platelets <40 $\times 10^9$/l, fibrinogen <1.5 g/l); immunoadsorption may be as effective	As for anti-GBM disease Immunoadsorption may be as effective	As for anti-GBM disease	As for anti-GBM disease; may need to include replacement immunoglobulins if continuing long term; immunoadsorption may be as effective	

Table 99-1 **Practical regimens for plasma exchange in renal disease.** *FSGS,* Focal segmental glomerulosclerosis; *HCV,* hepatitis C virus; *HUS,* hemolytic uremic syndrome; *TTP,* thrombotic thrombocytopenic purpura.

and usually in place of plasma exchange, such as in Goodpasture disease, rheumatoid arthritis, systemic lupus, or systemic vasculitis, and to remove anti-ABO or anti–human leukocyte antigen (HLA) antibodies in highly sensitized transplant recipients. In general, the reported efficacy has been equal to that of plasma exchange, although if used long term, immunoadsorption can be much more cost-effective in single patients because there is no requirement for replacement albumin or plasma. Specific ligands have also been immobilized onto columns for more specific removal of potentially pathogenic serum factors; ligands used include anti–human IgG, C1q, phenylalanine, hydrophobic amino acids, acetylcholine receptor, and β-adrenoreceptor peptides, and blood group–related oligosaccharides. Immunoadsorption of all varieties is not widely available because the initial column costs are high and few centers have much clinical experience. Costs of all other plasma exchange modalities are dominated by the costs of replacement albumin and plasma; equipment costs do not vary much among modalities, and all require skilled and trained nursing staff. Plasma filtration requires minimal extra support or training for dialysis nurses because the equipment is very similar to normal hemodialysis machines.

COMPLICATIONS

The complication rate of plasma exchange is not high.[3] The Swedish registry reported no fatalities during 20,485 procedures, and an overall adverse incidence rate of only 4.3% of all exchanges (0.9% for severe adverse events) of which 27% were paresthesias, 19% transient hypotension, 13% urticaria, and 8% nausea.[4] The Canadian apheresis registry has collected data on 144,432 apheresis procedures since 1981 and reported adverse events occurring in 12% of procedures (mostly minor), and overall in 40% of patients. Severe events occurred in only 0.4% of procedures. Three deaths were probably related directly to the procedure: one from a transfusion-related acute lung injury and two from complications from central venous catheters.[5] An overall complication rate of 1.4% has been reported in more than 15,000 treatments in patients receiving albumin, and 20% in patients receiving FFP.[1,3,5,6] Plasma exchange by centrifugation had a lower risk for adverse events than by filtration.

Other complications directly attributable to plasma exchange include citrate-induced hypocalcemia (presenting with perioral tingling and paresthesias) and citrate-induced metabolic alkalosis. Citrate is usually present in FFP (up to 14% by volume) or is administered in the extracorporeal circuit as an anticoagulant; it binds free calcium in plasma. Symptomatic hypocalcemia can be averted by infusing 10 to 20 ml of 10% calcium gluconate during each plasma exchange. Alkalosis is rare and is caused by metabolism of citrate to bicarbonate and failure to excrete the latter in patients with renal impairment.

Plasma exchange predictably increases the risk of bleeding as a result of depletion of coagulation factors in patients receiving albumin as sole replacement colloid. Prothrombin time is increased by 30%, and partial thromboplastin time by 100% after a single plasma volume exchange. Patients at risk of bleeding (pulmonary hemorrhage, postbiopsy, postoperative) should receive FFP (300 to 600 ml) with replacement fluids. Dilutional hypokalemia is avoided by adding potassium to the replacement albumin. An increased incidence of infection secondary to hypogammaglobulinemia has not been confirmed in recent series.[3-6] Sepsis related to intravenous access is the most common infectious complication of plasma exchange. Hypotension can occur for a variety of reasons related to extracorporeal circuits, sepsis, and allergic reactions, but also if saline is used for exchanges with a concomitant reduction in serum oncotic pressure during the procedure. Cascade filtration can lead to hemolysis (in up to 20% patients) but rarely necessitates transfusion.

MECHANISMS OF ACTION

Plasma exchange removes large-molecular-weight substances from the plasma, including antibodies, complement components, immune complexes, endotoxin, lipoproteins, and von Willebrand factor (vWF) multimers. The pathogenicity of autoantibodies in anti–glomerular basement membrane (anti-GBM) disease (Goodpasture disease) provided the impetus for development of plasma exchange therapy, but it is now clear that antibodies, although necessary, are not alone sufficient to cause the necrotizing glomerulonephritis (GN) in that disease. Therefore, plasma exchange may well have benefits in addition to clearance of autoantibodies. The clearance of antibodies from patients is variable and depends on a number of factors, including the rate of equilibration of macromolecules between the intravascular and extravascular compartments. IgM antibodies are cleared more effectively by centrifugal plasma exchange than other classes of immunoglobulin because they are retained in the vascular compartment almost wholly. A rebound increase in antibody production will occur unless there is concomitant immunosuppression to prevent resynthesis.

Plasma exchange has also been shown to remove immune complexes, which may have clinical significance in cryoglobulinemia and systemic lupus, and fibrinogen and complement components. There is no good evidence that removal of cytokines has any clinical significance. Plasma exchange reduces plasma viscosity, with consequent improved blood flow in the microvasculature.

INDICATIONS FOR PLASMA EXCHANGE

Evidence to support specific indications for plasma exchange is variable in quality. Direct comparison between randomized controlled trials can be unsatisfactory because of variations in dose and frequency of plasma exchange and in immunosuppressive and other adjunctive therapy. The American Society for Apheresis (ASFA) reviewed all indications for plasma exchange in 2010 and summarized available trial data.[7,8] In this chapter, evidence from available randomized trials is discussed alongside observational data. The indications are summarized in Tables 99-2 and 99-3.

Anti–Glomerular Basement Membrane Antibody Disease (Goodpasture Disease)

Plasma exchange removes anti-GBM antibodies very effectively. Most patients can be depleted of pathogenic antibodies after 7 to 10 plasma volume exchanges if further antibody synthesis is inhibited by the concurrent use of cyclophosphamide and corticosteroids. Before the introduction of this therapy, the mortality from Goodpasture disease was higher than 90%, and only 11% of patients who were not dialysis dependent at presentation survived with preserved renal function. The use of plasma exchange improved the outcome considerably: 70% to 90% of patients now survive. However, only 50% of survivors retain independent renal function, and no more than 10% of those who are dialysis dependent at presentation. There has been only one small controlled trial of plasma exchange in the treatment of Goodpasture disease, which used a low intensity of plasma exchange.[7,9] A total of 17 patients were randomized to receive corticosteroids and cyclophosphamide, with or without plasma exchange. Only two of the eight who received plasma exchange developed

Conditions for Which There Is Strong Evidence for the Benefit of Plasma Exchange					
Indication	**Randomized Controlled Trials (No. of Patients)**	**Controlled Trials (No. of Patients)**	**Case Series (No. of Patients)**	**Replacement Fluid**	**Comments**
ANCA-associated systemic vasculitis	8 (300)	1 (26)	22 (347)	Albumin unless pulmonary hemorrhage or need to prevent coagulopathy	Proven of benefit only in dialysis-dependent patients. Should consider daily exchanges in fulminant cases or with pulmonary hemorrhage.
Anti–glomerular basement membrane antibody disease	1 (17)	0	17 (430)	Albumin unless pulmonary hemorrhage or need to prevent coagulopathy	Minimum course 14 days to remove antibodies effectively. Especially beneficial in nonoliguric patients pre-dialysis. Patients with creatinine >5.5 mg/dl (500 μmol/l) unlikely to benefit.
Cryoglobulinemia	0 (1 using immunoadsorption; 17 patients)	0	18 (195)	Albumin	Long-term maintenance treatment needed in some patients. Ensure blood warmer on return lines or warm replacement fluids.
Thrombotic thrombocytopenic purpura	7 (301)	2 (133)	17 (915)	Plasma or cryo-poor plasma	Daily. Often with corticosteroids. The only treatment that has improved mortality.
ABO-incompatible kidney transplantation	0	0	21 (>700)	Albumin ± plasma (compatible with donor and recipient or AB)	Used pretransplant to reduce titers of antibodies and often continued for a few days after surgery to allow successful transplantation
Antibody-mediated kidney transplant rejection	3 (61)	8 (342)	35 (499)	Albumin	Daily or alternate day. Significantly better evidence for benefit has emerged in the last 15 years.
HLA desensitization for transplantation (in highly sensitized patients)	0	4 (240)	28 (436)	Albumin	Always in combination with immunosuppression and continued until cross-match negative. Usually five plasma exchanges are needed to reduce Ab levels sufficiently.

Table 99-2 Conditions for which there is strong evidence for the benefit of plasma exchange. *ANCA,* Antineutrophil cytoplasmic antibody; *HLA,* human leukocyte antigen.

Conditions for Which There Is Some Evidence for the Benefit of Plasma Exchange					
Indication	**Randomized Controlled Trial (No. of Patients)**	**Controlled Trials (No. of Patients)**	**Case Series (No. of Patients)**	**Replacement Fluid**	**Comments**
Catastrophic antiphospholipid antibody syndrome	0	0	6 (60)	Plasma	Should be done daily. Combination of plasma exchange or IVIG, heparin, and corticosteroids (from registry data) gives best outcomes.
Recurrent FSGS after transplantation	0	2 (19)	43 (117)	Albumin	Often in combination with cyclophosphamide or rituximab. May need long-term maintenance treatment.
Atypical hemolytic uremic syndrome	0	0	8 (50)	Plasma or cryo-poor plasma	Daily plasma exchange initially. Eculizumab likely to reduce the use of long-term plasma exchange.
Myeloma	5 (182)	0	6 (105)	Albumin	Daily or alternate day for 7-10 exchanges. Despite negative randomized trial in 2005, plasma exchange should be considered if high light-chain load, severe renal failure, and oliguria persist despite conservative management.
Rapidly progressive glomerulonephritis (may include patients with ANCA-associated disease in older literature)	7 (196)	0	21 (295)	Albumin	No good evidence for benefit in immune complex disease of any cause.
Scleroderma	0	3 (75)	6 (60)	Albumin	No good evidence for benefit, but some patients have reported improvement with therapeutic trial of plasma exchange.
Systemic lupus (not nephritis)	1 (20)	1 (4)	14 (128)	Albumin	For cerebritis, lupus-associated TTP, severe hemolysis, or pulmonary hemorrhage.

Table 99-3 Conditions for which there is some evidence for the benefit of plasma exchange. *aHUS,* Atypical hemolytic uremic syndrome; *FSGS,* focal segmental glomerulosclerosis; *IVIG,* intravenous immunoglobulin.

end-stage renal disease (ESRD) compared with six of the nine who received drugs alone.

Long-term data from 71 patients with Goodpasture disease confirmed the benefit of a treatment regimen including plasma exchange because most patients with mild to moderate renal failure retained independent renal function over 10 to 25 years,[10] and renal recovery was possible even in some of those with the most severe renal disease. Combining all the available published data for patients with Goodpasture disease, 76% of patients presenting with serum creatinine below 5.5 to 6.8 mg/dl (500 to 600 µmol/l) will retain renal function, in contrast to 8% of those who are dialysis dependent at presentation.

Recommendation

All patients presenting predialysis should receive intensive plasma exchange with daily 4-liter exchanges initially for 14 days (regimen shown in Table 99-2). For dialysis-dependent patients, we recommend plasma exchange with immunosuppression only for those who have biopsy or clinical evidence of recent-onset disease. Pulmonary hemorrhage is an independent indication for plasma exchange. Treatment of Goodpasture disease is discussed further in Chapter 24.

Small-Vessel Vasculitis

The majority of patients with rapidly progressive glomerulonephritis (RPGN), other than anti-GBM disease, have small-vessel vasculitis with ANCA detectable in their serum, and there is increasing evidence that these autoantibodies are pathogenic. Plasma exchange was initially introduced in such patients because of the similarity of the histologic changes to those seen in Goodpasture disease, and the supposition that immune complexes may be instrumental in disease pathogenesis. Several trials of plasma exchange in non–anti-GBM RPGN have been reported.[7,11] Most of the early trials included patients with a variety of diseases, used a low intensity of plasma exchange, and often excluded those with oligoanuria. These trials showed no overall benefit of plasma exchange in addition to conventional immunosuppression; however, those patients with the most severe disease did seem to benefit. Combining the results of the controlled trials, 31 of 42 (74%) dialysis-dependent patients treated with plasma exchange recovered renal function compared with only 8 of 25 (32%) treated with drugs alone. The most recent randomized, controlled trial (MEPEX Methylprednisolone or Plasma Exchange in severe ANCA-associated vasculitis) randomized 137 patients with ANCA-associated systemic vasculitis and serum creatinine above 5.5 mg/dl (500 µmol/l) to plasma exchange or intravenous methylprednisolone in addition to oral corticosteroids and cyclophosphamide.[11] Sixty-nine percent of patients recovered renal function when treated with plasma exchange compared with 49% of those receiving intravenous methylprednisolone, although this difference was not maintained at 3 years. An ongoing trial is examining the possible benefit of plasma exchange in patients with less severe ANCA associated vasculitis (the PEXIVAS [Plasma Exchange and Glucocorticoid Dosing in the Treatment of Anti-Neutrophil Cytoplasm Antibody-Associated Vasculitis] trial). Patients with both ANCA and anti-GBM antibodies (so-called double-positive patients) and RPGN do not seem to respond well to plasma exchange and rarely, if ever, recover renal function.[12]

Recommendation

We perform plasma exchange in patients with small-vessel vasculitis who present with severe renal failure (serum creatinine >5.5 mg/dl [approximately 500 µmol/l] or dialysis dependent) or pulmonary hemorrhage. The regimen is shown in Table 99-2.

Other Crescentic Glomerulonephritis

Crescent formation is a common histologic finding in a number of other patterns of GN, including postinfectious GN, GN associated with infective endocarditis, IgA nephropathy, membranoproliferative glomerulonephritis (MPGN), and membranous nephropathy. Such patients were often included in in studies of treatment of RPGN, and plasma exchange has been used in the treatment of a number of these conditions. Over 400 patients with such diseases have been treated with plasma exchange with no good evidence for any benefit in crescentic GN not caused by anti-GBM disease or vasculitis.[7,8] In crescentic IgA nephropathy, there are anecdotal reports of short-term benefit in patients with severe renal impairment, but longer-term follow-up has proved disappointing.

Recommendation

We reserve plasma exchange in IgA nephropathy and other GN for patients with rapidly deteriorating renal function and extensive fresh crescents in the biopsy specimen.

Focal Segmental Glomerulosclerosis

Plasma exchange and protein A immunoadsorption have been used to treat patients with primary focal segmental glomerulosclerosis (FSGS) or recurrent disease after transplantation. The results have been less good in primary disease, as less than 40% of patients achieve either partial or complete remission,[7,8,13] and we do not recommend plasma exchange in this setting. Plasma exchange for recurrent disease is discussed later and in Chapter 108.

Thrombotic Microangiopathies

In both HUS and thrombotic thrombocytopenic purpura (TTP), endothelial activation leads to TMA, but through distinct mechanisms. There are no randomized controlled trials.

Infection-Associated Hemolytic Uremic Syndrome

Infections leading to HUS cause diarrhea, most commonly Shiga toxins (Stx-associated HUS). The prognosis is generally good, especially in childhood. Most children will recover fully with supportive care and management of fluid and electrolyte imbalance and hypertension. Two controlled trials of plasma infusion (at least 10 ml/kg daily) in childhood HUS complicated by dialysis-dependent renal failure showed no clinical benefit (as determined by hypertension, renal dysfunction, and proteinuria) in either short- or medium-term follow-up.[14] There has been no study of plasma exchange in childhood Stx-associated HUS. Plasma exchange and infusion have not been subjected to any controlled trials in adult Stx-associated HUS, but uncontrolled observations suggest possible benefit.[7,15] The 2011 outbreak of enterohemorrhagic and Stx-producing *Escherichia coli* O104:H4 in Europe led to 855 confirmed cases of HUS, but despite severe illness in many patients a retrospective analysis of 491 treated patients did not support any major benefit of plasma exchange in addition to intensive supportive care.[16]

Thrombotic Thrombocytopenic Purpura

Patients with TTP usually have a defective vWF cleaving protease (ADAMTS13), an enzyme that normally degrades large vWF multimers, either because of an inherited deficiency or autoantibodies directed against the protease. Accumulation of vWF multimers leads to systemic platelet activation under conditions of high shear stress (the microcirculation) and thrombosis. The rationale for plasma infusion and plasma exchange in TTP is therefore to replenish vWF cleaving protease, to remove antibodies against it, and to remove the

large vWF multimers from circulation. There are well-designed randomized controlled trials in the treatment of TTP.

The first prospective, controlled trial compared plasma infusion with plasma exchange (1 to 1.5 plasma volumes at least seven times in the first 9 days).[17] All patients received aspirin and dipyridamole. Of patients receiving plasma exchange, 47% had a platelet count exceeding 150×10^9 cells/l and no new neurologic features, compared with only 25% of those receiving plasma infusion over the first 2 weeks. At 6 months, survival was substantially better in those given plasma exchange (50% versus 78%). More recent series using plasma exchange have reported mortality rates as low as 15%,[7] and there may be an association of reduced early mortality with more intensive plasma exchange. Renal impairment is not an independent predictor of poor outcome in TTP and does not in itself warrant more intensive therapy, and clinical course does not correlate with ADAMTS13 activity. Fever, age older than 40 years, and hemoglobin below 9 g/dl have been associated with a worse outcome. Whether FFP or its cryosupernatant fraction is better as replacement fluid remains unclear.

Thrombotic thrombocytopenic purpura may also be induced by drugs, including ticlopidine, clopidogrel, mitomycin C, cyclosporine, tacrolimus, gemcitabine, and quinine, and the evidence for benefit of plasma exchange in this context is poor.[7]

Atypical Hemolytic Uremic Syndrome

The less common forms of HUS in which there is no clear diarrheal prodrome (atypical HUS) are now known to be commonly caused by mutations, polymorphisms, or acquired dysregulation of the complement pathway, especially of factor H, factor I, and membrane cofactor protein, leading to uninhibited activation of complement. Other causes include infections or drugs that cause platelet or leukocyte activation and complement activation and consumption. Direct activation of endothelial cells may also be a cause. Plasma exchange and infusion have not been evaluated in controlled trials in atypical HUS, but uncontrolled series suggest benefit, and current guidelines recommend early initiation of plasma exchange with FFP (see Chapter 29), both to remove potential complement inhibitors or autoantibody and to replace absent or defective complement regulators.[7] TMA occurring after renal transplantation has also responded to plasma exchange.

Recommendation

We use plasma exchange in all adults with TTP or atypical HUS and perform all exchanges against FFP or cryo-poor FFP.

Systemic Lupus

Plasma exchange has been used extensively in patients with lupus. Most studies have included patients with diverse patterns of disease, often with only mild renal involvement. A randomized, prospective trial could show no benefit of plasma exchange over conventional immunosuppression for renal, serologic, or clinical outcomes, both in the short and long terms.[18] However, patients with crescentic lupus nephritis and those with the most severe renal dysfunction (dialysis dependency) were excluded. Anecdotal evidence suggests that plasma exchange may benefit patients with systemic lupus and crescentic GN, pulmonary hemorrhage, cerebral lupus, catastrophic antiphospholipid syndrome, severe antibody-induced hemolysis, lupus-associated TTP, or severe lupus unresponsive to conventional drugs or in patients for whom cytotoxic therapy has been withdrawn because of bone marrow suppression or other toxicity. Immunoadsorption may be more successful in the severe forms of lupus nephritis. A variety of techniques have been used, including standard protein A and anti-Ig absorption, and also phenylalanine, tryptophan, and dextran sulfate ligands, all of which bind immunoglobulin, rheumatoid factors, and immune complexes to varying degrees and all of which have been reported to induce remission in patients with severe disease after failure of conventional therapy.

Recommendation

We reserve plasma exchange for lupus patients with rapidly progressive renal failure and class IV lupus nephritis with crescents, for patients with severe neurologic involvement or severe hemolysis, for patients with myelosuppression who are thought unable to tolerate cyclophosphamide, and for those with catastrophic antiphospholipid syndrome. The treatment of lupus is further discussed in Chapter 26.

Cryoglobulinemia

In type I cryoglobulinemia, usually associated with myeloma or lymphoma, a monoclonal immunoglobulin causes hyperviscosity and cryoprecipitation. Such antibodies are easily removed by plasma exchange, often with immediate clinical benefit. Cytotoxic agents are used simultaneously to inhibit further paraprotein production. There are no controlled trials of the use of plasma exchange, but symptoms are closely related to the presence of the cryoimmunoglobulin, and hence treatment with plasma exchange appears effective.[7]

Patients with type II (mixed essential) cryoglobulinemia develop a monoclonal antibody (usually IgM) with specificity for a second, usually polyclonal, immunoglobulin. Type II cryoglobulins occur most commonly in association with hepatitis C virus infection and lymphoma. The resulting immune complexes can be deposited in the microcirculation and are particularly associated with MPGN (see Chapter 21). Plasma exchange is effective at clearing the immune complexes, although in long-term follow-up the cryoglobulins often recur, and sustained benefit has not been clearly demonstrated. However, many of the acute features of cryoglobulinemia do resolve with plasma exchange, particularly arthralgia, skin lesions, and digital necrosis, and patients with RPGN can recover renal function. Concomitant immunosuppression with cytotoxic agents or, more commonly now, rituximab may prevent resynthesis of the cryoproteins, although some patients require long-term intermittent plasma exchange to control symptoms. Immunosuppressive treatment should be used with caution in patients with hepatitis C virus–associated cryoglobulinemia, who may respond to antiviral therapy including interferon and ribavirin. A single randomized controlled trial in 17 patients with hepatitis C–associated cryoglobulinemia added immunoadsorption apheresis (with dextran sulfate) to antivirals and immunosuppression and showed significant clinical improvements.[19]

Cryofiltration apheresis (in which a normal plasma filter is used to separate plasma, which is then cooled to precipitate the cryoglobulin before return to the patient) selectively removes cryoglobulins, avoids large volumes of replacement fluids, and avoids deficiency of clotting factors, but needs to be combined with immunosuppression to prevent synthesis of further cryoglobulin. Few centers currently perform this technique, especially since the widespread introduction of rituximab for cryoglobulinemia.

Myeloma

Plasma exchange may have benefit in myeloma with either cast nephropathy or light-chain renal toxicity, although the most important therapy seems to be urgent initiation of chemotherapy, especially thalidomide, lenalidomide, or bortezomib. Two small controlled trials performed over 15 years ago provided conflicting

results.[7] A large prospective, controlled trial was reported in which 97 patients with myeloma and progressive acute kidney injury (creatinine >200 µmol/l [2.3 mg/dl] with an increase >50 µmol/l over the previous 2 weeks despite conventional management) were randomized to receive plasma exchange (five to seven sessions of 50 ml/kg over 10 days) in addition to chemotherapy (VAD [vincristine, adriamycin and dexamethasone] or melphalan and prednisolone).[20] This study showed no benefit of plasma exchange on mortality or recovery of renal function. However, patients had a wide degree of renal dysfunction and relatively few had a renal biopsy performed to confirm cast nephropathy. A retrospective review suggested that those with myeloma and high light-chain loads or severe renal failure may benefit if plasma exchange reduces light chains rapidly.[21] A single study using bortezomib in patients with renal disease and myeloma showed significant improvements even in patients with dialysis-requiring renal failure but without plasma exchange. Promising early data suggest that HD using novel membranes allowing the removal of large-molecular-weight molecules and lengthy dialysis sessions (6 to 8 hours) may prove superior to plasma exchange in removing light chains and improving renal function, and a trial is ongoing.

Recommendation

We reserve plasma exchange in myeloma for patients with high light-chain loads and cast nephropathy on biopsy.

Transplantation

Antibody-Mediated Rejection

Studies in the 1980s suggested that combining plasma exchange with cyclophosphamide could deplete circulating antibodies in patients with vascular or antibody-mediated rejection, but a review of 157 patients included in five trials could not demonstrate any significant difference in the outcome of acute vascular rejection in patients treated with or without plasma exchange.[7,8] More recently, at least 11 trials including more than 300 patients with more clearly defined antibody-mediated rejection, and case series of more than 500 patients, have suggested that plasma exchange, usually combined with intravenous immunoglobulin (IVIG) and/or rituximab, but sometimes antithymocyte globulin, may effectively reverse 55% to 100% of such rejection episodes.[7]

There is no convincing evidence that plasma exchange has any role in the treatment of chronic rejection.

Anti–Human Leukocyte Antigen Antibodies

Highly sensitized patients with preformed anti-HLA antibodies have been treated before and after transplantation with plasma exchange or immunoadsorption to reduce cytotoxic antibody levels, often with high-dose IVIG.[7] Patients usually received intensive immunoadsorption or plasma exchange before transplantation to ensure a current negative cross-match immediately before transplantation; some received longer-term immunoadsorption or plasma exchange in combination with immunosuppressive therapies in the months preceding transplantation. Most recent studies have shown that patients with donor-specific antibody titers of less than 1 : 32 often have these depleted completely with preoperative plasma exchange, allowing successful renal transplantation. Such patients do have an increased risk of antibody-mediated rejection—approximately 40%—but despite this, 90% have 1-year graft survival.

ABO-Incompatible Renal Transplantation

Plasma exchange is widely used to remove natural anti-A or anti-B blood group antibodies from the recipient before living donor transplantation from an ABO-incompatible donor. Various protocols are in use, but all rely on depletion of specific antibody over 2 to 5 days before transplantation by exchanging a single plasma volume for human albumin solution (in addition to routine immunosuppression, sometimes including rituximab and IVIG). Plasma exchange is sometimes continued for one or two sessions after transplantation or if antibody-mediated rejection occurs.[22] One-year graft survival rates of up to 85% have been reported with such protocols, although rejection episodes are more common than in ABO-compatible transplants. Patients with increasingly high antibody titers are being treated in this way. More recently, immunoadsorption using synthetic A- or B-oligosaccharide epitopes linked to Sepharose has been developed. Such columns specifically remove anti-A or anti-B antibodies, but any clinical benefit remains uncertain, and the costs are high.

Recurrent Focal Segmental Glomerulosclerosis

Plasma exchange, double-filtration plasma exchange, and protein A immunoadsorption have all been used to treat recurrence of nephrotic syndrome after transplantation in patients with recurrent FSGS.[7,23,24] An incompletely defined circulating factor causing increased permeability of glomerular capillaries can be found in most patients with recurrent FSGS. There are no controlled trials of plasma treatments in recurrent FSGS, and most series are small. One study demonstrated an 82% reduction in urinary protein excretion in eight patients with recurrent nephrosis during plasma protein adsorption; however, the effect was transient and persisted for less than 2 months in seven of the eight patients.[23] Other investigators have obtained remissions (complete and partial) in up to 80% of patients, and a significant reduction in graft loss resulting from recurrent disease compared with historic controls.[24] More intensive treatment regimens have led to more persistent remissions. All three apheresis modalities have also been used prophylactically in patients deemed to be at high risk of recurrence, with variable success.

Recommendations

We recommend use of plasma exchange for patients with recurrent disease, initially daily for 7 to 10 days. If proteinuria is successfully reversed, this may need to be continued less frequently (weekly, then every other week, then monthly), for 2 to 3 days on each occasion. Management of recurrent FSGS is discussed further in Chapter 108.

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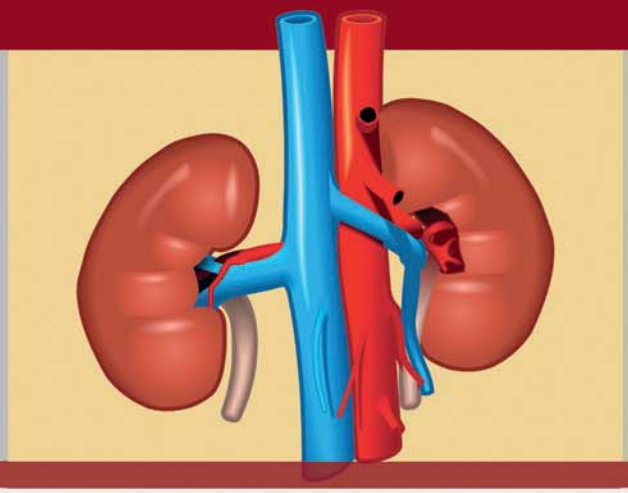

SECTION XVIII

Transplantation

CHAPTER 100

Immunologic Principles in Kidney Transplantation

Karl L. Womer

Important to an effective immune response is the ability of T cells to recognize a wide variety of nonself antigens, which allows for restrained immune activation and subsequent antigen-specific killing. This task is accomplished through the generation of a diverse repertoire of T cells in a single individual with specificity for an enormous number of potential foreign antigens presented as peptides on the surface of major histocompatibility complex (MHC) molecules. Variations in MHC structure from individual to individual increase the variety of peptides that can be presented to T cells, which protects the species as a whole by ensuring adequate T cell responses to a given foreign organism in at least one member of the population. Although slight, these MHC polymorphisms are recognized as foreign after kidney transplantation between non–genetically identical humans and induce alloresponses that in the absence of immunosuppression result in rejection of the allograft (see Box 100-1 for graft terminology). In this chapter, basic immunologic principles important to the field of kidney transplantation are reviewed.

ISCHEMIA-REPERFUSION INJURY

The immunologic responses after kidney transplantation occur in well-defined stages,[1] as depicted in Figure 100-1. Initial insults to the graft during donor organ procurement and subsequent transplantation into the recipient are referred to as ischemia-reperfusion injury (IRI). The pathogenesis of IRI involves biochemical, cellular, vascular endothelial, and tissue-specific factors, with inflammation as a common feature.[2] Acute ischemia leads to tissue damage and endothelial cell activation that initiates the innate or antigen-nonspecific immune response. Innate immunity occurs rapidly, with limited specificity, and without memory and includes both cellular elements (neutrophils, macrophages, dendritic cells [DCs], and natural killer [NK] cells) and molecular components (Toll-like receptors [TLRs], complement proteins, chemokines, and cytokines, among others).

Toll-like receptors are expressed by a number of cells, including monocytes and macrophages, lymphocytes, DCs, NK cells, neutrophils, and epithelial and endothelial cells. Engagement of TLRs by endogenous molecules called *danger-associated molecular patterns* (DAMPs) that are released by cells during IRI leads to release of cytokines, including tumor necrosis factor α (TNF-α) and interleukin (IL)–6. These proinflammatory mediators induce tubular epithelial cell production of the chemokine CXCL8 (IL-8), which attracts neutrophils by activation of their surface chemokine receptor, CXCR2. Neutrophil accumulation is the prime cellular mediator of microvascular plugging and local tissue destruction in IRI. In the next phase, monocyte or macrophage infiltration occurs and likely contributes to extension of early injury as well as repair.[3] These events contribute to delayed graft function and amplify the adaptive or antigen-specific phase of transplantation immunity (T cells and antibody-producing B cells) that can negatively affect long-term graft survival. NK cells likely also function as a bridge between innate and adaptive immunity in IRI, in part through bidirectional crosstalk between NK cells and DCs that plays a relevant role in the mechanisms leading to activation and maturation of DCs.[4] Likewise, whereas activation of the complement system plays an important role in IRI as a manifestation of the innate immune system, complement may also regulate adaptive immune responses. T and B cells constitute the primary arms of the adaptive immune response, but they also play an important role in the acute and possibly healing phases of IRI.[2] The immunologic events described here are not specific to allografts, as they also occur in syngeneic grafts during IRI.

ANTIGEN PRESENTATION

Antigen-Presenting Cells

Antigen-presenting cells (APCs) are specialized cells capable of activating T cells. Antigen is endocytosed by APCs and then displayed by MHC molecules on their surface. T cells recognize and interact with the antigen-MHC complex to become activated. DCs, macrophages, and B cells are all considered "professional APCs," although DCs are the most potent at antigen presentation. Alloimmune responses are initiated by activation of APCs (mostly DCs) through innate immune recognition systems, as described previously. DCs are highly versatile cells, determining whether the environment indicates that antigen should lead to an immune response or alternatively to tolerance.[5] In the graft and surrounding tissues after transplantation, DCs of either donor or host origin become activated and move to T cell areas of secondary lymphoid organs (SLOs).

The trafficking pattern of naive T cells is restricted to SLOs, such as the lymph node and spleen, but also possibly to tertiary lymphoid structures formed in tissues after inflammation, including those in allografts.[6] They traverse from blood to lymphoid organs, where they pass through the T cell areas and become activated on encounter with donor antigen (alloantigen) presented by activated DCs in the context of MHC molecules. Thus, the movement of DCs and naive T cells is coordinated to bring them into contact in the T cell areas of SLOs, which appears essential for effective priming.[7] Once activated, T cells are able to leave SLOs via lymph vessels to enter the blood and ultimately peripheral tissues, particularly into sites of inflammation. B cells are activated when antigen engages their antigen receptors, initially in the border of T cell and B cell areas of SLOs, where helper T cell function is provided.[8]

Antigen experienced memory cells may be activated by other APCs, such as graft endothelium.[9] Patients normally have no preexisting immunoreactivity to alloantigen, unless they have been exposed to alloantigen through pregnancy, blood transfusion, or prior transplantation. However, microbial antigens that cross-react with alloantigens (molecular or antigenic mimicry) can lead to the generation of alloantigen-specific memory cells through a process termed *heterologous immunity.*[10]

Graft Terminology

Autograft (autologous graft): A graft from one part of the body to another. Examples include skin and vascular grafts. No rejection occurs.

Isograft (isogenic or syngeneic graft): A graft from one member of a species to a genetically identical member of the same species. Examples include grafts between identical twins and between members of the same inbred rodent strain. No rejection typically occurs.

Allograft (allogeneic graft): A graft between nonidentical members of the same species. Examples include grafts between unrelated or related nonidentical humans and between members of different inbred rodent strains. Rejection occurs by lymphocytes reactive to alloantigens on the graft (i.e., alloresponse).

Xenografts (xenogeneic grafts): A graft between members of different species. Examples include pig or baboon to human, and rat to mouse. Rejection occurs by lymphocytes reactive to xenoantigen on the graft (i.e., xenoresponse).

Box 100-1 Graft terminology.

T Cell Ontogeny and Major Histocompatibility Complex Specificity

Allografts induce alloimmune responses because of the recognition of nonself antigens (e.g., MHC) from the graft by recipient T cells. During T cell ontogeny during embryogenesis, multilineage bone marrow precursors migrate to the thymus, where ultimate rearrangement of the T cell receptor (TCR) gene occurs, resulting in irrevocable T cell commitment. TCR gene rearrangement is random and ensures that a diverse repertoire of T cells exists to be able to respond to the enormous number of potential foreign antigens.[11] The mature T cell repertoire is determined in the thymus by two processes, positive and negative selection. Positive selection is dependent on a certain degree of antigen-specific T cell affinity to self-MHC molecules expressed on thymic cortical epithelial cells. This process ensures that mature T cells will interact effectively with MHC to allow recognition of foreign antigen in the context of self-MHC. Negative selection then occurs by deletion of T cells with excessively high affinity for self-peptide and MHC, thereby preventing release of high-affinity T cells with autoimmune potential.

Mature T cells expressing their clone-specific TCRs then exit the thymus as either CD4 or CD8 T cells. The TCRs of CD4 T cells (also called *helper T cells*) are selected to interact with class II MHC molecules, whereas the TCRs of CD8 T cells (precursors of cytotoxic T lymphocytes or CTLs) interact with class I MHC molecules. A fundamental principle of immunology is that T cells do not recognize intact foreign proteins directly, but instead as peptides presented by self-MHC on APCs. However, allelic variation among MHC molecules from individual to individual is quite small, resulting in similarities between donor and recipient MHC structure. Thus, unique to the transplant setting, recipient TCRs have a strong affinity for intact donor MHC molecules and can recognize them directly, which explains in large part the high proportion of T cells responding to alloantigen.[12] In fact, only $1/10^5$ to $1/10^6$ T cells will respond to any given nominal antigen (e.g., peptide derived from tetanus toxin or influenza hemagglutinin). However, the frequency of T cells that respond to foreign MHC molecules (alloantigens) is much higher (up to 5% to 10% of all T cells).

Pathways of Allorecognition

Recipient T cells may encounter alloantigen by either the direct or indirect pathways of allorecognition (Fig. 100-2). As previously

Generation of Alloimmune Responses

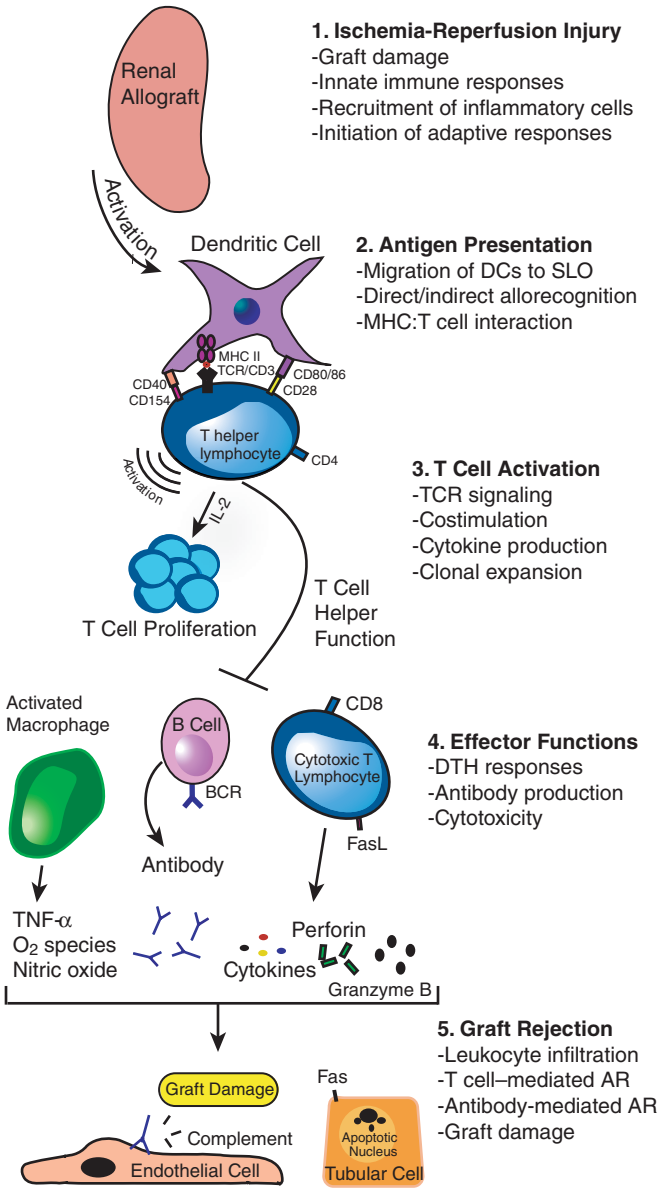

Figure 100-1 Generation of alloimmune responses. Immunologic responses after renal transplantation represent a series of well-defined stages that result in rejection of the allograft in the absence of exogenous immunosuppression. Graft damage after ischemia-reperfusion injury during procurement and transplantation activates innate (antigen-nonspecific) immune responses, which recruit inflammatory cells and initiate adaptive (antigen-specific) immune responses. After activation, dendritic cells *(DCs)* of donor (direct pathway) or recipient (indirect pathway) origin migrate to secondary lymphoid organs *(SLO),* where they present alloantigen to T cells through major histocompatibility *(MHC)* structures on their cell surface. Following T cell receptor *(TCR)* signaling and appropriate costimulation, T cells become activated to produce large amounts of cytokine and undergo clonal expansion. CD4 T cells provide help to B cells, CD8 T cells, and macrophages for the production of alloantibody, cellular cytotoxicity, and delayed-type hypersensitivity *(DTH)* responses, respectively. These effector functions result in destruction of the graft by acute rejection, which may be T cell and/or antibody mediated. *AR,* Acute rejection; *IL-2,* interleukin-2; *TNF-α,* tumor necrosis factor α.

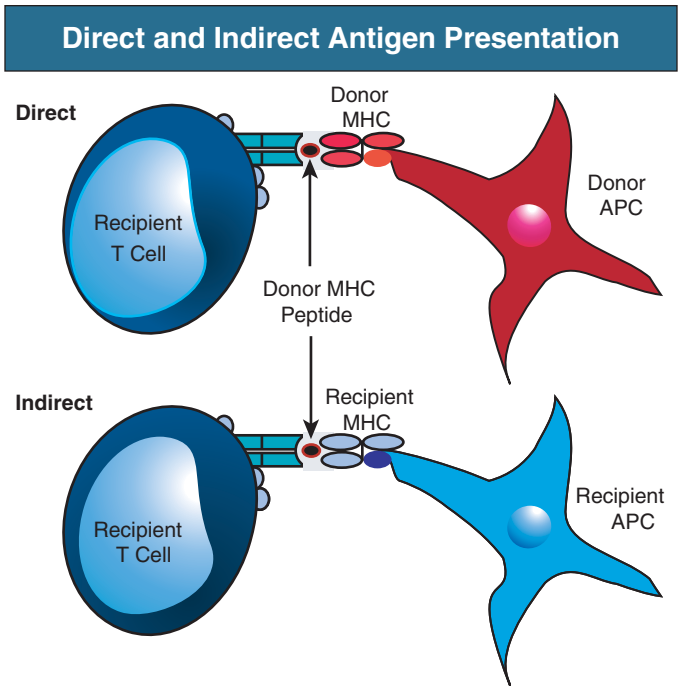

Figure 100-2 Direct and indirect antigen presentation. In direct allorecognition, donor antigen *(shown in red)* is presented to recipient T cells as a peptide in the context of intact donor major histocompatibility complex *(MHC)* molecules on the surface of donor antigen- presenting cells *(APCs)*. In indirect allorecognition, the donor antigen is processed by recipient APCs and presented as a peptide in the context of recipient MHC molecules.

alluded to, direct antigen presentation involves recipient T cell recognition of donor MHC peptides in the peptide groove of intact donor MHC molecules on the surface of donor APCs. By this mechanism, donor APCs migrate from the graft to recipient lymphoid organs and activate alloreactive recipient T cells to initiate the alloimmune response. It has been suggested that the direct pathway may be particularly active early after transplantation, when a large number of donor APCs are present in the allograft. However, direct antigen presentation may also occur later when recipient T cells recognize intact donor MHC molecules on cells of the graft (e.g., endothelium). The best evidence of direct allorecognition is the strong *in vitro* response generated in the mixed lymphocyte reaction (MLR), whereby lymphocytes are cultured with allogeneic APCs. B cells also recognize intact donor MHC antigen via their B cell receptors (BCRs).

Indirect antigen recognition is the physiologic mechanism of foreign antigen presentation. Foreign antigen is taken up by APCs, processed intracellularly, and then presented as peptides on MHC molecules. During indirect allorecognition, donor MHC molecules are shed from the graft and processed by recipient APCs, where they are presented as peptides to recipient T cells in the context of recipient MHC molecules.[13] Because donor MHC molecules are continually shed from the graft and presented by recipient APCs, indirect allorecognition may play a larger role in the late alloresponse, including chronic rejection. However, the relative contribution of direct versus indirect allorecognition to the alloresponse at different time points after transplantation remains the subject of debate.

Major Histocompatibility Complex

Class I and II MHC molecules are designed for presentation of antigen from different sources for different purposes (Fig. 100-3).

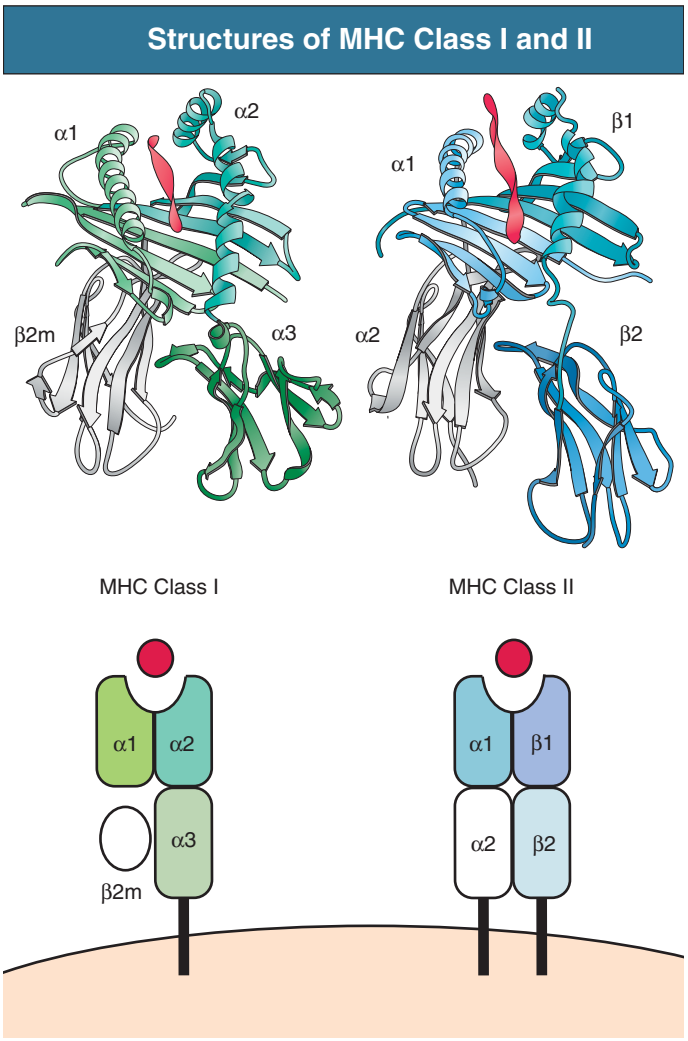

Figure 100-3 Structures of major histocompatibility complex (MHC) class I and II. MHC class I is composed of a heavy chain divided into α1, α2, and α3 domains noncovalently associated with β_2-microglobulin *(β2m)*. The α1 and α2 domains each form a long α helix and β sheet to make up the floor and walls of the peptide-binding groove (peptide indicated by *red ribbon*). MHC class II is a dimer composed of α and β chains. Each chain is divided into two domains, with α1 and β1 domains forming the two α helices and β pleated sheet that surround the peptide-binding groove.

The class I system is designed to sample cytosolic proteins to detect tumors or intracellular pathogens, such as virus and intracellular bacteria. Class I molecules are recognized by CD8 T cells and thus provide a surveillance mechanism to target infected or malignant cells for destruction by CTLs. The class II system is designed to sample extracellular proteins that have been taken up and processed by APCs. Class II molecules are recognized by CD4 T helper cells and allow for the generation of immune responses to invading pathogens that are phagocytosed by APCs. Cross-presentation is a process by which certain APCs take up, process, and present extracellular antigen on class I molecules to CD8 T cells.[14] This mechanism is necessary for immunity against tumors and viruses that do not infect APCs. MHC products also play other important roles, including the positive and negative selection of developing T cells described earlier, stimulation of naive and memory T cells that is necessary for their survival (homeostatic proliferation), the induction of T cell tolerance and anergy, and interaction with NK cells and other inhibitory and activating receptors.

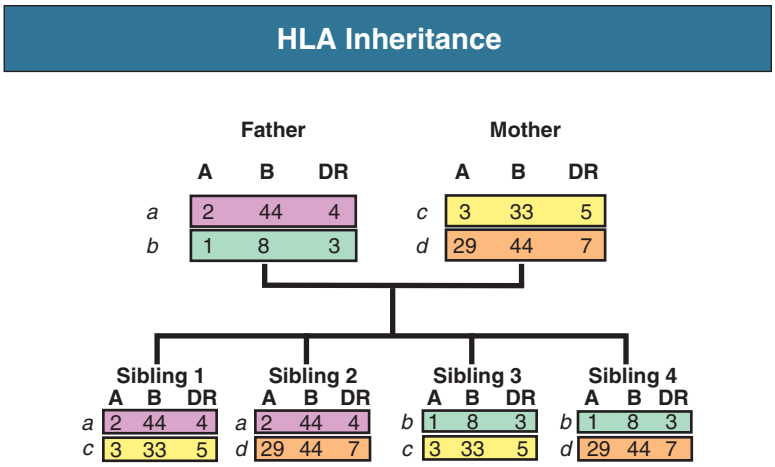

Figure 100-4 Human leukocyte antigen (HLA) inheritance. HLA antigens are inherited and expressed in a Mendelian co-dominant fashion, whereby one copy of each HLA gene, called a *haplotype* (e.g., a, b, c, d), is inherited from each parent. Efforts are made to match both class I (HLA-A and HLA-B) and class II (HLA-DR) antigens.

The MHC gene locus (in humans, human leukocyte antigen [HLA]) maps to a 3.5-million–base-pair region on the short arm of chromosome 6 and is divided into three regions: the class II region, the class III region, and the class I region. Only the class I and II regions encode proteins involved in antigen presentation. The key MHC genes are the class I genes (HLA-A, HLA-B, and HLA-C) and the class II genes (HLA-DP, HLA-DQ, and HLA-DR). The class I and II proteins share overall structural homology but are functionally different.[15] The molecular structure of MHC class I and II proteins is presented in Figure 100-3.

Class I proteins are expressed on virtually all nucleated cells, although the amount expressed varies. Class II proteins have a more restricted cell distribution, generally limited to bone marrow–derived professional APCs, including DCs, B cells, macrophages, and Langerhans cells, but also other cells, including renal parenchymal and endothelial cells. Both class I and II antigens can be induced on a variety of cells by interferon-γ (IFN-γ) in synergy with other cytokines during rejection episodes.

Human Leukocyte Antigen Typing and Transplantation

Major histocompatibility complex class I and II genes are highly polymorphic in the regions that encode the peptide-binding groove. These polymorphisms help to ensure survival of the species by increasing the variety of peptides that can be presented to T cells. Thus, MHC polymorphisms decrease the chance of encountering pathogens that induce poor immune responses within a population and therefore could lead to the demise of the species.[16] However, it is also these polymorphisms that predispose to allograft rejection, because the antigen presenting structures of one individual are regarded as foreign by another nonidentical individual.

Originally, polymorphisms were defined by HLA serologic (antibody) typing using sera from multiparous women or persons who had received blood transfusions. The development of molecular biology techniques (polymerase chain reaction [PCR] sequencing) has allowed the analysis of the HLA allelic sequence diversity at the DNA level. By DNA typing, many more polymorphisms (alleles) have been identified: currently 2188 for HLA-A, 2862 for HLA-B, 1746 for HLA-C, and 1393 for HLA-DR, with an increasing number of sequences added each year. The most currently updated source for HLA alleles can be identified at the website www.ebi.ac.uk/imgt/hla. Although PCR techniques allow for rapid DNA sequence-based typing of human populations, serologic methods are still often used for identifying HLA antigens in kidney transplantation.

Human Leukocyte Antigen Inheritance

Human leukocyte antigen genes are inherited in a Mendelian co-dominant fashion, meaning that a copy of each HLA gene (i.e., one haplotype) is inherited from each parent and expressed as antigens. HLA typing identifies the specific alleles carried by a person. The term *HLA matching* means assigning a donor kidney to a recipient with as few mismatches as possible. In kidney transplantation, efforts are made to match HLA-A, HLA-B, and HLA-DR genes and proteins. It can be predicted that siblings from the same set of parents will have a 25% chance of having zero mismatches, a 50% chance of one haplotype mismatch, and a 25% chance of two haplotype mismatches (Fig. 100-4).

Non–Major Histocompatibility Complex Antigens

Minor histocompatibility antigens are normal proteins that are themselves polymorphic within a given species. Even when a transplant donor and recipient are identical with regard to MHC genes, amino acid differences in these minor proteins can lead to rejection. Minor antigens are encoded by a large number of chromosomes and are presented only as peptides in the context of recipient MHC (indirect allorecognition). Minor antigens are responsible for the need for immunosuppression after donation between HLA matched nonidentical twin siblings. The prototypic minor histocompatibility antigen, the male or H-Y antigen, is derived from a group of proteins encoded on the Y chromosome. Alloresponses to this antigen are responsible for rejection of male mouse skin grafts by otherwise identical female recipients and may explain observations of reduced long-term graft survival in human male-to-female donations.

Major histocompatibility complex I-related chain A (MICA) antigens are surface glycoproteins with functions related to innate immunity. Exposure to allogeneic MICA during transplantation can elicit antibody formation.[17] ABO blood group glycolipids expressed on endothelial and red blood cells are other notable non-MHC antigens. Finally, immune responses to autoantigens have been associated with allograft damage.[18]

T CELL ACTIVATION

T cells are required for rejection, because animals experimentally deprived of T cells through mutation or genetic manipulation are unable to reject allografts. Alloreactive T cells can be found in the naive and memory T cell populations, but both require recognition of nonself MHC molecules to become activated. Reactions mediated

by naive T cells take longer to develop than those mediated by memory T cells, which can be generated more quickly and with higher numbers of cells (secondary response). During allograft rejection, both populations are activated simultaneously.

T Cell Receptor

Each T cell bears about 30,000 identical antigen-receptor molecules. Each receptor consists of two different polypeptide chains, termed the TCR α and β chains, which are linked by a disulfide bond. The genes encoding the TCR chains are members of the immunoglobulin (Ig) supergene family, which are found on B, T, and NK cells. The α:β heterodimers are very similar in structure to the Fab fragment of an Ig molecule and account for antigen recognition by most T cells (Fig. 100-5). In contrast to the Ig receptors of B cells, TCRs do not recognize antigen in its native state, but instead recognize a composite ligand of a peptide bound to an MHC molecule. A minority of T cells bears an alternative, but structurally similar, receptor composed of a different polypeptide heterodimer (γ:δ).

CD4 and CD8 Coreceptors

T cells fall into two major classes with different effector functions, distinguished by the expression of the cell-surface proteins CD4 and CD8 (see Fig. 100-5). Both CD4 and CD8 have a cytoplasmic tail that can associate with signaling proteins important in T cell activation. CD4 and CD8 binding to MHC are required to make an effective response. Thus, these molecules are called *coreceptors.*

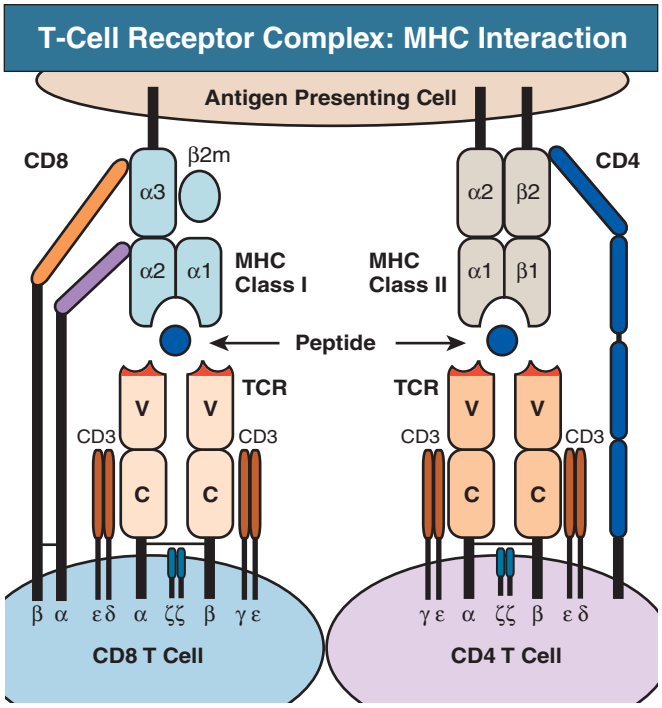

Figure 100-5 T cell receptor complex: major histocompatibility complex (MHC) interaction. Each T cell receptor *(TCR)* consists of an α and a β chain linked by a disulfide bond. The α:β heterodimers are similar in structure to the Fab fragment of an immunoglobulin (Ig) molecules (see Fig. 100-7), including variable *(V)* and constant *(C)* regions. Diversity in the T cell repertoire is encoded in the V domains of the α and β chains in three complementarity determining regions (CDRs) that form the antigen binding site at the end of the TCR *(highlighted in red).* CD8 is a disulfide-linked α:β heterodimer or α:α homodimer, with each chain containing a single Ig-like domain linked to the membrane by a polypeptide chain. CD8 binds to the conserved region of the α3 domain of the class I MHC molecule on antigen-presenting cells (APCs), but also interacts with the class I MHC α2 domain, probably through the α chain. CD4 is composed of four Ig-like domains and binds to a conserved site on the β2 domain of the class II MHC molecule on APCs. Triggering of the TCR by antigen initiates a signaling cascade started by the signaling complex made up of CD3 γ, ε, and δ chains, as well as the ζ chain homodimer. *β2m,* β_2-microglobulin.

T Cell Receptor Engagement of Antigen: Signal 1

The TCR α:β heterodimer recognizes and binds its peptide-MHC ligand[19] but cannot signal to the cell that antigen has bound. In the functional receptor complex, α:β heterodimers are associated with a complex of four other signaling chains (two ε, one δ, one γ) collectively called *CD3* (see Fig. 100-5). Engagement of the TCR by MHC, along with the other required receptor engagements, initiates the signaling process from the CD3 complex, leading to cell proliferation and differentiation.[20]

T Cell Costimulation: Signal 2

Binding of the TCR-CD3 complex to the peptide-MHC complex on APCs delivers a signal that can induce the clonal expansion of naive T cells only when the appropriate costimulatory signal is delivered (Signal 2). CD8 T cells require a stronger costimulatory signal, and their clonal expansion is aided by CD4 T cells interacting with the same APC (i.e., T helper function). Costimulation is likely a checkpoint developed by the immune system to prevent the activation of self-reactive T cells that escaped negative selection in the thymus. Antigen binding to the TCR in the absence of costimulation not only fails to activate the T cell but leads to a state called *anergy,* in which T cells become refractory to subsequent activation, or even undergo apoptosis (programmed cell death). Thus, costimulation removes this inhibition and determines whether a T cell will proceed with clonal expansion and the development of effector functions. It is now clear that costimulatory molecules can provide positive or negative signals to T cells (Fig. 100-6). It is the integration of both positive and negative costimulatory signals during and after initial T cell activation, dictated by their temporal and spatial expression patterns, that ultimately determines the fate and functional status of the T cell response.[21]

T Cell Clonal Expansion and Differentiation

In most instances the number of T cells that react to a given antigen is quite small. Therefore, effective immune responses generally require clonal expansion and differentiation of T cells. These processes are largely driven by cytokines, including IL-2, which acts on the T cell in an autocrine fashion or by paracrine secretion to neighboring T cells. Activated T cells produce the alpha subunit (CD25) of the IL-2 receptor (IL-2R), enabling a fully functional signaling receptor composed of α, β, and γ subunits that can bind IL-2 with high affinity, which in turn initiates another pathway mediated in part through a protein called *mammalian target of rapamycin* (mTOR). A number of new proteins are then translated, allowing the cell to progress from the G1 phase to the S phase of the cell cycle, resulting in proliferation. The list of cytokines involved in this and later processes is large and continues to grow. Table 100-1 lists selected cytokines involved in allograft rejection, their sources, and their effects.

CD4 and CD8 T cells have different roles during immune responses. CD4 T cells are both effectors and regulators and are notable for heavy cytokine secretion. After prolonged stimulation, CD4 T cells sometimes tend to express groups of several cytokines, probably depending on the local environment, the nature of the antigen, and the type and activation status of the APCs. The so-called

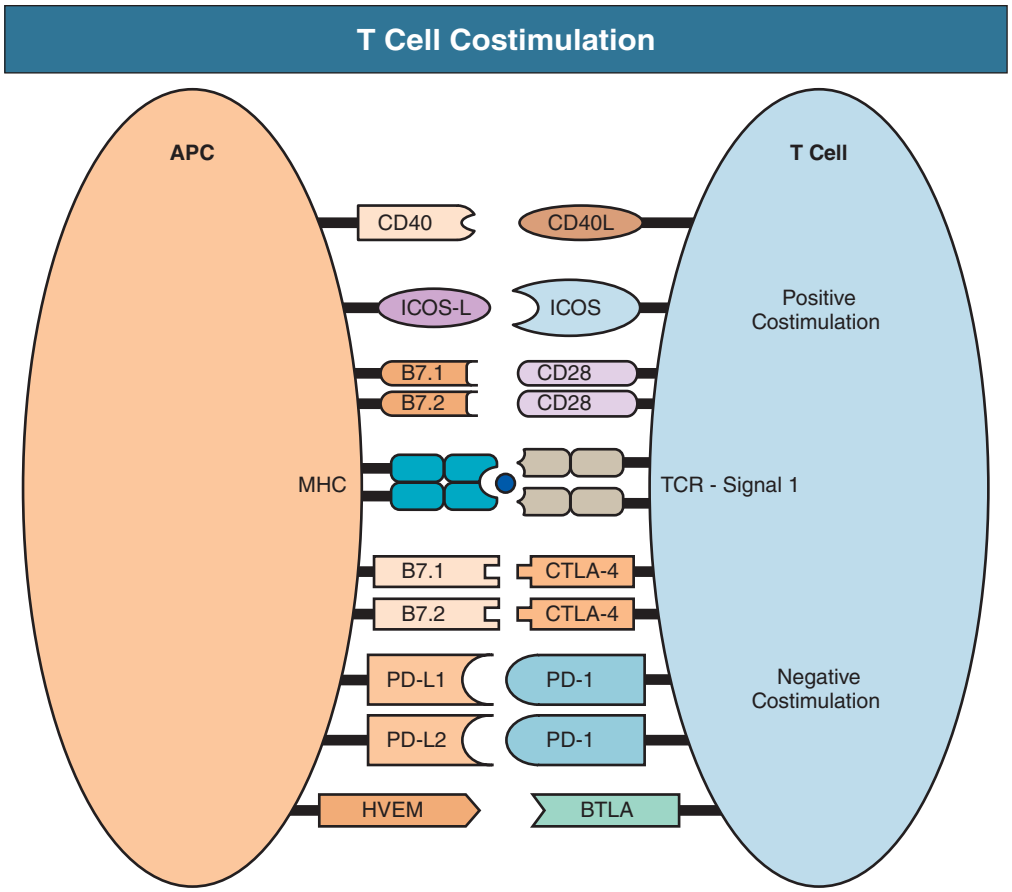

Figure 100-6 T cell costimulation. Binding of the T cell receptor *(TCR)*–CD3 complex to the peptide-MHC complex on an antigen-presenting cell *(APC)* delivers a signal that can induce the clonal expansion of naive T cells only when the appropriate costimulatory signal is delivered (Signal 2). CD28 and its ligands, B7.1 (CD80) and B7.2 (CD86), are the best-characterized costimulatory molecules and are members of the immunoglobulin (Ig) superfamily. Ligation of CD28 by B7 molecules is required for clonal expansion of naive CD4 T helper cells. Once activated, T cells express increased levels of CTLA-4 (CD152). CTLA-4 has an affinity 10 to 20 times greater than CD28 for B7 molecules and thus binds most or all of the B7 molecules, effectively shutting down the proliferative phase of the response. B and T lymphocyte attenuator (BTLA) and programmed death–1 (PD-1) are two other costimulatory molecules of the Ig superfamily that when engaged by their ligands (herpes virus entry mediator [HVEM] and PD-L1/PD-L2, respectively) provide inhibitory signals to T cells. Activated T cells express a number of proteins that contribute to sustaining or modifying the costimulatory signal to drive clonal expansion and differentiation. The inducible costimulatory molecule (ICOS) is a CD28 homologue, but unlike CD28 is not constitutively expressed on naive T cells. Rather, ICOS is induced only after T cell activation. Engagement of ICOS by B7H enhances T cell proliferation, cytokine production, and survival. Costimulatory molecules of the TNF and TNF-R superfamily include CD40 ligand (CD40L, CD154) on T cells and its receptor CD40 on APCs, such as B cells, dendritic cells (DCs), macrophages, and endothelial cells. Binding of CD40 by CD40L, which is upregulated by CD28 signaling, transmits activating signals to the T cell but also activates the APCs to secrete proinflammatory molecules and to express B7 molecules, thus stimulating further T cell proliferation.

Th1 (T helper 1) clones produce IL-2, IFN-γ, and lymphotoxin, whereas Th2 clones produce IL-4, IL-5, and IL-10. As the effects of these cytokines became known, it was apparent that the subdivision of production correlated with a categorization of function. Th1-derived cytokines are growth and maturation factors for CTLs (especially IL-2) and macrophages (particularly IFN-γ), whereas Th2-derived cytokines act similarly on B cells. Th2 cells also mediate B cell class switching to complement IgG fixing antibodies. Rejecting allografts typically express high levels of mRNA for both subsets of cytokines and cannot be considered a pure Th1 response. T helper 17 (Th17) cells are a subset of T helper cells stimulated by TGF-β and a number of other cytokines that are distinct from Th1 and Th2[22] clones and produce IL-17, IL-21, and IL-22.[23] Th17 cells are thought to play a key role in autoimmune disease, and their role in transplantation is currently under intense investigation.[24]

Memory Cells

Although there is limited knowledge of how memory T cells are generated or maintained, these cells are an important component of the immune response to infectious pathogens. In clinical transplantation, however, previous sensitization to alloantigen with formation of memory cells is associated with increased risk for acute rejection and premature graft failure. Memory responses to alloantigen frequently occur at the time of blood transfusion, pregnancy, and transplantation. However, alloantigen memory responses can develop as a result of antigen cross-reactivity during response to infection (heterologous immunity), but also by normal proliferation in response to lymphopenia induced by leukocyte-depleting agents in transplant recipients.

The principle of immunologic memory is that the immune response to a previously encountered antigen is swifter and more effective than the response to a new antigen. Memory cells seem to be more easily activated than naive T cells, with a lower requirement for costimulation, and in addition produce more cytokines. Furthermore, there is an increase in antigen-specific T cell frequency after exposure to a given antigen. Finally, exposure to antigen leads to a refinement of the antibody repertoire, resulting in a more effective memory response. Effector memory T cells are specialized for quickly entering inflamed tissues, because they can rapidly mature

Cytokines Involved in Allograft Rejection		
Cytokine	**Source**	**Biologic Activity**
IL-1	Macrophages, DCs, ECs, NK cells	Proinflammatory, adhesion molecule expression on ECs, NK cell function
IL-2	Activated T cells	T cell proliferation, CTL and NK cell function, Treg maintenance, Ig production by B cells, AICD of activated T cells
IL-4	Activated T cells	Activated T and B cell proliferation, Th2 differentiation, allergic responses, MHC II upregulation on B cells
IL-6	T cells, macrophages, ECs	Proinflammatory and anti-inflammatory, acute-phase responses
IL-10	T cells, macrophages, DCs	Anti-inflammatory, suppression of APC function, NK cell inhibition
IL-12	Macrophages, DCs	Proinflammatory, Th1 differentiation, NK cell and CTL activity, IFN-γ and TNF-α production by NK and T cells
IL-15	Epithelial cells, stromal cells, macrophages	NK cell proliferation, T cell proliferation, memory T cell survival
IL-17	T cells	Proinflammatory and allergic responses, Th17 function, cytokine production from many cell types
IFN-γ	Activated Th1 cells, CTLs, DCs, NK cells	MHC expression by EC, macrophage function, Th1 differentiation, Th2 suppression, adhesion and binding of T cells to ECs, NK cell activity
TGF-β	T and B cells, macrophages, platelets	Anti-inflammatory, wound healing, fibrosis
TNF-α	Macrophages, T and B cells, ECs, NK cells	Proinflammatory, acute phase responses, cytotoxicity

Table 100-1 Cytokines involved in allograft rejection. *AICD,* Activation-induced cell death; *CTLs,* cytotoxic T lymphocytes; *DCs,* dendritic cells; *ECs,* endothelial cells; *IFN-γ,* interferon-γ; *Ig,* immunoglobulin; *IL,* interleukin; *MHC,* major histocompatibility complex; *NK,* natural killer; *TGF-β,* transforming growth factor beta; *Th,* T helper (cell); *TNF-α,* tumor necrosis factor α; *Treg,* regulatory T cell.

into effector T cells and secrete larger amounts of cytokines after restimulation. Central memory T cells likely remain in the SLOs and do not produce as much cytokine.[25] Memory cells are believed to persist after an initial immune response through expression of the antiapoptotic genes *Bcl-2* and *Bcl-xL*, which are induced primarily by IL-2 and CD28 stimulation, although IL-15 may also provide survival signals. Long-term memory cell survival is likely a function of periodic interactions with self-MHC–peptide complexes on APCs (i.e., homeostatic proliferation).

EFFECTOR FUNCTIONS

Once activated and expanded, T cells exert effector functions that result in destruction of graft tissue. Although T cells are essential for acute organ allograft rejection, the precise mechanisms by which they mediate graft injury are uncertain. CD4 T helper cells may release numerous cytokines that affect the alloimmune response. For example, they may promote delayed-type hypersensitivity (DTH) responses that involve stimulating production of nitric oxide, reactive oxygen species, and TNF-α by macrophages. T cell cytokines may also act directly on parenchymal cells or indirectly through effects on the endothelium and vascular supply. TNF-α and TNF-β exert local cytotoxic effects on receptors on the graft, including endothelial cells (TNF-R1) and tubular cells (TNF-R2). IFN-γ, the prototypical Th1 cytokine, is released by both CD4 and CD8 T cells during rejection. IFN-γ induces MHC class II expression on endothelium and MHC class I expression on vascular endothelial cells, epithelial cells, and parenchymal cells in the graft. The precise role of class II expression by donor cells in the graft remains controversial because mouse kidney grafts lacking class II are rejected more vigorously. Although IFN-γ is strongly associated with rejection, it probably has other signaling roles that actually help to stabilize the graft. As cytokine production by CD8 T cells is generally lower than that of CD4 T cells, production of cytokines such as IL-2 by CD4 T cells provides help for the generation of CTLs from their CD8 T cell precursors. CD4 T cells may themselves become cytolytic T cells, by mechanisms similar to those used by CD8 CTLs (described later). CD4 T cells also provide help to B cells to enhance their production of alloantibodies. Finally, regulatory T cells (Tregs) may have important roles in suppressing immune responses and maintaining tolerance.

Cytotoxic T Lymphocyte Differentiation and Function

With rare exceptions, virtually all CTLs are MHC class I–restricted CD8 T cells. Activated CTLs possess two mechanisms to kill target cells that require cell-to-cell contact.[26] The first mechanism is by the release of specialized lytic granules. Perforin and granzyme B are two proteins found in granules of most CTLs and NK cells. Perforin, like complement components, has the ability to induce transmembrane pores. The granzyme B–perforin complex enters the cell through the mannose 6-phosphate receptor, and, after internalization, perforin allows granzyme B to enter the cell through the vesicle surface to induce programmed cell death through apoptosis.[27] A third cytotoxic protein, granulysin, is also able to induce apoptosis in target cells. The second mechanism is by Fas/Fas ligand (FasL) interactions. Fas (CD95) is a member of the TNF-R family and is the surface mediator of a pathway that, when activated by FasL on activated CTLs, induces the target cell to undergo apoptosis. Both pathways induce apoptosis through activation of the caspase cascade in target cells. As previously alluded to, CD8 CTLs also release several cytokines that exert direct cytotoxic effects, including IFN-γ, TNF-α and TNF-β.[28] Effector CD4 T cells that can mediate class II-restricted cytotoxicity to minor antigens have also been detected.

Macrophage Activation

The activated macrophage is an important mediator of DTH responses, which leads to localized tissue destruction. Resting macrophages must be activated to exert full inflammatory and cytopathic effects. Th1 cells provide help for this activation by interaction of CD40L with CD40 on the macrophage and by production of IFN-γ, which sensitizes the macrophage to respond to IFN-γ. It is possible

that T cell membrane–associated TNF-α and TNF-β can substitute for CD40L. CD8 T cells also produce IFN-γ and can activate macrophages. Production of TNF-α, oxygen radicals, and nitric oxide by activated macrophages are important for their cytopathic effects. Activated macrophages can also produce IL-12, which directs the differentiation of activated naive CD4 T cells into Th1 effector cells. Macrophage activation is inhibited by cytokines such as transforming growth factor β (TGF-β) and IL-10, many of which are produced by Th2 cells.

Humoral Immune Response

The extracellular spaces of the body are protected by the humoral immune response, in which antibodies produced by B cells cause the destruction of extracellular microorganisms and prevent the spread of intracellular infections. Membrane-bound Ig on the B cell surface serves as the antigen receptor and is known as the *B cell receptor* (Fig. 100-7). It is associated with antigen-nonspecific signaling molecules Igα and Igβ. Ig of the same specificity is then secreted as antibody by terminally differentiated B cells (i.e., plasma cells). B cells develop in the bone marrow and undergo sequential rearrangement of Ig gene segments to generate a diverse repertoire of antigen receptors that can interact with antigen in their environment. In a process similar to that for developing T cells in the thymus, immature B cells that are strongly self-reactive at this stage are inactivated by negative selection. In contrast to T cells, new B cells are continually produced in adulthood.

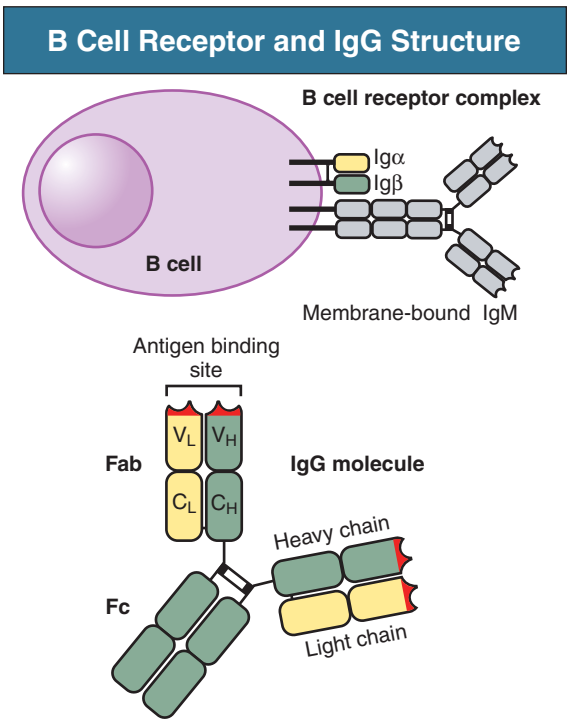

Figure 100-7 B cell receptor and IgG structure. B cell surface membrane–bound IgM associated with antigen-nonspecific signaling molecules Igα and Igβ forms the B cell receptor complex. The IgG molecule is made up of four polypeptide chains, comprising two identical light *(L)* chains *(yellow)* and two identical heavy *(H)* chains *(green)*. Each of the four chains has a variable *(V)* region at its amino terminus (*Fab* portion), which contributes to the antigen binding site, and a constant *(C)* region (*Fc* portion), which determines the isotype. The V domains contain hypervariable regions that determine antigen specificity called *complementarity-determining regions (highlighted in red)*.

B cell activation requires binding of antigen to the BCR. Although some polysaccharides and polymeric proteins can activate B cells directly, antibody responses to most proteins require both binding of the antigen to the BCR and interaction of the B cell with antigen-specific helper T cells. Helper T cells recognize peptide fragments derived from the antigen that are internalized and presented as peptide–MHC class II complexes on the B cell surface. Helper T cells stimulate B cells through the binding of CD40L with CD40 on B cells, through interaction of other TNF–TNF-R family ligands, as well as the directed release of cytokines. Although these helper T cells are generally of the Th2 subset, Th1 cells can also assist with B cell activation. Activated B cells also provide signals to T cells via B7 family molecules that promote their continued activation.

Secretion of antibodies, which bind pathogens or their toxic products, is the main effector function of B cells in adaptive immunity. The antibody molecule has two separate functions: One is to bind specifically to molecules from the pathogen that elicited the immune response, and the other is to recruit other cells and molecules to destroy the pathogen bound by the antibody. The five major classes of antibodies are IgM, IgD, IgG, IgA, and IgE. IgG is by far the most abundant Ig and has several subclasses (IgG1, IgG2, IgG3, and IgG4). The IgG molecule is made up of four polypeptide chains, comprising two identical light (L) chains of 25 kd and two identical heavy (H) chains of 50 kd that form a flexible Y-shaped structure (see Fig. 100-7). Each of the four chains has a variable (V) region at its amino terminus (Fab portion), which contributes to the antigen binding site, and a constant (C) region (Fc portion), which determines the isotype. The V regions of a given antibody contain hypervariable segments that determine antigen specificity by forming a surface complementary to the antigen and are referred to as *complementarity-determining regions* (CDRs).

After appropriate activation and help from T cells, previously naive B cells undergo vigorous proliferation, secrete IgM, and then undergo differentiation into memory B cells or antibody-secreting plasma cells. During this process the antibody isotype can change (to IgA, IgG, or IgE) in response to cytokines released by helper T cells, and the antigen-binding properties of the antibody can change by somatic hypermutation of the V region genes. T helper cells selectively activate higher-affinity mutants, resulting in high-affinity plasma cells and memory B cells. Antibodies can function in several different ways once bound to their target antigen. These mechanisms include fixation of complement, opsonization for phagocytosis by Fc receptor (FcR)–positive cells (including B lymphocytes, NK cells, macrophages, and neutrophils), opsonization for cell lysis by cells capable of antibody-dependent cellular cytotoxicity (NK cells, macrophages, neutrophils, and eosinophils), and induction of eosinophil degranulation.

Natural Killer Lymphocytes

Natural killer cells are a subset of peripheral lymphocytes, which share certain developmental and functional features with the more numerous CD8 T lymphocytes.[29] Unlike T or B cells, NK cells do not possess a clonotypically distributed, antigen-specific cell surface receptor that is generated by gene recombination. Instead, NK cells use an array of receptors that recognize the loss of HLA class I molecules on susceptible targets. Peripheral NK cells are mature, do not require costimulation and differentiation as with T cells, and immediately release cytotoxic granules and inflammatory cytokines such as TNF-α and IFN-γ on detection of relevant targets. Given the strong cytolytic function and potential for autoreactivity, NK cell activity is tightly regulated. Mechanisms of activation include cytokines, binding of antibody to Fc receptors, and binding of ligands to

activating and inhibitory receptors. NKG2D is an activating receptor expressed on all NK cells and NK T lymphocytes.[4] The presence of NKG2D ligands, including MHC class I–related antigen, has been reported on human transplant samples undergoing acute allograft rejection and acute tubular necrosis. Thus, NKG2D ligands in the graft may stimulate a cytolytic cellular immune response after transplantation by interacting with cells bearing NKG2D, including NK cells. The role NK cells play during rejection is still being investigated.[30]

Termination of the Immune Response

To avoid massive continued expansion of the lymphoid pool, it is important to have mechanisms in place to terminate the immune response. Once the source of antigen is destroyed, there is no longer an inciting stimulus to induce further activation and proliferation of lymphocytes. However, preexisting effector cells can cause antigen-specific tissue damage and must be deactivated. Several mechanisms accomplish this task. Once terminally mature, DCs switch cytokine production from IL-12 to IL-10, favoring the generation of regulatory mechanisms that suppress the function of effector T cells. As mentioned previously, induction of CTLA4 after T cell activation provides regulatory feedback to provide inhibitory signals to T cells that induce anergy. In the absence of continued cytokine production, T cells lack the necessary growth factors and undergo passive cell death. Finally, activated T cells undergo activation-induced cell death (AICD) by the expression of Fas and FasL on their surface. Engagement of Fas by its ligand triggers a death signal, leading to apoptosis of the cell. Although IL-2 is important for the clonal expansion of T cells, it is also essential for AICD. Finally, Tregs are important in maintaining self-tolerance after removal of effector T cells.[31]

ALLOGRAFT REJECTION

Allograft rejection is defined as tissue injury produced by the effector mechanisms of the alloimmune response, leading to deterioration of graft function.[32] There are two types of rejection: T cell–mediated rejection (TCMR) and antibody-mediated rejection (AMR). Both types of rejection can be early or late, fulminant or indolent, isolated or concomitant, and can share pathologic features on biopsy.[33] For the purposes of this chapter, the two types are described separately.

Recruitment of Cells into the Interstitium of Kidney Allografts

Allograft rejection is caused by several cellular elements of the immune system, including T cells, macrophages, B cells, plasma cells, eosinophils, and neutrophils. Although there are a variety of target cells in the graft, endothelial and tubular cells are particularly affected by these mediators. T cells serve as the main effectors and regulators of the alloimmune response, whereas macrophages serve as possible effectors but also aid in the removal of apoptotic cells. B cells and plasma cells serve in the production of alloantibodies, and neutrophils likely cause significant damage, particularly during AMR.

A three-step model has been proposed to explain the entry of cellular infiltrates into the allograft: tethering, adhesion, and transmigration. Table 100-2 lists several of the proteins involved in this process. The endothelium of postcapillary venules in the graft serves as the entry point of recipient leukocytes from the bloodstream. Selectins are constitutive and inducible lectin-like molecules on the endothelium that cause leukocytes to roll along the vessel wall, a process called *tethering.* Leukocytes slowed down by selectins come into more prolonged contact with the endothelium. As a result, leukocytes are stimulated by chemokines, a group of small proinflammatory molecules produced by inflamed tissue, which are fundamentally important in attraction of cells into an inflammatory infiltrate. Once secreted, chemokines bind locally to cell-surface proteoglycans on endothelial cells, allowing them to activate leukocytes as they roll by. As chemokines bind to receptors on leukocytes, they activate the adhesion function of integrins.

Integrins are αβ heterodimers formed by noncovalent association. The best characterized integrin, leukocyte function-associated antigen 1 (LFA-1), is expressed on most leukocytes. The ligands for LFA-1, including intercellular adhesion molecule 1 (ICAM-1), ICAM-2, and ICAM-3 (Ig superfamily gene members), are expressed weakly on resting endothelium but are induced by activation with cytokines, such as IL-1 and TNF-α. Likewise, activation of leukocytes by chemokines triggers the transition of their surface LFA-1 to a high-affinity state for ICAM, resulting in tight adhesion of the leukocyte to the endothelium. This adhesion contributes to antigen recognition, and through a process called *haptotaxis,* leukocytes are induced to move along the vessel wall by an adhesion gradient.

Transmigration is the final step in the process of cellular entry into the allograft. Rapidly after integrin engagement of their ligands, leukocytes flatten and then undergo diapedesis through gaps between

Proteins Involved in the Recruitment of Leukocytes into Allografts

Protein Type	Name	Ligand	Function
Selectins	CD62L (L-selectin) CD62L (P-selectin) CD62L (E-selectin)	Sialylated glycoproteins	Initial rolling of leukocytes on endothelium
Chemokines	MCP-1/CCL2	CCR2	Recruitment of monocytes, immature DCs, T cells, and NK cells
	MIP-1α/CCL3	CCR1	Recruitment of monocytes, immature DCs, T cells, and neutrophils
	RANTES/CCL5	CCR1, CCR4, CCR5	Recruitment of monocytes, DCs, T cells, NK cells, and neutrophils
	IL-8/CXCL8	CXCR1, CXCR2	Recruitment of neutrophils
	MIG/CXCL9	CXCR3	Recruitment of activated memory T cells
	IP-10/CXCl10	CXCR3	Recruitment of activated memory T cells
	Lymphotactin/XCL1	XCR1	Recruitment of T cells
Immunoglobulin superfamily	CD54/ICAM-1	LFA-1	Tight adhesion of leukocytes to endothelium
	CD102/ICAM-2	LFA-1	Tight adhesion of leukocytes to endothelium (not as strong as ICAM-1)
	CD50/ICAM-3		
	CD106/VCAM-1	VLA-4	Rolling and tight adhesion of leukocytes to endothelium
	CD31/PECAM-1	CD31	Extravasation of leukocytes across endothelium

Table 100-2 Proteins involved in the recruitment of leukocytes into allografts. *DCs,* Dendritic cells; *ICAM,* intercellular adhesion molecule; *LFA-1,* leukocyte function-associated antigen 1; *NK,* natural killer; *PECAM,* platelet endothelial cell adhesion molecule; *VCAM,* vascular cell adhesion molecule; *VLA-4,* very late antigen-4.

endothelial cells. Leukocyte secretion of proteases degrades the basement membrane, allowing their escape from the vessel. Once in the interstitium, secretion of metalloproteinases allows leukocytes to digest extracellular matrix to move through the tissue on a chemokine gradient by a process called *chemotaxis.* Once confronted with foreign antigen in the allograft, previously activated T cells are capable of releasing proinflammatory cytokines (helper T cells) or directly killing foreign cells (cytotoxic T cells). Recent work in mouse models of renal allograft rejection indicates that allorecognition by T cells occurs in perivascular sites by day one after allotransplantation, whereas alloimmune parenchymal damage begins at day three, coinciding with the emergence of T cell and monocyte, macrophage, and DC (MMDC) infiltrates. Finally, tubulitis and arteritis develop by day 7.[30]

Acute T Cell–Mediated Rejection

Tubulitis, invasion of the tubular epithelium by infiltrating T cells and myeloid cells of the MMDC series, is a characteristic feature of acute TCMR (Fig. 100-8). In fact, deterioration of renal function during TCMR correlates with tubulitis and arterial inflammation (endothelialitis), which is much less common. Although it is generally agreed that T cells orchestrate the process that results in damage to the allograft, the precise mechanisms are not clear. As described earlier, CTLs can kill target cells by release of cytotoxic molecules (perforin, granzyme B, and granulysin) or by engagement of Fas on target cells by FasL, with both mechanisms resulting in apoptotic death of the target cell. Human gene expression studies show an increase in mRNA for CTL-associated transcripts, including granzyme B, perforin, and FasL, as well as T-bet, a master transcription factor for effector Th1 lymphocytes, during rejection episodes. Moreover, lymphocytes expressing mRNA and perforin protein are closely associated with tubular epithelial cells. Some studies suggest that tubulitis may involve a specific subset of CTLs expressing the integrin CD103, which binds to its ligand E-cadherin on epithelial cells, resulting in retention of T cells in the tubules.

Proof of mechanisms in organ transplantation, however, relies on *in vivo* models in animals. Although class I MHC mismatched heart allografts show prolonged survival in perforin knockout mice, most available evidence with perforin/granzyme, Fas/FasL, and CD103 knockouts indicates that any one of these individual cytolytic pathways is dispensable, because acute rejection still occurs with these deficiencies in fully mismatched combinations.[34] These studies argue against cytotoxicity as a primary mechanism to explain graft epithelial cell deterioration. Likewise, CD103–E-cadherin interactions may not be responsible for creating the lesions of tubulitis, but rather may reflect damaged cells that lose the ability to exclude inflammatory cells. Thus, tubulitis may not be the cause of tubular cell deterioration but instead a sign that is has already occurred.

T cells may mediate rejection instead through the secretion of cytokines, either through direct effects of soluble products or through the ability to activate macrophages to organize a DTH response. DTH responses involve the release of reactive oxygen species, proteolytic enzymes, eicosanoids, and other products. These products may act directly on tubular epithelium and interstitial matrix or indirectly via effects on endothelium and the vascular supply.

Endarteritis is detected in a minority of biopsy specimens taken for acute TCMR and often responds only to anti–T cell therapies, arguing for a pathogenic role for T cells. Endarteritis is not always associated with interstitial inflammation, arguing for a T cell pathway distinct from that of tubulointerstitial rejection. Glomerulitis is an occasional feature of acute TCMR, and cells are typically a mixture of T cells and macrophages. Why the glomerulus becomes the target in only a minority of patients is not currently known. FOXP3+ CD4 Tregs are concentrated in tubules during rejection, although their role during TCMR continues to be debated.

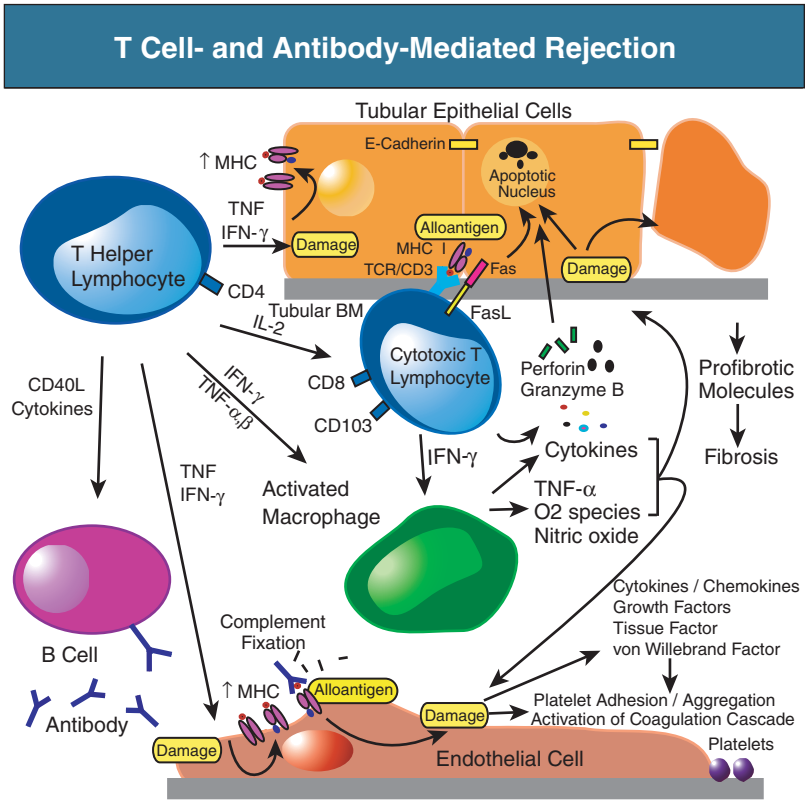

Figure 100-8 T cell– and antibody-mediated rejection. CD4 T cells induce epithelial and endothelial cell damage directly by secretion of cytokines but also indirectly by activation of cytotoxic T lymphocytes (CTLs) and macrophages. CTLs may cause apoptosis by releasing cytolytic granules containing granzymes and perforin or by exposure of Fas ligand *(FasL)* on the T cell surface. The integrin component CD103 is postulated to help retain T cells in epithelial layers by binding to E-cadherin, expressed most strongly in the distal nephron. Macrophages induce local tissue damage through secretion of cytokines, oxygen species, and nitric oxide (delayed-type hypersensitivity response). CD4 T cells secrete cytokines, which induce upregulation of major histocompatibility complex *(MHC)* molecules on epithelial and endothelial cells. CD4 T cells also provide help to B cells for production of alloantibody by engagement of CD40L and production of cytokines. Antigraft antibody is usually directed at MHC molecules, followed by activation of complement. Damaged endothelial cells secrete factors that activate coagulation systems and result in formation of microthrombi. Exposure of tubular cells and glomerular capillary loops to alloimmunity over time results in interstitial fibrosis, tubular atrophy, and glomerulosclerosis. *BM,* Basement membrane; *IFN,* interferon; *IL-2,* interleukin-2; *TCR,* T cell receptor; *TGF,* transforming growth factor; *TNF,* tumor necrosis factor.

Acute Antibody-Mediated Rejection

Acute AMR is recognized as a distinct clinicopathologic entity and may occur with or without a component of TCMR (see Fig. 100-8). Although typically a response to donor HLA antigens expressed on endothelial cells, AMR can occur to non-HLA antigens. Examples include ABO blood group antigens and the putative endothelial alloantigens, as suggested by the rare occurrence of AMR in HLA-matched nonidentical sibling grafts. Even autoantibodies have been implicated, such as those to angiotensin II type 1 receptors. The kidney typically shows an accumulation of neutrophils and monocytes in peritubular and glomerular capillaries, although the infiltrate can be quite sparse.[35] Tubulitis and endarteritis are generally minimal, unless a component of TCMR is present. FOXP3+ Tregs are more rare in the AMR infiltrate than that of TCMR,[36] perhaps indicating a factor in the poorer prognosis. A subset of acute AMR that can result in immediate graft failure is hyperacute rejection, which is caused by the presence of preformed anti–donor HLA antibody in sensitized recipients or of antibodies to mismatched ABO blood group loci. This type of AMR is rare now that crossmatching practices and/or desensitization protocols are routinely used by transplant centers.

Alloantibodies are cytotoxic through their ability to activate complement. The classical pathway appears most relevant; other pathways have not been shown to participate in acute or chronic AMR. C4d is an inactive fragment of C4b, an activation product of the classical pathway. C4b and C4d contain an occult sulfhydryl group that forms a covalent thioester bond with nearby proteins bound in the tissue after activation by Ig and C1. No functional role for C4d has been reported, but it remains in the tissue for several days after Ig and C1 have been released. C4d deposition is strongly associated with circulating antibody to donor HLA class I or II antigens and is currently the best single marker of complement-fixing circulating antibodies to the endothelium.

The acute effects of complement are well described and include chemoattraction of neutrophils and macrophages via C3a and C5a, vasospasm through the release of prostaglandin E_2 from macrophages, and edema through the release of histamine from mast cells. C3a and C5a increase endothelial adhesion molecules and various cytokines and chemokines.[37] The membrane attack complex, C5b-9, causes lysis of endothelial cells. Alloantibodies may also induce cell damage through complement-independent pathways by recruitment of leukocytes with Fc receptors (CD16 most commonly), including NK cells and macrophages (antibody-dependent cellular cytotoxicity). Finally, antibodies without leukocyte or complement participation can activate endothelial cells to produce chemokines and promote rejection in some animal models.[38]

A common feature of all types of AMR is the presence of microthrombi. As a result of antibody-mediated damage, von Willebrand factor is released from the endothelium, leading to platelet aggregation.[39] Animal models indicate that clotting activation is a direct consequence of complement fixation. Activation of endothelial protease-activated receptors by coagulation proteases, including thrombin, leads to the secretion of many proinflammatory cytokines.[40]

Chronic Rejection

Late allograft dysfunction is caused by a combination of alloimmune mechanisms (i.e., chronic rejection) and alloimmune-independent mechanisms, including hypertension, calcineurin inhibitor toxicity, and recurrent disease.[41] Chronic rejection may occur by either cellular or humoral mechanisms, or both. Histologic features characteristic of chronic rejection are transplant glomerulopathy, peritubular capillaropathy (see later), transplant arteriopathy, and, less specifically, tubular atrophy and interstitial fibrosis.

Transplant glomerulopathy is defined by the widespread duplication or multilamination of the glomerular basement membrane (GBM), sometimes accompanied by mesangial expansion and accumulation of mononuclear cells in glomerular capillaries. GBM duplication may be caused by a number of insults to the allograft glomerulus, including recurrent or *de novo* immune complex glomerular disease and thrombotic microangiopathy. However, it is believed that chronic antibody-mediated injury predominates, because the majority of cases of transplant glomerulopathy are associated with circulating antibody to donor class II MHC antigens (sometimes class I antigens), and approximately 30% to 50% of these patients have C4d deposition in the peritubular capillaries (PTCs).[42] It is believed that the absence of C4d deposition in the remainder of patients represents intermittent antibody involvement or antibodies directed at non-MHC antigens that do not fix complement.

Similar to findings in transplant glomerulopathy, multilamination of PTCs can be demonstrated by electron microscopy (peritubular capillaropathy). It is believed that repeated episodes of antibody-mediated injury to the endothelium result in repair mechanisms that are characterized by duplication of the basement membrane. What leads to episodic antibody injury is unknown, but it may represent the fluctuating donor-specific antibody levels observed in some patients followed longitudinally. Neointimal thickening can be observed in either C4d-positive or C4d-negative chronic rejection. Known as *transplant arteriopathy,* this lesion is characterized histologically by thickening of the arterial intima without duplication of the elastica (in contrast to fibroelastic thickening seen in hypertension.) Macrophages and T cells may sometimes be demonstrated within the thickened intima, providing evidence of cell-mediated immunologic activity.

Although not specific for rejection, interstitial fibrosis with tubular atrophy is another important histologic feature of chronically rejected allografts. One putative mechanism of fibrosis is by epithelial-mesenchymal transition (EMT) of tubular cells to activated myofibroblasts that migrates into the interstitium.[43] Steps in this conversion include loss of cell-cell adhesion, loss of E-cadherin, acquisition of α–smooth muscle actin, actin reorganization, tubular basement membrane disruption, cell migration, and production of profibrotic molecules.

The current criteria for chronic active AMR are histologic evidence of chronic injury (in the absence of other possible causes), immunopathologic evidence of antibody action (i.e., C4d staining), and evidence of circulating antibody reactive to the donor. Chronic AMR appears to arise through a series of stages.[35] The first common event is alloantibody production (stage I), followed by antibody interaction with alloantigens resulting in the deposition of C4d in the PTCs and glomeruli (stage II), followed by pathologic changes (stage III), and followed finally by graft dysfunction (stage IV). Although the factors promoting progression from stage 1 to stage IV are not currently understood, the hypothesized stages provide a useful organizing structure for ongoing clinical trials to intervene in the earlier stages (I or II).

TRANSPLANTATION TOLERANCE

Transplantation tolerance is a state characterized by the absence of a destructive immune response in the recipient toward a well-functioning donor allograft, with a fully intact immune system and no exogenous immunosuppression.[44,45] As with self-tolerance, transplantation tolerance is achieved through control of T cell reactivity

by both central and peripheral mechanisms. Central tolerance involves thymic deletional mechanisms that eliminate T cells with reactivity against self-antigens (or donor antigens in the case of transplantation tolerance) and positive selection of T cells without such reactivity. In experimental transplant models, central tolerance is achieved by elimination of the preexisting mature T cell population by irradiation and/or cytotoxic agents, followed by infusion of donor hematopoietic progenitor cells. Reconstituted donor antigen "reeducates" the thymus to delete developing T cells with antidonor reactivity, leading to a state of chimerism, in which both donor and recipient cells coexist. Translating this approach to the clinical setting, however, requires a functional thymus, which may not be present in the adult human.

Peripheral tolerance mechanisms include deletion, anergy, and regulation. With self-tolerance, these mechanisms serve to prevent deleterious autoimmune responses from T cells that escape central deletion. Various approaches to induce peripheral transplant tolerance with the goal of inhibiting deleterious alloimmune responses are currently under investigation, including costimulatory blockade, pharmacologic manipulation of DCs, and the induction of donor antigen–specific Tregs. One of the most significant hurdles to the development of clinical tolerance strategies is the lack of reproducible immune monitoring assays to detect the presence or absence of tolerance, which would determine when immunosuppressive medications could be safely withdrawn. Although transplantation tolerance is not yet a clinical reality, progress in the field is being made.[46,47]

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CHAPTER 101

Immunosuppressive Medications in Kidney Transplantation

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Much of the success of kidney transplantation is a result of advances in immunosuppressive medications that are used during the induction and maintenance phases and for treatment of acute rejection.[1] The term *maintenance immunosuppression* is usually used to describe drug regimens consisting historically of small-molecule agents that are administered to stable kidney transplant recipients. Increasingly, community nephrologists and primary care physicians are becoming involved in the care of stable kidney transplant recipients. In contrast, biologic agents that are used as induction protocols before the maintenance stage or for the treatment of acute rejection episodes are commonly managed by transplant surgeons and nephrologists in inpatient settings. This chapter discusses the immunosuppressive agents that are commonly used for prevention of rejection in renal transplantation by most transplant centers, with specific emphasis on their biologic mechanisms of action, pharmacokinetics, and side effect profile. These agents are divided into small-molecule drugs and biologic agents for the purposes of this discussion.

SMALL-MOLECULE DRUGS

Corticosteroids

Corticosteroids have been a cornerstone of transplant immunosuppression for the past 50 years, both as maintenance immunosuppression and for treatment of acute rejection.

Mechanism of Action

Corticosteroids suppress production of numerous cytokines and vasoactive substances, including interleukin (IL)–1, tumor necrosis factor α (TNF-α), IL-2, major histocompatibility complex class II, chemokines, and proteases. Corticosteroids also cause neutrophilia (often with a left shift), but neutrophil chemotaxis and adhesion are inhibited. They also affect nonhematopoietic cells including intrarenal cells.

Corticosteroids act as agonists of glucocorticoid receptors but at higher doses have receptor-independent effects. Corticosteroid receptors (CRs) belong to a family of ligand-regulated transcription factors called *nuclear receptors*. CRs are normally present in the cytoplasm in an inactive complex with heat shock proteins. The binding of corticosteroids to the CRs dissociates heat shock protein (HSP) from the CR and forms the active corticosteroid-CR complex, which migrates to the nucleus and dimerizes on palindromic DNA sequences in many genes; this action is called the *corticosteroid response element*. The binding of CR in the promoter region of the target genes can lead to either induction or suppression of gene transcripts (e.g., of cytokines). CRs also exert effects by interacting directly with other transcription factors independent of DNA binding.

A key way by which corticosteroids regulate immune responses is by regulation of the transcription factors activator protein 1 (AP-1) and nuclear factor κB (NF-κB). Normally, NF-κB is present as an inactive complex with inhibitor of nuclear factor κB (IκB), but it can be released by IκB kinase. Corticosteroids stimulate IκB, which then competes with the IκB–NF-κB complex for degradation by the IκB kinase. Corticosteroids also stimulate lipocortin, which inhibits phospholipase A_2, thereby inhibiting the production of leukotrienes and prostaglandins. The total immunosuppressive effect of corticosteroids is complex, reflecting effects on cytokines, adhesion molecules, apoptosis, and activation of inflammatory cells.

Pharmacokinetics

The major corticosteroids used are oral prednisone (or prednisolone) and intravenous methylprednisolone. The oral agents have good oral bioavailability and short half-lives (60 to 180 minutes) but long biologic half-lives (18 to 36 hours). Corticosteroids are eliminated by hepatic conjugation and are excreted by the kidneys as inactive metabolites. Coadministration of inducers of enzymes that metabolize corticosteroids (e.g., phenytoin, rifampin) decreases their half-life, whereas concomitant use of P-450 3A4 inhibitors (e.g., ketoconazole) has the opposite effect. Because corticosteroid levels are not routinely monitored, dosage adjustment during concurrent therapy with these medications becomes problematic. For treatment of acute rejection, pulse doses of 250 to 1000 mg of methylprednisolone are typically used, with no evidence that the higher dosage is more efficacious.

Side Effects

Side effects of corticosteroid therapy are common and associated with significant morbidity, particularly cataracts, osteoporosis, and avascular necrosis of the femoral heads (Table 101-1). Other side effects include hypertension, hyperglycemia, hyperlipidemia, cushingoid features, psychiatric disturbances, sleep disorders, peptic ulcer disease, pancreatitis, colonic perforation, increased appetite with weight gain, growth retardation, and myopathy. Infection risk is also increased and is excessive if high-dose pulse therapy is prolonged. It is interesting to note that corticosteroids are not associated with increased incidence of malignant disease. Although corticosteroids are generally considered safe in pregnancy, fetal adrenal suppression has been reported.

Calcineurin Inhibitors

Calcineurin inhibitors (CNIs), including cyclosporine and tacrolimus, are fungus-derived small molecules that are the mainstays of current maintenance immunosuppressive regimens. Considerable variability exists in their pharmacokinetics, interactions, and side

Common Side Effects of Small-Molecule Immunosuppressive Medications							
	Cyclosporine	**Tacrolimus**	**Mycophenolate**	**Azathioprine**	**Corticosteroids**	**mTOR Inhibitors**	**Leflunomide**
Renal	Nephrotoxicity, type 4 RTA, HTN, diuretic resistance, hyperkalemia, hypomagnesemia, hypophosphatemia	Nephrotoxicity, type 4 RTA, HTN, diuretic resistance, hyperkalemia, hypomagnesemia, hypophosphatemia			HTN, hypokalemia, diuretic resistance	Synergistic nephrotoxicity with CNIs, delayed recovery from ATN, proteinuria, hypokalemia, HTN	
Gastrointestinal		Diarrhea, abdominal pain	Diarrhea, nausea and vomiting, gastritis, esophagitis, oral and colonic ulcers	Nausea and vomiting, hepatotoxicity, pancreatitis	Peptic ulcers, gastritis, esophagitis, diarrhea, colonic perforation	Diarrhea	Nausea, diarrhea, hepatitis
Hematologic	Thrombotic microangiopathy	Thrombotic microangiopathy	Anemia, leukopenia, thrombocytopenia	Anemia, leukopenia, thrombocytopenia	Leukocytosis, polycythemia	Thrombotic microangiopathy, anemia, thrombocytopenia	Anemia, leukopenia
Metabolic	Hyperlipidemia, hyperuricemia, gout, glucose intolerance	New onset diabetes			Hyperlipidemia, hyperuricemia, hyperglycemia, osteoporosis, vascular necrosis, increased appetite and weight gain	Hyperlipidemia	
Cosmetic	Gingival hyperplasia, coarsened facial features	Alopecia			Hirsutism, acne, cushingoid facies, buffalo hump	Impaired wound healing, oral ulcers	Alopecia
Neuromuscular	Encephalopathy, insomnia, myopathy, tremors	Encephalopathy, insomnia, myopathy, tremors			Psychosis, insomnia, myopathy	Reflex sympathetic dystrophy	
Other	Edema	Myocardial hypertrophy	Viral infections, pulmonary edema in elderly, progressive multifocal leukoencephalopathy		Cataracts	Lymphocele, interstitial pneumonitis, rash, edema	Rash

Table 101-1 Common side effects of small-molecule immunosuppressive medications. *ATN,* Acute tubular necrosis; *CNIs,* calcineurin inhibitors; *HTN,* hypertension; *mTOR,* mammalian target of rapamycin; *RTA,* renal tubular acidosis.

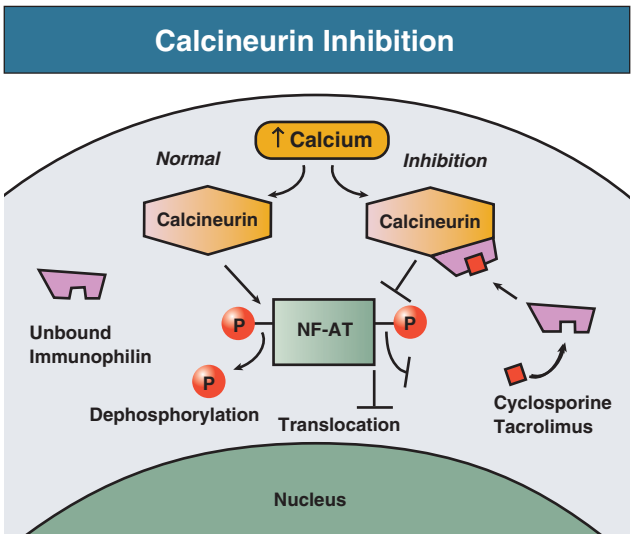

Figure 101-1 Calcineurin inhibition. During normal T cell activation, calcium release activates calcineurin's phosphatase activity, causing dephosphorylation of the transcription factor, nuclear factor of activated T cells *(NF-AT),* and subsequent translocation to the nucleus. Cyclosporine and tacrolimus form a complex with immunophilins (cyclophilin or FK-binding protein 12, respectively), which bind calcineurin and sterically inhibit the phosphatase activity, preventing dephosphorylation and nuclear translocation of NF-AT.

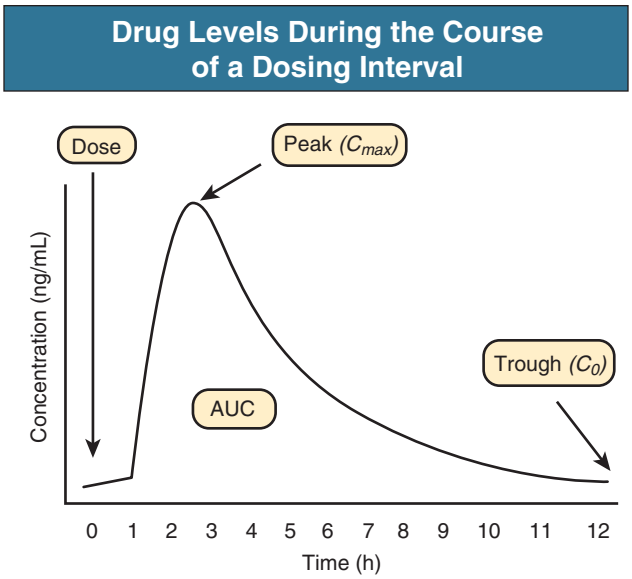

Figure 101-2 Drug levels during the course of a dosing interval. The drug concentration is lowest just before the dose is taken (C_0), then rises to a peak concentration at a certain time after the dose (C_{max}). The area under the concentration-time curve (AUC) describes total drug exposure during the entire administration interval.

effect profiles, which raises the question of which agent to use in the individual patient. Cyclosporine is a cyclic, lipophilic undecapeptide with several *N*-methylated amino acids, which may explain its resistance to inactivation in the gastrointestinal tract. Tacrolimus is a macrolide lactone antibiotic. Both drugs are highly soluble in lipids.

Mechanism of Action

Both CNIs exert their effect by binding to cytoplasmic proteins called *immunophilins* (Fig. 101-1). Cyclosporine binds to cyclophilin, whereas tacrolimus binds to FK-binding protein 12 (FKBP12).[2] Such binding enhances the immunophilin's affinity for and subsequent inhibition of calcineurin, which is a calmodulin-activated serine phosphatase important for dephosphorylation of inactive nuclear factor of activated T cells (NF-AT). Nuclear translocation of dephosphorylated (active) NF-AT, in association with other transcription factors, initiates downstream events leading to T cell activation (see Chapter 100). The tacrolimus-FKBP12 active complex inhibits calcineurin with greater molar potency than the corresponding cyclosporine complex. Cyclosporine and tacrolimus can interfere with activation of calcineurin on substrates other than NF-AT, which likely explains many of the side effects of calcineurin inhibition. Treatment with CNIs also causes upregulation of the cytokine transforming growth factor β (TGF-β), which has significant immunosuppressive properties but also promotes the deposition of matrix proteins and tissue fibrosis. Finally, these two agents can suppress the immune response by calcineurin-independent pathways as well. This mechanism generally involves blockade of intracellular signaling pathways specific for T cells. The ability of these agents to interfere with two distinct mechanisms of T cell activation contributes to their highly specific immunosuppressive properties.

Pharmacokinetics, Monitoring, and Drug Interactions

After a dose of CNI, there is an initial absorptive phase, during which blood concentrations reach a peak level (C_{max}).[3] Typically, C_{max} occurs during the first 2 to 3 hours after the dose and corresponds to the time of maximum calcineurin inhibition. Drug levels then fall as a result of metabolism (also known as the *elimination phase*) until they are at the lowest, or trough, level (C_0) immediately before the next dose. The total drug exposure throughout the period from one dose until the next is the area under the concentration-time curve (AUC; Fig. 101-2). For both CNIs, most of the interpatient and intrapatient variability occurs in the absorption rather than in the elimination phase.

The oil-based formulation of cyclosporine requires solubilization in bile and is plagued by highly variable and unpredictable bioavailability The microemulsion preparation of cyclosporine (modified) has enhanced bioavailability and less dependence on bile secretion. In blood, cyclosporine resides primarily in erythrocytes (60% to 70%) and leukocytes, with some binding to lipoproteins and, to lesser extent, other plasma proteins. Cyclosporine is metabolized primarily by CYP3A4, a member of the cytochrome P-450 superfamily. Metabolism occurs mostly in the liver. Interindividual differences in CYP3A4 activity and the large number of exogenous and endogenous substances capable of altering its function and expression explain the wide variation in clearance rates. One factor is the multidrug resistance 1 gene product, P-glycoprotein, which is variably expressed in the intestine and reduces the absorption of several xenobiotics, including CNIs, by transport out of intestinal epithelial cells. The average half-life of cyclosporine is about 19 hours, with excretion primarily in bile. Generic formulations of cyclosporine modified exist, although they may not have identical pharmacokinetics and therefore may not be readily interchangeable.

The absorption of tacrolimus, like that of cyclosporine, is highly variable; bioavailability ranges from 5% to 67%. Absorption is not bile dependent but does depend on gastrointestinal transit time and is affected by the presence or absence of food as well as the lipid content of food. Clearance appears to be faster in children, necessitating administration of higher or more frequent doses. Ethnic differences exist as well, with African Americans and Latin Americans requiring higher doses than Caucasians to achieve equivalent therapeutic levels. These differences may in part be caused by expression

of alternative subtypes of CYP3A (e.g., CYP3A5). In blood, tacrolimus distributes primarily to erythrocytes, with whole-blood concentrations 10 to 30 times higher than in plasma. In contrast to cyclosporine, no lipoprotein binding occurs. Tacrolimus has 20- to 30-fold higher potency than cyclosporine on a molecular weight basis. Similar to cyclosporine, metabolism occurs through the CYP3A4 system, with pharmacokinetics also affected by intestinal P-glycoprotein. Both CNIs are generally administered twice daily.

Because of their narrow therapeutic index, the variability of concentrations among patients after a dose, and the potential for drug interactions, monitoring of CNIs is required to ensure both safety and adequacy. Both cyclosporine and tacrolimus bind to cells and to plasma components (primarily lipoproteins for cyclosporine and albumin for tacrolimus) in the blood and therefore must be assayed in the whole blood. Four assays are currently used to monitor levels of CNIs in the blood: high-performance liquid chromatography (HPLC), monoclonal radioimmunoassay (RIA), monoclonal and polyclonal fluorescent polarization immunoassays, and the specific enzyme-multiplied immunoassay. Cyclosporine trough levels measured by HPLC or RIA are comparable because both techniques measure levels of the parent compound only. However, these concentrations are one-third lower compared with concentrations measured by techniques that detect the parent compound plus its metabolites.

Given the complementary influence of both CYP3A4 and P-glycoprotein on the pharmacokinetic profiles of CNIs, it is assumed that CNI-drug interactions are similar. It is interesting to note that drugs that competitively inhibit CYP3A4 activity, such as ketoconazole, usually also inhibit P-glycoprotein, thereby increasing the bioavailability of CNIs and potential for toxicity. Likewise, drugs such as phenobarbital that increase CYP3A4 levels tend to upregulate P-glycoprotein, decreasing overall bioavailability. In this case, the likelihood of rejection increases. Despite similar drug interactions, the age-related and ethnic differences in pharmacokinetics between the two CNIs are likely to influence the degree and importance of such interactions. See Table 101-2 for common interactions.

Drugs and Other Substances That Interact with Calcineurin Inhibitors

Increase Blood Levels (P450-3A4 and/or P-Glycoprotein Inhibitors)	Decrease Blood Levels (P450-3A4 and/or P-Glycoprotein Inducers)
Ketoconazole	Rifampin
Fluconazole	Rifabutin
Itraconazole	Phenytoin
Voriconazole	Carbamazepine
Erythromycin	Phenobarbital
Clarithromycin	St John's wort
Diltiazem	Caspofungin
Verapamil	
Nicardipine	
Cimetidine	
Methylprednisolone	
Metronidazole	
Ezetimibe	
Metoclopramide	
Fluvoxamine	
Human immunodeficiency virus (HIV) protease inhibitors	
Lovastatin	
Atorvastatin	
Simvastatin	
Grapefruit juice	
Chamomile	
Wild cherry	

Table 101-2 Drugs and other substances that interact with calcineurin inhibitors.

Side Effects

Cyclosporine and tacrolimus have similarities and differences in their toxicity profiles (see Table 101-1). Both can cause nephrotoxicity, hyperkalemia, hypomagnesemia and hypophosphatemia (secondary to urinary loss), renal tubular acidosis (type 4), hypertension, diabetes, and neurotoxicity. Certain side effects, such as gingival hyperplasia, hirsutism, hypertension, hyperuricemia, and hyperlipidemia, are more common with cyclosporine, whereas tremor and glucose intolerance are more common with tacrolimus. Cyclosporine may also be associated with coarsening of facial features, especially in children, and bone pain responsive to calcium channel blockers. Tacrolimus, especially in combination with mycophenolate mofetil (MMF), has been suspected of inducing more BK virus nephropathy.

The most common and vexing problem with CNIs is nephrotoxicity, with the importance evident from cardiac and liver transplant recipients, in whom large doses of CNIs are associated with progression to end-stage renal disease. Both reversible hemodynamic and irreversible structural components underlie the nephrotoxicity of CNIs. Reversible vasoconstriction is caused by direct vascular effects but is also due to activation of the renin-angiotensin system (RAS), endothelin, thromboxane, and the sympathetic nervous system. Over time, chronic renal injury occurs, which is notable for afferent arterial hyalinosis and tubulointerstitial fibrosis. It is presumed that these lesions are the result of prolonged renal vasoconstriction with ischemia. Experimentally, chronic cyclosporine nephropathy is exacerbated by sodium restriction and volume depletion, which stimulates the RAS, and can be ameliorated by angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Cyclosporine toxicity and to a lesser extent tacrolimus toxicity are potentiated in combination with sirolimus and everolimus. Finally, CNIs in high doses can cause thrombotic microangiopathy (TMA), probably by direct endothelial cell injury and dysfunction.

Mycophenolate

Mycophenolate mofetil and enteric-coated mycophenolate sodium (EC-MPS) are important components of immunosuppressive regimens that are associated with some of the most successful outcomes in kidney transplantation.[4] Because of its well-documented efficacy and acceptable side effect profile, MMF has become by far the most frequently used antiproliferative agent.

Mechanism of Action

The immunosuppressive effects of both these agents are likely to be mediated through the active metabolite mycophenolic acid (MPA). MMF is a morpholinoethyl ester of MPA, a potent reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), isoform 2. EC-MPS is a salt that combines an acid—MPA—with a base—sodium. The enteric coating delays MPS release so that the MPA is absorbed in the small intestine rather than in the stomach. MPA noncompetitively inhibits IMPDH, which is the rate-limiting enzyme in the *de novo* synthesis of guanosine monophosphate (GMP). Inhibition of IMPDH creates a relative deficiency of GMP and a relative excess of adenosine monophosphate (AMP). GMP and AMP levels act as a control on *de novo* purine biosynthesis; therefore, MPA, by inhibiting IMPDH, creates a block in *de novo* purine synthesis that selectively interferes with proliferative responses of T and B cells. Some other cell types, including gastrointestinal epithelial cells, use the *de novo* pathway. Thus, MPA may act directly to inhibit replication of gastrointestinal epithelial cells, leading to disruption of fluid

absorption and diarrhea. However, most other cell types, including neurons, depend primarily on the alternative pathway for DNA synthesis and cell division and thus are relatively spared from toxicity.

Pharmacokinetics

Mycophenolate mofetil, being a prodrug of MPA, is absorbed rapidly and completely from the gastrointestinal tract and undergoes extensive presystemic de-esterification to become MPA, the active form. Food intake can delay the rate of MMF absorption but does not affect the extent. However, coadministration of antacids or cholestyramine decreases absorption by approximately 20% and 40%, respectively. EC-MPS has shown bioavailability equivalence as well as similar efficacy to that of MMF despite reaching higher levels with the use of proton pump inhibitors (PPIs). MPA undergoes enterohepatic circulation, and its plasma concentration shows a secondary peak at 6 to 12 hours after intravenous or oral administration. The mean contribution of enterohepatic circulation to the overall AUC of MPA is 37% (range, 10% to 61%). The majority of MPA is metabolized in the liver through a phase II glucuronidation process. The major metabolite of MPA is the pharmacologically inactive 7-*O*-glucuronide metabolite (MPAG), although two other metabolites, MPA-acyl-glucuronide (AcMPAG) and MPA-phenyl-glucoside (glucoside-MPA), are isolated from the plasma of renal transplant patients. AcMPAG has shown *in vitro* pharmacologic activity (inhibition of IMPDH) as well as proinflammatory effects and potentially is responsible for the gastrointestinal toxicity of MPA.

The glucuronide metabolites are excreted into the bile, a process that is mediated by the multidrug resistance–related protein 2 (MRPR2), then undergo de-glucuronidation back to MPA by enzymes that are produced by colonic bacteria. Blockade of MRPR2 by an inhibitor, such as cyclosporine but not tacrolimus, decreases the biliary excretion of MPAG and increases plasma MPAG levels. This eventually leads to lower plasma levels of MPA because the glucuronide metabolites no longer can be reabsorbed as MPA by enterohepatic cycling. Thus, tacrolimus-treated patients have higher exposure to MPA than cyclosporine-treated patients do, and it is possible that tacrolimus results in greater intestinal exposure to the metabolites of MPA because of greater enterohepatic circulation.[5] The ultimate elimination pathway for the glucuronide metabolites is through the kidney, and more than 95% of an administered dose eventually is found in the urine as glucuronide metabolites.

For the most part, MMF and EC-MPS have been used exclusively in a fixed-dose regimen. However, studies have established a strong association of MPA AUC and its pharmacologic effects, specifically prevention of acute rejection. Furthermore, considerable interindividual variability is found in MPA AUC and trough concentrations in patients who receive a fixed dose of MMF. These data lend support to recent efforts to evaluate the role of therapeutic drug monitoring in increasing the therapeutic potential of MMF and EC-MPS.

Side Effects

Mycophenolate mofetil and EC-MPS have similar side effect profiles, including gastrointestinal toxicity, bone marrow suppression, and increased infections, especially those of viral cause (see Table 101-1). Gastrointestinal disturbances include oral ulcerations, esophagitis, gastritis, nausea and vomiting, diarrhea, and colonic ulcers. Diarrhea and leukopenia frequently necessitate dose reduction, which can precipitate rejection. Because the metabolites of MPA appear to play a major role in the gastrointestinal disturbances associated with MMF, there is little rationale for enteric coating of the prodrug to reduce these symptoms. In fact, randomized controlled trials have found no significant difference in gastrointestinal adverse events between MMF and EC-MPS.[6,7] MMF is not routinely used during pregnancy because of its teratogenicity in experimental animal models and clinical reports of major fetal malformations (mycophenolate embryopathy).

Azathioprine

The use of azathioprine has decreased dramatically in kidney transplantation with the introduction of MMF. Azathioprine is metabolized in the liver to 6-mercaptopurine and further converted to the active metabolite thioinosinic acid by hypoxanthine-guanine phosphoribosyltransferase. Because allopurinol (a xanthine oxidase inhibitor) will increase the levels of thioinosinic acid, doses of azathioprine must be reduced by two thirds in patients taking allopurinol. More often, MMF is substituted for azathioprine.

Azathioprine suppresses the proliferation of activated T and B cells and reduces the number of circulating monocytes by arresting the cell cycle of promyelocytes in the bone marrow. The antiproliferative effect is mediated by the metabolites of azathioprine, including 6-mercaptopurine, 6-thiouric acid, 6-methylmercaptopurine, and 6-thioguanine. These compounds are incorporated into replicating DNA and halt replication. They also block the *de novo* pathway of purine synthesis by formation of thioinosinic acid; this effect confers specificity of action on lymphocytes that lack a salvage pathway for purine synthesis.

The major side effect of azathioprine is bone marrow suppression, leading to leukopenia, thrombocytopenia, and anemia (see Table 101-1). The mean cell volume is commonly increased in patients taking azathioprine, and red cell aplasia can occasionally occur. The hematologic side effects are dose related and usually reversible on dose reduction or temporary discontinuation of the drug. Other common side effects are increased risk of malignant disease (especially of skin cancers), hepatotoxicity, pancreatitis, and hair loss. Azathioprine is generally considered safe in pregnancy.

Mammalian Target of Rapamycin Inhibitors

The mammalian target of rapamycin (mTOR) inhibitors are proliferation signal inhibitors with potent immunosuppressive activity. Sirolimus, also called *rapamycin,* was the first agent used in transplantation and is a macrolide product of a soil fungus found in Easter Island.[8] Everolimus is a rapamycin analogue with similar mechanism of action, immunosuppressive properties, and side effect profile. Although initially used in regimens with the intent of minimizing exposure to CNIs, the mTOR inhibitors have been associated with their own set of toxicities that have prevented their widespread use.

Mechanism of Action

Sirolimus has structural similarity to tacrolimus and binds the immunophilin FKBP12. The affinity of sirolimus for FKBP12 is higher than that of everolimus. mTOR inhibitors do not inhibit calcineurin or the calcium-dependent activation of cytokine genes but instead inhibit cytokine receptor–mediated signal transduction and cell proliferation and block lymphocyte responses to cytokines and growth factors. The sirolimus-FKBP12 or everolimus-FKBP12 complex binds with high affinity a kinase enzyme called *mammalian target of rapamycin* or mTOR, which is a serine-threonine kinase of the phosphatidylinositol 3-kinase pathway that acts during costimulatory and cytokine-driven pathways. mTOR inhibits an inhibitor (4E-BP1) and activates a ribosomal enzyme (p70 S6 kinase), both of which are important for translation of the mRNAs for certain proteins needed for progression from the G_1 phase to the S phase of DNA synthesis. mTOR has been identified as the principal controller of cell growth and proliferation. The sirolimus-FKBP12 complex

inhibits mTOR-mediated signal transduction pathways by blocking postreceptor immune responses to costimulatory signal 2 during G_0 to G_1 transition and to cytokine signaling during G_1 progression. It also inhibits IL-2– and IL-4–dependent proliferation of T and B cells, leading to suppression of new ribosomal protein synthesis and arrest of the G_1-S phase of the cell cycle. Proliferation of nonimmune cells, such as fibroblasts, endothelial cells, hepatocytes, and smooth muscle cells, is also impaired by inhibition of the growth factor–mediated responses (e.g., basic fibroblast growth factor, platelet-derived growth factor, vascular endothelial cell growth factor, and TGF-β). In addition, it has been shown that mTOR contributes to several protein synthesis pathways that could be involved in oncogenesis.

Pharmacokinetics

The oral bioavailability of sirolimus is poor (10% to 16%), with significant interindividual and intraindividual variability. Peak concentrations occur approximately 1 to 2 hours after an oral dose, and sirolimus distributes extensively into tissues, including blood cells. The oral bioavailability of everolimus is higher than that of sirolimus. High-fat meals increase sirolimus levels while decreasing everolimus levels. Because sirolimus has a relatively long half-life (approximately 62 hours), it is reasonable to wait 1 week (approximately three half-lives to achieve steady state) before monitoring sirolimus blood levels after initiation or dose adjustment. Sirolimus is metabolized by the P-450 3A4 isoenzyme and P-glycoprotein system and thus has interactions similar to those described for the CNIs (see Table 101-2). When sirolimus or everolimus is administered simultaneously with cyclosporine, C_{max} and AUC for both compounds are increased. Therefore it is recommended that cyclosporine and mTOR inhibitors be administered 4 hours apart. Cyclosporine clearance may be reduced during concurrent therapy.

Side Effects

The mTOR inhibitors have a wide variety of toxicities (see Table 101-1). The most common adverse effects associated with sirolimus are dose-dependent hyperlipidemia (particularly hypertriglyceridemia), thrombocytopenia, and leukopenia. Other adverse effects include anemia (especially in combination with MMF), impaired wound healing and dehiscence, formation of lymphoceles, oral ulcers, reduced testosterone levels, pneumonitis, and diarrhea. Although not inherently nephrotoxic, the mTOR inhibitors result in renal graft damage through several mechanisms. When it is used in combination with full-dose cyclosporine (and probably also tacrolimus), sirolimus potentiates CNI-induced toxicity. In patients with renal impairment, sirolimus is associated with marked yet potentially reversible proteinuria and worsening of established proteinuria. Sirolimus can also cause delayed recovery from acute tubular necrosis. Finally, cases of TMA have been reported, and there is concern that higher doses of sirolimus may inhibit endothelial cell growth. Sirolimus-based regimens have been associated with a reduced incidence of post-transplantation malignant neoplasms. Some physicians regard sirolimus as the preferred immunosuppressive agent in transplant patients who develop malignant neoplasms, but this is based on limited data about kidney transplant recipients and skin cancer. Sirolimus is not routinely used during pregnancy because of its teratogenicity in experimental animal models, although successful pregnancies have been reported.

Dihydroorotate Dehydrogenase Inhibitors

Leflunomide and its derivative, FK778, are pyrimidine synthesis inhibitors with immunosuppressive as well as antiproliferative effects. These agents inhibit dihydroorotate dehydrogenase, which is a key rate-limiting enzyme in *de novo* pyrimidine synthesis. Unlike other cell types, activated lymphocytes expand their pyrimidine pool by nearly eightfold during proliferation, whereas purine pools increase only twofold. Thus, inhibition of dihydroorotate dehydrogenase prevents lymphocytes from accumulating sufficient pyrimidines to support DNA synthesis.

Leflunomide tablets are 80% bioavailable. After oral administration, leflunomide is metabolized to teriflunomide, which is responsible for essentially all of the activity *in vivo* and is monitored during therapy. Metabolism occurs in the liver, with excretion in the urine and bile. Because of its very long half-life (approximately 2 weeks), a loading dose of 100 mg for 3 to 5 days is generally used to reach steady-state levels quickly. Side effects include gastrointestinal adverse events, alopecia, bone marrow suppression, severe hepatitis, interstitial lung disease, and life-threatening skin reactions. Leflunomide use is not safe during pregnancy, and unless female leflunomide users receive cholestyramine therapy to eliminate the drug from the body, pregnancy must be avoided for 2 years after discontinuation. Although it is not approved for use in kidney transplantation, leflunomide has recently been assigned orphan drug status for the prevention of rejection in solid organ transplantation, largely on the basis of modest antiviral activity *in vitro* against BK virus and cytomegalovirus. However, the efficacy and safety of leflunomide have not been completely assessed in well-controlled and adequate studies. Furthermore, the manufacturers of FK778 discontinued development because of a lack of benefit over current options with regard to prevention of rejection and treatment of BK virus nephropathy.

BIOLOGIC AGENTS

Biologic agents in the form of polyclonal antibodies and monoclonal antibodies (mAbs) are frequently used in kidney transplantation either as induction therapy or for the treatment of rejection. Polyclonal antibodies are derived from horses or rabbits; historically, mAbs have been murine in origin. However, because foreign proteins can elicit an immune response, there has been an attempt to replace murine monoclonal products with humanized or chimeric mAbs (Fig. 101-3). Humanized antibodies are produced by merging the DNA that encodes the antigen-binding portion of a monoclonal mouse antibody with human antibody–producing DNA. Mouse hybridomas are then used to express this DNA to produce hybrid antibodies that are not as immunogenic as the murine variety. Chimeric antibodies use the same strategy but for the entire variable region and thus are more immunogenic than humanized antibodies. Polyclonal antibodies and mAbs can be divided further into two groups: depleting agents and immune modulators.

Polyclonal Antilymphocyte Sera

Polyclonal antilymphocyte agents are produced by immunizing animals with human thymus–derived lymphoid cells. Although rabbit antithymocyte globulin (ATG) is currently the preferred preparation, equine preparations have historically been used. Most regimens involve daily intravenous administration of ATG for 5 to 7 days either as induction therapy or for treatment of corticosteroid-resistant rejection. ATG contains antibodies that react against a variety of targets, including red blood cells, neutrophils, dendritic cells, and platelets. ATG binds to multiple epitopes on the surface of T cells and induces a rapid lymphocytopenia by several mechanisms, including complement-dependent cytolysis, cell-dependent phagocytosis, and apoptosis. ATG is a potent immunosuppressive, and

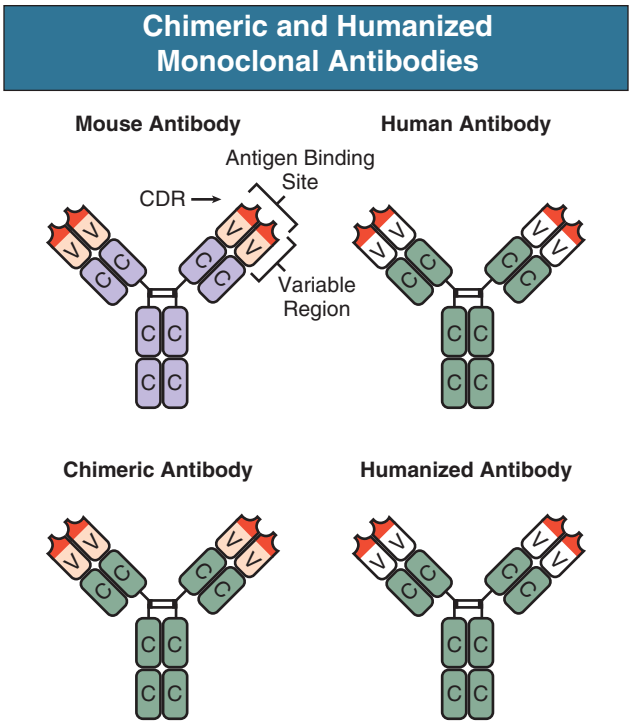

Figure 101-3 Chimeric and humanized antibodies. Chimeric antibodies consist of human constant *(C)* regions and mouse variable *(V)* regions. A chimeric antibody therefore retains the antigen binding site of the mouse antibody but with fewer amino acid sequences foreign to the human immune system than a standard mouse antibody. Humanized monoclonal antibodies retain only the minimum necessary parts of the mouse antibody for antigen binding, the complementarity-determining region (*CDR, highlighted in red*), and therefore are even less immunogenic in the human host.

T- and B-lymphocyte counts can remain depressed up to 24 hours after administration. The lack of specificity coupled with marked immunosuppression increases the risk of infection and malignant neoplasms. As polyclonal agents are xenogeneic proteins, they may elicit a number of side effects, including fever and chills. The initial lysis and activation of T cells that follow ATG administration may generate significant first-dose effects, with release of TNF-α, interferon-γ (IFN-γ), and other cytokines. Less commonly, ATG can induce a serum sickness–like syndrome and rarely acute respiratory distress syndrome (ARDS).

Murine Monoclonal Anti-CD3 Antibody

OKT3, a murine IgG2a mAb targeting the ε chain of the CD3–T cell receptor complex, was used for the treatment of acute rejection but is no longer available.

Humanized Monoclonal Anti-CD52 Antibody

Alemtuzumab is a humanized IgG1 mAb directed against CD52, a glycoprotein present on circulating T and B cells, monocytes-macrophages, NK cells, and granulocytes. Although it is currently approved only for the treatment of B cell chronic lymphocytic leukemia, alemtuzumab has been used as an induction agent in renal transplantation, given its powerful depletional properties and favorable cost profile compared with other induction agents. Treatment results in a rapid and effective depletion of peripheral and central lymphoid cells, which may take months to return to pretransplantation levels. Side effects of alemtuzumab include first-dose reactions, neutropenia, anemia, and, rarely, pancytopenia and autoimmunity (e.g., hemolytic anemia, thrombocytopenia, and hyperthyroidism). The risks of immunodeficiency complications such as infection and malignant neoplasia with alemtuzumab are still not clear, and additional controlled trials are necessary to establish dosing, safety, and efficacy.

Monoclonal Anti-CD25 Antibody

The α subunit of IL-2R (CD25) is upregulated on activated T cells and leads to the expression of high-affinity IL-2R that on engagement by IL-2 triggers the activated T cell to undergo proliferation. Basiliximab is a chimeric mAb with specificity for CD25; it induces relatively mild immunosuppression and is used as an induction agent to prevent rejection[9,10] but not to treat established rejection. Although the exact mechanism of action is not fully understood, it is clear that significant depletion of T cells does not play a major role. Saturation of the IL-2R α subunit persists for up to 25 to 35 days after treatment with basiliximab. Although saturation is important as a determinant of minimal blood concentrations, it is not predictive of rejection. No major side effects have been associated with anti-CD25 therapy.

B Cell–Depleting Monoclonal Anti-CD20 Antibody

Rituximab is an engineered chimeric mAb that contains murine heavy- and light-chain variable regions directed against CD20 plus a human IgG1 constant region.[11] The CD20 antigen, a transmembrane protein, is found on immature and mature B cells as well as on malignant B cells. CD20 mediates proliferation and differentiation of B cells. Rituximab directly inhibits B cell proliferation and induces apoptosis and lysis by complement-dependent cytotoxicity, antibody-dependent cell cytotoxicity, and activation of tyrosine kinases as a direct effect of the antibody's binding to its CD20 ligand. Rapid and sustained depletion of circulating and tissue-based B cells occurs after intravenous administration, and recovery does not begin until approximately 6 months after completion of treatment. Although plasma cells are usually CD20 negative, many are short-lived and require replacement from CD20-positive precursors. In addition, CD20-positive B cells can act as secondary antigen-presenting cells (APCs), thereby enhancing T cell responses. Thus, by targeting CD20 on precursor B cells, rituximab decreases the production of activated B cells and limits their antibody production as well as antigen presentation capability.

Most adverse events are first-infusion effects, such as fevers and chills, and are generally of mild severity. Moreover, these adverse effects occur less frequently during subsequent infusions. Viral infections, including reactivation of hepatitis B virus and JC virus (progressive multifocal leukoencephalopathy [PML]), have been reported, although it is not known whether these events are specific to the agent or instead reflect the overall state of immunosuppression. Antichimeric antibodies develop in some patients, but their true incidence and therapeutic significance are uncertain.

Rituximab has been used in kidney transplantation to treat antibody-mediated rejection as well as in combination with intravenous immunoglobulin (IVIG) to reduce high-titer anti-HLA antibodies in highly sensitized patients awaiting renal transplantation.[12] Rituximab is also used as induction therapy after desensitization therapy for ABO blood group–incompatible and high-risk positive-crossmatch kidney transplantation. Finally, rituximab is often used to treat post-transplantation lymphoproliferative disease.

Intravenous Immunoglobulin

Intravenous immunoglobulin products are known to have powerful immunomodulatory effects on inflammatory and autoimmune conditions. The mode of action of IVIG is not understood. In renal transplantation, the most important effect appears to be a reduction of alloantibodies through inhibition of antibody production and increased catabolism of circulating antibodies. Additional potential mechanisms include inhibition of complement-mediated injury, inhibition of inflammatory cytokine generation, and neutralization of circulating antibodies by anti-idiotypes.

Side effects related to IVIG administration include minor self-limited reactions, such as flushing, chills, headache, myalgia, and arthralgia. Rarely, anaphylactic reactions may occur. Delayed reactions include severe headache and aseptic meningitis, which respond to analgesics. More recently, severe thrombotic events have been linked to the administration of IVIG products. Of concern to renal transplant recipients is osmotic injury of the proximal tubular epithelium after administration of sucrose-containing IVIG preparations. This tubular injury is self-limited and can be minimized or avoided by use of sucrose-free preparations.

In combination with plasma exchange, IVIG appears to offer significant benefits in the desensitization of positive-crossmatch and ABO-incompatible patients to allow successful transplantation as well as in the treatment of antibody-mediated rejection. Alone or in combination with rituximab, IVIG has been successful in the desensitization of highly sensitized wait-listed patients to increase the chances of finding a compatible donor.

Belatacept

Costimulation blockade is an immunosuppression alternative for kidney transplant recipients. Belatacept, a first-in-class costimulation blocker, is a fusion protein that binds to CD80 and CD86 on APCs and prevents kidney transplant rejection. It is for intravenous use only. It affects the CD28 pathway as well as the cytotoxic T-lymphocyte antigen 4 (CTLA-4) pathway, the latter of which is required for the function of T regulatory cells (Tregs) and tolerance of transplanted tissue. Patients treated with belatacept had higher rates of acute rejection during the first year of treatment in comparison with cyclosporine-treated patients. Belatacept seems to have a better metabolic risk profile and preservation of GFR. It is approved only for Epstein-Barr virus (EBV)–seropositive patients, because of increased risk of post-transplant lymphoproliferative disorder (PTLD), especially of the central nervous system in EBV-seronegative patients.[13] There is also increased risk of PML, an often progressive and fatal CNS infection caused by the JC virus, a polyomavirus. The most common adverse reactions observed are anemia, leukopenia, and gastrointestinal symptoms, as well as hypokalemia or hyperkalemia. It is now used in *de novo* renal transplant recipients as well as for conversion from CNIs.

Other Agents Used

Two other agents are increasingly used in transplantation.

Bortezomib

Bortezomib is an antineoplastic agent originally approved for the use in plasma cell dyscrasias such as multiple myeloma and several types of lymphomas. Bortezomib inhibits proteasomes, enzyme complexes that regulate protein homeostasis. Specifically, it reversibly inhibits chymotrypsin-like activity at the 26S proteasome, leading to activation of signaling cascades, cell-cycle arrest, and apoptosis. It targets mature rapidly proliferating antibody-producing plasma cells, but also interferes with T cell function and interleukin and TNF production. It has been used for the treatment of both primary and refractory antibody-mediated rejection and in desensitization protocols to reduce donor-specific antibody (DSA) levels pretransplant.[14] It is given as a rapid intravenous injection in a 21-day cycle. Each cycle consists of four doses, and two to six cycles are usually required. It is metabolized by the liver. The development of thrombocytopenia and peripheral neuropathy limits its use. Gastrointestinal symptoms are common. Herpes zoster prophylaxis is required.

Eculizumab

Eculizumab was originally approved for paroxysmal nocturnal hemoglobinuria. It is a humanized mAb directed against complement protein C5, preventing cleavage into C5a and C5b. Blocking the formation of C5b inhibits the subsequent formation of terminal complex C5b-9 or membrane attack complex (MAC). Later it was used for the treatment and prevention of atypical hemolytic uremic syndrome.[15] Because of cost, its use in antibody-mediated rejection is usually as a rescue therapy for fresh allografts failing other treatments for rejection. It prevents antibody-dependent complement-mediated cytotoxicity that occurs before the antibody clearance is complete by other agents. It is also used for prevention of antibody mediated rejection in crossmatch-positive transplants and catastrophic antiphospholipid syndrome. Eculizumab is associated with an increased incidence of meningococcal infections. Patients should receive the meningococcal vaccine before therapy as well as antibiotic prophylaxis.

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CHAPTER 102

Evaluation and Preoperative Management of Kidney Transplant Recipient and Donor

William R. Mulley and John Kanellis

Renal transplantation provides superior long-term outcomes compared with dialysis, in both quantity and quality of life, although the benefit gained varies among individuals.[1] The improvement in outcomes coupled with the shortage of available organs has led to an expansion of donor criteria and an increasing tendency for centers to accept marginal donor kidneys.[2] In this chapter, we review current recommendations for the evaluation and preoperative management of both the kidney transplant donor and the recipient.

RECIPIENT EVALUATION

Many units now accept patients who were previously excluded from transplantation, such as those with human immunodeficiency virus (HIV) infection, obesity, and diabetes. This is because of the availability of newer treatment options for some conditions and a greater understanding of the impact of these conditions on patient and graft survival along with changing societal attitudes regarding equality of access to transplantation. Some absolute contraindications to transplantation remain (Table 102-1), including significant current infection or malignant disease, noncompliance or substance abuse, and any condition likely to severely limit life expectancy (<1 to 2 years).[3-5]

Whereas the application of guidelines for transplant suitability may be relatively straightforward for patients with a single comorbidity, it is not as simple for those with multiple medical conditions, who represent a growing group of potential transplant recipients. Determination of suitability in such patients often requires input from specialists in a variety of medical and surgical disciplines along with allied health professionals. The final decision needs to be a joint one between clinician and patient after full and open discussion of the likely risks and benefits followed by regular reassessment of suitability while the patient awaits transplantation.

A summary of guidelines published by national and international transplantation associations[3-5] is presented in Box 102-1. Some of the important areas to consider in evaluating the transplant recipient are discussed here.

Cardiovascular Disease

Cardiovascular disease is a significant problem in patients with end-stage renal disease (ESRD) and a major cause of death in transplant recipients. Hence, cardiovascular evaluation is critical in the evaluation of the transplant recipient.

Coronary Heart Disease and Left Ventricular Dysfunction

Chronic kidney disease (CKD) itself is a major risk factor for coronary heart disease. However, the vascular lesion, clinical features, and response to treatment may be quite different in patients with ESRD compared with the normal population. The role of pretransplantation screening and intervention for coronary heart disease is controversial, making definite recommendations difficult. However, given the high incidence of cardiac events in the peritransplantation period and its major contribution to post-transplantation mortality, we favor aggressive screening and intervention in at-risk patients while avoiding unnecessary tests and procedures in low-risk candidates. Patients may be stratified into risk groups on the basis of history and examination, resting electrocardiography, and chest radiography. Further screening is unnecessary in asymptomatic patients without risk factors because of a very low incidence of coronary events.[6] Further investigation is recommended, however, in patients with abnormal test results or significant risk factors, such as previous cardiac ischemic events, diabetes, smoking, age older than 50 years, hypertension, prolonged dialysis duration (>2 years), or a family history of coronary heart disease.[3-5]

Symptomatic patients should proceed directly to coronary angiography; noninvasive functional testing should be used to screen for the need for angiography in asymptomatic patients.[7] Exercise echocardiography or myocardial perfusion scintigraphy is preferred; however, pharmacologically driven testing may be necessary if exercise is not possible. Whereas a normal result does not exclude coronary heart disease, both testing modalities have negative predictive values for myocardial infarction or cardiac death in excess of 96% in patients with renal failure.[8] If significant coronary heart disease is identified, treatment before transplantation should be instituted. Treatment consists of medical management including aggressive risk factor modification, angioplasty and stenting or coronary artery bypass grafting in patients with significant stenoses.[7] A suggested approach is presented in Figure 102-1.

In patients with clinical or radiologic evidence of left ventricular dysfunction, transthoracic echocardiography should be performed to assess the severity and nature of the dysfunction. A cause should be sought and treated when possible. Severe left ventricular dysfunction may improve significantly after transplantation; therefore it is not in itself an absolute contraindication to transplantation. It is, however, associated with reduced post-transplantation survival; thus in patients with significant comorbidities it does represent a contraindication to transplantation unless, in rare instances, combined heart and kidney transplantation is appropriate.[3-5]

Cerebrovascular Disease

Patients with a history of recent transient ischemic attack or stroke are at greatest risk of recurrence early after the primary event; and because stroke after transplantation is associated with a high rate of mortality,[9] a waiting time of 6 months is recommended. Meanwhile, aggressive risk factor modification should be undertaken to limit the likelihood of further stroke. Routine screening for cerebrovascular

Contraindications to Renal Transplantation

Current Absolute Contraindications to Transplantation	Previous Contraindications to Transplantation*
Active sepsis	HIV infection
Current uncontrolled malignant disease	Hepatitis B and C
Uncontrolled psychosis	Obesity
Active drug dependence	Mood disorders
Any medical condition with a severely shortened life expectancy (<1-2 years)	Age above 60 years
Positive T cell CDC crossmatch	Previous malignant disease
	Blood group incompatibility

Table 102-1 Contraindications to renal transplantation. *CDC,* Complement-dependent cytotoxicity; *HIV,* human immunodeficiency virus. *These conditions are now acceptable under certain circumstances—see text.

Recipient Evaluation Checklist

History and Examination
- Cause of renal failure and risk of recurrence
- Sensitization (transfusion, pregnancy, previous transplant)
- Past and current infections (TB, hepatitis, HIV)
- Immunization (especially hepatitis B)
- Malignancy
- Cardiovascular risks (smoking, hypertension, diabetes)
- Pulmonary, gastrointestinal disease
- Genitourinary tract
- Psychiatric, psychological history
- Surgical issues (weight, iliac vessels, abdomen, previous surgery)

Laboratory and Radiologic Investigations
- Viral serology (HIV, CMV, EBV, hepatitis B and C)
- Liver function tests
- Bone-related issues (PTH, calcium, phosphate)
- Chest radiograph
- Electrocardiogram
- Prostate-specific antigen (for men older than 50 to 60 years)
- Mammogram or breast ultrasound (women older than 50 years or with family history of breast cancer)
- Pap smear (sexually active women)

Immunologic Investigations
- ABO blood group and HLA typing
- Screening for HLA antibodies and autoreactive antibodies
- Crossmatching

Box 102-1 Recipient evaluation. *CMV,* Cytomegalovirus; *EBV,* Epstein-Barr virus; *HIV,* human immunodeficiency virus; *HLA,* human leukocyte antigen; *PTH,* parathyroid hormone; *TB,* tuberculosis.

disease is not advocated in asymptomatic patients. Evidence suggests a benefit in further investigation of patients with a carotid bruit and treatment with carotid endarterectomy if a significant stenosis is found.[10] Patients with polycystic kidney disease at high risk of cerebral aneurysm rupture, such as those with a previous personal or family history of cerebral hemorrhage, should be screened for cerebral aneurysm before transplantation; however, there is no conclusive evidence to support doing so in those without such risk factors. Risk of cerebral aneurysm in polycystic kidney disease is discussed further in Chapter 46.

Assessment and Management of Cardiac Status in Potential Transplant Recipients

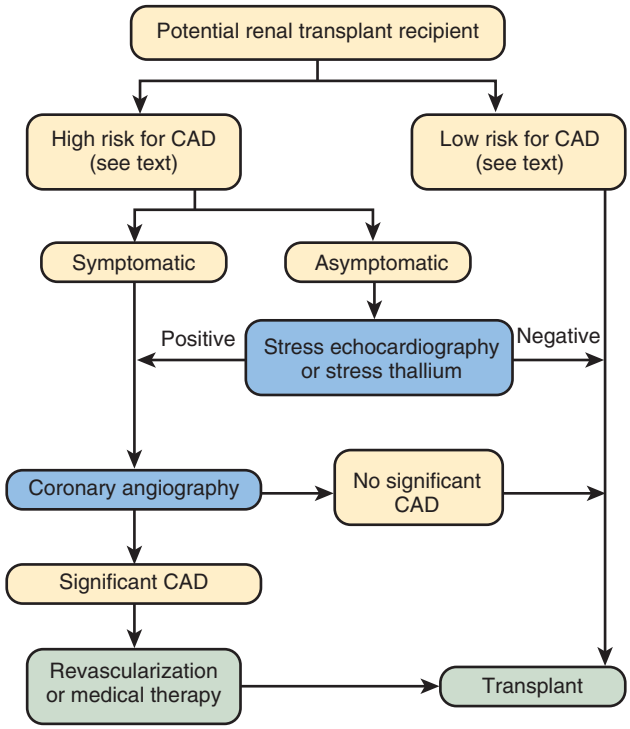

Figure 102-1 Assessment and management of coronary artery disease in potential transplant recipients. *CAD,* Coronary artery disease.

Peripheral Vascular Disease

Asymptomatic patients with strong femoral and peripheral pulses generally require no further investigation. Patients with diabetes, history of claudication, or reduced pulses require vascular imaging beginning with Doppler ultrasound. Significant disease involving the iliac vessels may make transplantation difficult or impossible and may worsen ischemia in the distal leg. Although it is not an absolute contraindication to transplantation, peripheral vascular disease is associated with increased mortality[11] and should be considered in conjunction with the patient's other comorbidities.

Cancer

Cancer is a major cause of death in renal transplant recipients. Further increases in the incidence of malignant disease are likely with increased graft survival and acceptance of older recipients. The incidence of malignant disease is also increased in transplant recipients compared with the general population.[12] However, the effect of transplantation on different types of cancers is not uniform, nor is the effect of different immunosuppressive agents.[13] Some cancers, such as nonmelanoma skin cancers (61% to 82% at 20 years) and lymphoma, have a markedly increased incidence in transplant recipients compared with the general population; the incidence of other malignant neoplasms, such as breast and prostate, is not as markedly increased.[14] In patients with a previous malignant neoplasm, guidelines have been devised on the basis of the likelihood of recurrence after transplantation (Box 102-2). In general, the longer the cancer-free interval before transplantation, the smaller the recurrence risk. For most malignant neoplasms, a period of 2 to 5 years

Guidelines for Transplantation in Patients with Previous Malignancies

Usual Waiting Time of 2 Years
- Most cancers

No Waiting Time Necessary
- Incidental renal carcinoma
- *In situ* carcinoma
- Focal neoplasm (defined as a localized tumor without metastases)
- Low-grade bladder cancer
- Basal cell skin cancer

Waiting Time of More Than 2 Years May Be Necessary
- Melanoma
- Breast cancer
- Colorectal cancer
- Uterine cancer

Box 102-2 Guidelines for transplantation in patients with previous malignant disease.[65]

is recommended.[3-5] There are several exceptions. A longer waiting time (≥5 years) is recommended for breast cancer with nodal involvement, melanoma, and colorectal cancer worse than Dukes stage B1; no waiting time is thought necessary for nonmelanocytic skin cancers confined to the skin, *in situ* cancers of bladder and cervix, focal microscopic low-grade prostate cancer, and small (<7 cm) incidentally discovered and surgically removed renal cell carcinomas. Given the heterogeneity of malignant neoplasms, waiting periods before transplantation need to be individualized, taking into account the patient's other comorbidities.

Although extensive screening of all potential recipients is not warranted, guidelines appropriate for the general population should be adopted in screening for breast, cervical, prostate, and colorectal cancer. Chest radiography is performed as part of the routine assessment. More comprehensive and targeted evaluation is recommended in patients with a strong family history or suggestive clinical features of malignant disease or conditions associated with an increased risk of malignant disease, such as renal imaging in patients with acquired cystic disease of the kidney for possible renal cell carcinoma.[3,4]

Infectious Complications

All patients are screened for previous exposure to Epstein-Barr virus and cytomegalovirus (CMV) to assess the risk of infection, either primary or reactivation. This guides the appropriate use of prophylactic antiviral agents. For example, patients who are negative for CMV IgG who receive a kidney from a CMV-positive donor are at the highest risk of infection and may benefit from prolonged prophylaxis compared with the lower-risk CMV-negative donor to a CMV-negative recipient (see Chapter 105). Screening for other infections should be tailored to geographic location; a guide for screening is presented in Table 102-2. Immunization against hepatitis B should be undertaken in all potential recipients. Immunization against encapsulated organisms (pneumococci, *Haemophilus influenzae,* and meningococci) should also be considered in patients at high risk of antibody-mediated rejection in case rescue therapy—for example, splenectomy or complement inhibition with eculizumab—is required.

Before highly active antiretroviral therapy (HAART), HIV infection was considered an absolute contraindication to transplantation because of very poor patient survival.[15] In the HAART era, HIV infection is seen as a manageable chronic disease, and transplantation is offered to HIV-positive patients at many centers that have experience in managing HIV infection and transplantation. Reports of short- to medium-term results suggest excellent patient and graft survival in carefully selected recipients.[16] Longer-term studies are under way to further explore these outcomes. Patients with sustained CD4 counts above 200/ml and undetectable HIV viral loads, without an acquired immunodeficiency syndrome (AIDS)–defining illness, can be considered for transplantation. Patients with hepatitis B may be considered for renal transplantation if there is no evidence of active viral replication (hepatitis B virus [HBV] DNA or hepatitis B early antigen [HBeAg] positive), advanced liver disease or cirrhosis (as determined by liver biopsy), or hepatocellular carcinoma.[3-5] Immunosuppression can increase HBV replication; hence, treatment before transplantation is indicated in patients with active disease, and although data to support prophylactic antiviral therapy, such as entecavir, after transplantation are scarce, it is commonly practiced while immunosuppression is at its highest (initial 12 to 24 months). Early reports suggest that mortality may be increased in HBV-positive patients after transplantation compared with HBV-negative recipients.[17] The significance of these findings is unclear in the current era with more effective treatment options and if only patients with inactive disease undergo transplantation. Frank disclosure of possible risks involved is recommended.[3-5]

Patients with hepatitis C should be assessed by measurement of hepatitis C virus (HCV) viral load and a liver biopsy. Treatment should be instituted before transplantation; however, candidates who do not clear the virus may still proceed with transplantation because mortality in this group is improved compared with those remaining on dialysis.[18] HCV-positive patients may in some units, with informed consent, receive a kidney from an HCV-positive donor. Any possible increased risk may be offset by a significantly reduced waiting time. Patients with hepatitis B and C should be screened every 12 months for hepatocellular carcinoma by liver ultrasound and serum alpha fetoprotein. Those with cirrhosis may be considered for combined kidney-liver transplantation.

Patients at high risk of tuberculosis reactivation after transplantation (previous tuberculosis, abnormal chest radiograph, or positive tuberculin skin test result; residence in an endemic area) who have not been previously treated should receive prophylactic isoniazid after transplantation (see Chapter 105). Recently, interferon-γ (IFN-γ) ELISPOT assays have been proposed to replace or supplement the tuberculin skin test because they appear more sensitive for detecting latent tuberculosis infection.[19] The need to screen patients is determined by the likelihood of previous exposure.

Screening Tests for Occult Infection

Routine Serology	Where Indicated, Tests for the Following Conditions and Infections	Other Routine Investigations
Cytomegalovirus Epstein-Barr virus Hepatitis B virus Hepatitis C virus HIV	HTLV Human herpesvirus 8 Malaria Schistosomiasis *Strongyloides stercoralis* *Trypanosoma cruzi* Tuberculosis	Chest radiograph Urine culture

Table 102-2 Screening tests for occult infection. Routine screening tests for occult infection. *HIV,* Human immunodeficiency virus; *HTLV,* human T-lymphotropic virus.

Previous graft loss caused by polyoma (BK) viral nephropathy is not a contraindication to repeated transplantation. Waiting for serum and urine BK polymerase chain reaction test results to become negative appears to be preferable,[20] whereas the value of graft nephrectomy before repeated transplantation is unclear. Vigilant screening for recurrence is recommended.[5]

Obesity

Transplantation in obese patients (body mass index [BMI] >30 kg/m^2) generally improves survival compared with matched waiting list controls, but inferior outcomes for patient and graft survival, delayed graft function and wound healing, and infective complications have been reported in obese compared with nonobese patients, particularly those with a BMI above 36 kg/m^2.[21] There are several reports to the contrary, however, including a recent multivariate analysis of registry data suggesting that obesity is not associated with worse graft and patient survival when comorbidities are controlled for.[22] Nevertheless, the overweight or obese patient is more likely to develop new-onset diabetes after transplantation, which can adversely affect graft and patient survival. Potential transplant recipients with obesity should be advised to lose weight as a means to decrease this risk before transplantation.

Recurrent Disease

The risk of disease recurrence needs to be discussed as part of the informed consent process, particularly in certain primary renal diseases (e.g., focal segmental glomerulosclerosis). Graft loss attributed to recurrent disease has increased in recent years but still accounts for only 5% of graft loss.[23] The risks and management of recurrent disease are discussed in Chapter 108.

Gastrointestinal Disease

Screening for gastrointestinal disease is not warranted in the asymptomatic patient.[4,5] Patients with active acute or chronic pancreatitis should not undergo transplantation until they have been clear of symptoms for 12 months. Patients with active peptic ulcer disease should be treated before transplantation with proton pump inhibitors, and this should be continued to prevent ulceration after transplantation. Patients with symptomatic diverticular disease require colonoscopy and potential colonic resection in severe cases before transplantation because they are at increased risk of perforation on immunosuppressive medications.[4] Whereas symptomatic cholecystitis should be treated surgically before transplantation, asymptomatic cholelithiasis does not require surgery before transplantation because cholecystectomy after transplantation is required in less than 10% of these patients and results in no increased mortality or morbidity compared with pretransplantation cholecystectomy and no deleterious effects on graft function.[24]

Genitourinary Disorders

Screening for genitourinary disorders before transplantation is indicated in those with a history or renal ultrasound suggestive of urinary obstruction, especially in children, in whom urologic problems are a major cause of ESRD. If obstruction is found, urologic assessment, which may include voiding cystourethrography and urodynamic studies, is indicated to determine the best course of action to ensure bladder emptying and limit bladder pressures after transplantation; this may involve bladder augmentation, urinary diversion, or self-catheterization.

Native nephrectomy before transplantation should be considered for recurrent or persistent renal sepsis, particularly in the setting of nephrolithiasis. Very large polycystic kidneys may need to be removed to accommodate the transplant kidney. Whether previous grafts should be removed before repeated transplantation is controversial. Nephrectomy of a failed graft is commonly performed on withdrawal of immunosuppression in patients with early graft failure (<12 months)[25] to alleviate symptoms such as pain over the graft, fever, and weight loss.[26] Other indications include graft sepsis and allowance of room for the new graft. However, unless there is a convincing reason to remove the graft, it is generally left *in situ*. In these circumstances the patient may need to stay on minimal immunosuppression (e.g., prednisolone, 5 mg/day) for 3 to 6 months to minimize graft tenderness and inflammation. Graft nephrectomy may be associated with an increased risk of human leukocyte antigen (HLA) sensitization,[25] perhaps relating to loss of antigen-dependent tolerogenic mechanisms[27]; this, however, is not a universal finding. Another advantage of leaving the previous transplant *in situ* is preservation of any residual renal function and urine output.

Pulmonary Disease

Initial assessment by physical examination and chest radiography is indicated for all potential recipients; further testing, such as pulmonary function tests or computed tomographic scanning, is performed if it is clinically indicated. Recent guidelines suggest that patients with a short life expectancy associated with pulmonary disease, such as cor pulmonale, uncontrolled asthma, and severe obstructive lung disease (FEV_1 <25% of predicted or P_{O_2} <60 mm Hg [8 kPa] on room air), or those needing home oxygen should be excluded from transplantation.[5] Many units require patients to cease smoking before acceptance because smokers have an increased risk of death and graft loss. Cessation of smoking demonstrates positive lifestyle behavior and good compliance, suggesting that these factors will be optimized in the post-transplantation period.

Psychosocial Issues

Psychosocial issues can have a major impact on transplant outcomes. Patients should be evaluated by a health professional experienced in judging capacity to consent and assessing likely compliance with a transplant medication regimen. Compliance with the post-transplantation treatment regimen is vital to minimize premature graft loss. Predicting compliance can be challenging and may be based on pretransplantation compliance, such as adherence to dialysis management regimens. If compliance is unlikely, as judged by medical, psychiatric, psychological, and social work assessment, transplantation should not proceed.[3-5]

Cognitive impairment is not an absolute contraindication to transplantation as long as appropriate supports and proxy arrangements are in place. Patients with psychiatric illnesses including depression, bipolar affective disorder, and psychosis require assessment by a psychiatrist to determine transplant suitability and to devise a management plan to cope with possible consequences of immunosuppressive medications such as corticosteroids.[3-5] Drug and alcohol addiction should be addressed with rehabilitation and demonstrated abstinence before the patient is listed for transplantation.

Presence of Multiple Comorbidities

Increasingly patients with multiple comorbidities are referred for consideration of transplantation as the boundaries for acceptance onto transplant programs broaden. Each problem in itself is often

Reevaluation of Suitability for Transplantation		
Cardiac reevaluation every 1-2 yr depending on risk factors (e.g., diabetes)	**Cancer surveillance relevant to age, sex, and risk factors**	**Comorbidity reassessment**
Stress echocardiogram or thallium scan Angiography if indicated (see Fig. 102-1)	Prostate-specific antigen Mammography Pap smear Colonoscopy if indicated Skin cancer check	Viral hepatitis Liver function tests Alpha fetoprotein Liver ultrasound HIV CD4 count ? AIDS-defining illness Other (see discussion of individual organ systems)

Table 102-3 Reevaluation of suitability for transplantation. *AIDS,* Acquired immunodeficiency syndrome; *HIV,* human immunodeficiency virus.

not an absolute contraindication; however, taken together they may mean the patient has significantly reduced overall survival prospects. Controversially, some societies have suggested that patients must have specified long-term survival prospects—for example, an 80% chance of surviving 5 years—to be accepted for transplantation from a deceased donor. In addition, risk calculators have been devised based on registry data to allow such predictions.[28]

Reevaluation of Patients on the Waiting List

Patients may wait several years on the transplant list before receiving an opportunity to undergo transplantation. It is vital that when their opportunity comes, they are still suitable. A targeted reassessment of waiting-list patients therefore should be conducted at regular intervals (Table 102-3). General measures, such as cancer screening (e.g., skin, prostate, breast, and cervical), should be continued on a regular basis as indicated. Reassessment of cardiac status is advocated on the basis of risk. Diabetic and other high-risk patients should be reassessed every 1 to 2 years.[7] The value of reassessing low-risk patients is more questionable, but given that CKD is a strong risk factor for cardiac disease, repeated stress testing by exercise or pharmacologically driven echocardiography or myocardial perfusion scintigraphy at least every 3 years seems appropriate. Patients with preexisting medical conditions (e.g., HIV infection and viral hepatitis) require regular specialist reviews, with any issues arising brought to the attention of the transplant team. Surgical reassessment may be needed in patients with peripheral vascular disease, if patients gain weight, or if a complication such as peritonitis occurs while the patient awaits transplantation. Patients should be temporarily removed from the waiting list if they develop a serious infection or other illness until it is resolved.

DONOR EVALUATION

Donor kidneys can be obtained from both deceased and living donors.

Deceased Donors

Classification of the Deceased Donor

Deceased donors can be classified as either heart-beating donors with loss of brainstem function (donation after brain death [DBD]) or non–heart-beating donors (donation after cardiac death [DCD]).

Classification of DCD Donors
As per Maastricht classification (Kootstra, 2007) (also known as non–heart–beating donors)
Uncontrolled
Category I: Dead on arrival to hospital
Cause of death is usually obvious (e.g., severe head injury) and no resuscitation is given.
Category II: Unsuccessful resuscitation
The patient is brought to the emergency department while being resuscitated, but this is not effective. Alternatively, arrest occurs in hospital and patient is unable to be resuscitated.
Controlled
Category III: Awaiting cardiac arrest
Severe brain injury without brain death. Patients are usually ventilator dependent. Arrest occurs once support is withdrawn.
Category IV: Cardiac arrest while brain dead
Patient suffers cardiac arrest after being declared brain dead. Alternatively, this occurs during brain death testing and the patient is not or cannot be successfully resuscitated.
Category V: Unexpected cardiac arrest in a critically ill patient
Example: Unsuccessful resuscitation after unexpected cardiac arrest in intensive care.

Box 102-3 Classification of donation after cardiac death (DCD) donors.[29]

In recent years the proportion of DCD donors has been increasing in many countries as a result of policies aiming to maximize the opportunities for donation.

Donation after brain death donors can be further divided into standard criteria donors and extended-criteria donors. The definition of extended-criteria donor varies; in the United States it refers to heart-beating donors older than 60 years or 50 to 59 years old with two or three of the following criteria: a history of hypertension; elevated serum creatinine at donation (>1.5 mg/dl or 130 µmol/l); or death from a cerebrovascular accident. In some jurisdictions, the term *marginal donor* is loosely used to describe donors who are less than optimal for some reason—usually the presence of significant underlying disease (hypertension, diabetes, vascular disease, renal impairment) or advanced age (older than 65 years).

Donation after cardiac death can occur by several mechanisms. The Maastricht classification separates these types of donors into controlled and uncontrolled categories (Box 102-3).[29] Controlled donors are those who suffer cardiac arrest after withdrawal of support or after brain death. Uncontrolled donors are those who are deceased on arrival to the hospital or who have a failed cardiopulmonary resuscitation. From a practical point of view, a system that uses controlled donors is easier to implement than one using uncontrolled donors. This is largely related to factors surrounding ethical considerations and the consent process involving relatives of the donor.

The survival of kidneys from extended-criteria donors and from some categories of DCD donors is generally inferior to that of kidneys retrieved from standard criteria donors.[30,31] Many matching schemes attempt to allocate these less ideal grafts to recipients who are predicted to have a lower-than-average overall survival, but practice varies considerably among countries with regard to these issues.

Evaluation of the Deceased Donor

In most circumstances, organ donor coordinators screen potential deceased donors after referral from hospital intensive care units or emergency departments. Patient records are assessed and relatives

are interviewed about important aspects of the clinical history. The assessment focuses on general health (including history of infections and cancer), social history (especially drug use and sexual history), and laboratory evidence of renal impairment or other diseases (Box 102-4). Patients with sepsis, acute hepatitis, or HIV infection are excluded from donation, as are those with a history of malignant disease. Nonmelanoma skin cancers do not lead to exclusion, nor do primary brain tumors unless they are of a high grade or the donor has received chemotherapy or had a craniotomy or cerebral shunt inserted.[32] In some centers, donors potentially carrying HBV or HCV are accepted only for recipients positive for these viruses. The risk of an unknown donor malignant neoplasm is approximately 1.3%; however, the risk of transmitting a donor malignant neoplasm is lower at approximately 0.2%.[33]

Evaluation of renal function is determined by history, urinalysis, and serum creatinine concentration. In some patients a biopsy (often performed at retrieval) may provide useful information, particularly with extended-criteria donors.[34] Serum creatinine concentration at admission should be in the near-normal range (estimated glomerular filtration rate [eGFR] >60 ml/min), but a temporary decline in renal function is acceptable if the function is expected to recover. Proteinuria (>0.5 g/24 h) may indicate structural renal damage and is a valid reason for nonacceptance.

The use of kidneys from very small donors varies among centers. Donors younger than 5 or 6 years are generally associated with high risk of failure, especially from vascular thrombosis.[35] For this reason, some centers occasionally transplant two kidneys—transplanted *en bloc,* using the aorta and inferior vena cava as conduits.[36]

Deceased Donor Evaluation Checklist

Medical History
- Hypertension, diabetes
- Malignant disease
- Infections: past and current (TB, hepatitis, HIV)
- Transfusions
- Trauma
- Surgical history
- Hospitalizations

Social History
- Intravenous drug use
- Alcohol, smoking
- Sexual behavior
- Tattoos, acupuncture
- Overseas travel
- Incarceration

Examination
- Blood pressure
- Cardiac, vascular
- Lymphadenopathy
- Abdominal

Laboratory and Technical
- Serum creatinine
- Urinalysis, urine culture
- Liver function tests
- Coagulation profile, complete blood count
- Blood culture
- *Virology, depending on geographic region: antibodies to CMV, EBV, HSV-1 and HSV-2; HHV-6, HHV-7, HHV-8; HCV, HBV (including HBsAg, anti-HBcAg, IgG and IgM), HIV, West Nile virus, rabies, HTLV-1
- Parasites, depending on geographic region: malaria, babesiosis, toxoplasmosis, Chagas disease, syphilis
- Fungi in appropriate regions: *Coccidioides, Histoplasma*
- Tuberculosis (depending on geographic region)
- Chest radiograph
- Electrocardiogram
- Biopsy if there is concern for chronic kidney disease

Operating Room Evaluation
- Intra-abdominal examination to detect occult malignant diseases
- Macroscopic appearance of kidneys

Box 102-4 Deceased donor evaluation checklist. *CMV,* Cytomegalovirus; *EBV,* Epstein-Barr virus; *HBcAg,* hepatitis B core antigen; *HBsAg,* hepatitis B surface antigen; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HHV,* human herpesvirus; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *HTLV,* human T cell lymphotropic virus; *TB,* tuberculosis. *Choice of virological investigations according to local risks.

Deceased Donor Management Before Transplantation

In the brain-dead donor, maintenance of adequate blood pressure and oxygenation are important to prevent warm ischemic renal injury. The use of pressor agents, volume resuscitation, and other conditioning strategies is complex and has been the subject of several guideline documents (see the Intensive Care Society website, www.ics.ac.uk). In this category of donor, the kidneys are generally not subject to significant warm ischemia at the time of organ retrieval unless the donor suffers prolonged hemodynamic compromise.

In DCD, once death is certified and deemed irreversible, either rapid surgical exposure of the great vessels with cooling of the organs followed by prompt retrieval is required, or, alternatively, the kidneys are cooled *in situ* by insertion of perfusion catheters through the femoral vessels (see also Chapter 103). Surgical retrieval can then take place after a period of delay to variably allow one or more of the following: family counseling, donor assessment, or relocation from one hospital area to another (e.g., from the intensive care unit or emergency department to the operating theater). DCD is inevitably associated with warm ischemic renal injury. This is responsible for the higher rate of delayed graft function that is seen in this group. The need for dialysis support after transplantation is approximately 50% but varies from 30% to 90%, depending on the Maastricht category of donor.[29]

Living Donors

Live kidney donation is currently accepted in most countries on the basis of the demand for deceased donor organs—which far outweighs the supply—as well as the apparent very low level of risk to the majority of healthy donors.[37] Added to this are the detrimental effects for the recipient of waiting on dialysis and the excellent, generally superior results obtained through use of living donors.

Living donors may be related, unrelated, altruistic, or part of a donor exchange or list-exchange program. In many countries with well-established transplant programs, half or more of all transplants are now performed with living donors. In Japan, Brazil, and the Middle East, more than 80% of transplants use living donors. The superior outcomes of transplantation from living donors compared with that from deceased donors has supported the development of living donor paired exchange and living donor–deceased donor exchange.[38] In the first instance, living donors who are incompatible with their intended recipients are exchanged between recipients. In

the other instance, the donor donates to the wait list in exchange for the intended recipient's receiving priority on the list.[39]

In some countries, either a state-organized or a free-market system results in the purchase of living donor kidneys; this is a highly controversial area.[40] The Declaration of Istanbul on organ trafficking and transplant tourism and the World Health Organization both condemn the exploitation of living donors who are thought to be vulnerable (illiterate, impoverished, undocumented immigrants, prisoners, and political or economic refugees).[41]

In recent times, many units have extended their selection of donors to include patients who are mildly hypertensive, overweight, or hyperlipidemic or who have other abnormalities (such as isolated microhematuria or previous stone disease).[42] Whereas donation appears to be safe in the short to medium term for most of these patients, adequate studies have not been performed to assess the longer-term medical or psychological effects.

Mortality and Morbidity

Mortality related to living donation is a catastrophic and unexpected event. Registry data and institutional surveys suggest the perioperative risk of donor death is approximately 3 in 10,000.[43] Donor mortality and major complications appear equivalent with laparoscopic and open donor nephrectomy. In open surgery, the risks are related to perioperative complications, including pulmonary emboli, pneumonia, and ischemic events. With laparoscopic surgery, complications are largely a result of catastrophic intraoperative events or postoperative bleeding related to securing of the vascular pedicle.[43,44]

In the longer term, survival of donors appears to be similar to that of controls in the general population (Fig. 102-2).

Numerous series report early operative complications after laparoscopic and open donor nephrectomy with rates of 3% to 38%.43 These reports variably include events such as bleeding, wound infection, urinary retention, pneumonia, asymptomatic and symptomatic pneumothorax, ileus, and need for transfusion, among other things. This enormous variability relates to both definition of complication and accuracy of reporting.

Case series report that physical and psychological function in living donors is higher than the community norm. Physical issues reported by donors after donation frequently include a temporary decrease from baseline in energy; some note a longer time to full recovery than anticipated and incision pain (after open nephrectomy) that lasts longer than expected. Psychological factors usually include an improved relationship with the recipient, an improved self-image, and frequently a positive effect on the donor's life. Longer-term psychological morbidity appears minimal; however, some series have reported an association with anxiety, depression, or other psychological issues in a small proportion of the patients.[45,46] Even though most donors have a positive experience, a small number for a variety of reasons do regret the decision to donate (0% to 5%). Psychological evaluation before donation is therefore extremely important, as is the need to provide support and counseling after donation. This issue is particularly important when the transplant does not go as well as anticipated.

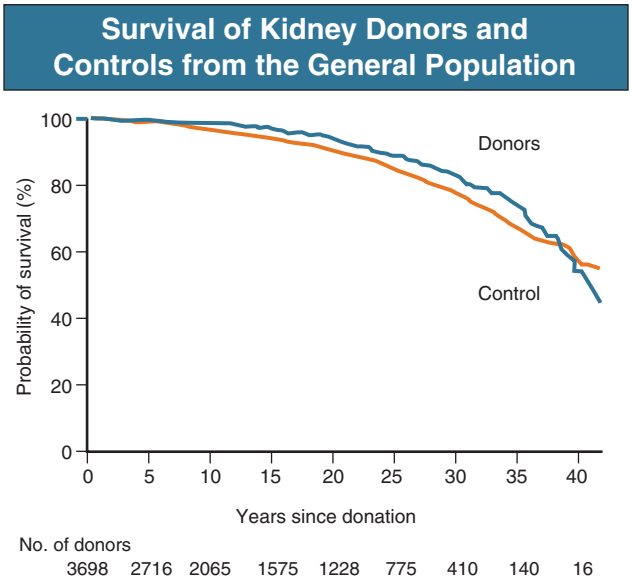

Figure 102-2 Survival of living kidney donors. The survival of living related donors is similar to the expected survival derived from the general population. Error bars at 5-year intervals indicate 95% confidence intervals for the probability of survival among kidney donors. *(Modified with permission from reference 37.)*

Evaluation of the Living Donor

Several groups have developed guidelines for the evaluation of the living donor, including the Amsterdam forum[47] and consensus guidelines published by several U.S. transplant centers.[48] An outline of the usual donor evaluation is shown in Boxes 102-5 and 102-6. It includes a thorough history and examination, blood and urine screening tests, chest radiography, electrocardiography, age- and family history–appropriate cardiac stress test, and radiographic

Living Donor Evaluation Checklist: History and Examination

History
- Hypertension
- Diabetes (including gestational)
- Infections
- Cancer (including skin lesions)
- Vascular disease
- Renal calculi
- Gout
- Urinary tract
- Family history
- Medications (including NSAIDs, herbs)
- Smoking
- Illicit and intravenous drug use
- Sexual history
- Vocation, sport interests
- Level of physical activity, exercise
- Psychiatric history, psychological factors
- Willingness to donate
- Relationship with recipient

Examination
- Blood pressure
- Weight and height, BMI
- Joints, skin
- Cancer (including skin lesions, breast)
- Lymph nodes
- Vascular disease
- Heart and lungs
- Abdomen

Box 102-5 Living donor evaluation checklist: history and examination. *NSAIDs,* Nonsteroidal anti-inflammatory drugs; *BMI,* body mass index.

Living Donor Evaluation Checklist: Investigations

Laboratory and Radiologic Investigations

- Urinalysis (blood, protein)
- Urine microscopy and culture (blood, organisms)
- Serum electrolytes, urea, and creatinine
- Liver function tests
- Full blood examination
- Fasting blood glucose and/or oral glucose tolerance test
- Fasting lipids
- 24-hour urine, creatinine clearance or GFR measurement by iothalamate, Cr-EDTA, DTPA clearance, 24-hour urine protein, or protein excretion by other methods (e.g., protein-creatinine ratio)
- Serum uric acid, calcium, phosphate
- Viral screening: HBV, HCV, HIV, CMV, EBV serology
- Syphilis screening (RPR)
- TB screening (PPD)
- Electrocardiogram
- Chest radiograph
- Females: Pap smear, mammography (according to age and family history)
- Males: prostate-specific antigen (according to age and family history)
- Additional cardiac investigations (where indicated by age, history, risk factors)
- Stress test
- Echocardiography
- Ambulatory blood pressure

Renal Imaging (According to Local Expertise)

- Computed tomographic angiography
- Magnetic resonance imaging angiography
- Catheter angiography

Box 102-6 Living donor evaluation checklist: investigations. *CMV,* Cytomegalovirus; *Cr-EDTA,* chromium-labeled ethylenediaminetetraacetic acid; *DTPA,* diethylenetriaminepentaacetic acid; *EBV,* Epstein-Barr virus; *GFR,* glomerular filtration rate; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HIV,* human immunodeficiency virus; *PPD,* purified protein derivative test; *RPR,* rapid plasmin reagent; *TB,* tuberculosis.

Acceptable GFR in Living Donors by Age

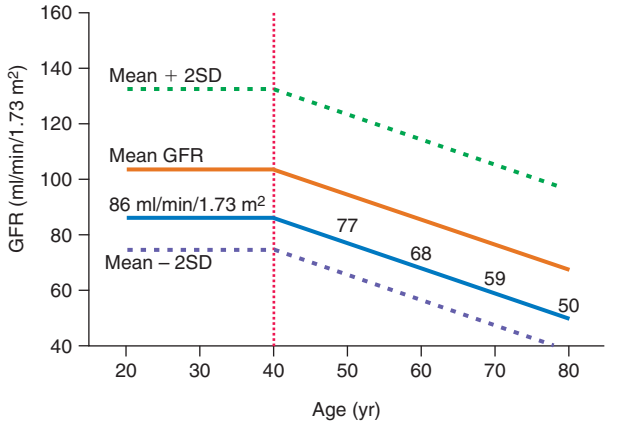

Figure 102-3 Acceptable glomerular filtration rate *(GFR)* in living donors by age. Diagram explaining the minimum acceptable age-associated GFR in living donor candidates. The *solid orange line* shows the variation with age of mean GFR. The *outer dashed lines* show the +2 and –2 population standard deviation (SD) limits. GFR is constant up to the age of 40 years and then declines at the rate of 9 ml/min/1.73 m^2 per decade. The reference plot is based on an analysis of data for 428 living renal transplant donors who had chromium 51–labeled ethylenediaminetetraacetic acid (^{51}Cr- EDTA) GFR measurements. The *solid blue line* shows the acceptable lowest GFR for young adults of 86 ml/min/1.73 m^2, declining to 50 ml/min/1.73 m^2 at age 80 years. For transplant donors with preoperative GFR values above the solid blue line, the GFR of the remaining kidney will still be above 37.5 ml/min/1.73 m^2 at age 80 years. *(Modified with permission from the revised British Transplantation Society/Renal Association U.K. guidelines for living donor kidney transplantation, available at www.bts.org.uk/.)*

assessment of the kidneys and vessels. An assessment of the anatomy may be achieved by computed tomographic angiography or magnetic resonance angiography, depending on the particular center. Formal renal arteriography, although informative, is no longer necessary, given the anatomic detail obtainable noninvasively with modern radiologic techniques.

Assessment of Renal Function

Most centers use a glomerular filtration rate (GFR) of 80 ml/min/1.73 m^2 as the lower limit for donors. It is accepted that this is an overgeneralization, potentially representing too low a limit for the younger donor (e.g., younger than 40 years) and too high a limit for the older donor (e.g., older than 60 to 65 years). For this reason, an alternative approach is to consider the age-specific GFR and to accept donors only if they fall within the average for this figure. This method has been recommended by the British Transplantation Society (guidelines available at www.bts.org.uk) and is presented in Figure 102-3. An alternative approach uses the life expectancy of the donor.[49] By use of these calculations, a 30-year-old donor would require a GFR of 123 ml/min/1.73 m^2; the required GFR for a 70-year-old would be approximately 68 ml/min/1.73 m^2.

Hypertension and Proteinuria in the Living Donor

Donation may be acceptable for some hypertensive individuals if blood pressure is well controlled, GFR is as expected for donation and age, and there are no features of end-organ involvement from hypertension.[47,48] The evaluation for hypertension should include blood pressure measurements on three separate occasions. Borderline elevated levels should be further evaluated with ambulatory blood pressure monitoring. If elevated blood pressure is detected and the prospective donor is still under consideration, echocardiography (looking for left ventricular hypertrophy), ophthalmologic evaluation (looking for hypertensive retinal changes), and assessment for microalbuminuria (suggesting hypertensive renal damage) should be undertaken. The prospective donor should be excluded if any of these features are present. Guidelines typically exclude from donation those with urine protein higher than 300 mg/24 h (with or without hypertension). It is our view that the presence of microalbuminuria (with or without hypertension) should also lead to exclusion, given the likely underlying renal and systemic microvascular pathology this signifies, particularly in those with other cardiovascular risk factors.

Obesity and Abnormal Glucose Tolerance in the Living Donor

Although many centers accept obese living donors, several issues need to be addressed. These include the impact of obesity on perioperative complications, future renal function, and cardiovascular health. In one study, obese (BMI >30 kg/m^2) patients had an

increased rate of proteinuria and renal impairment 10 to 20 years after nephrectomy.[50] Obese individuals may therefore be more prone to development of renal disease after donation, but this issue has not been carefully studied.

Future risk of diabetes is another important consideration. In addition to close assessment of those who are overweight, prospective donors with an abnormal fasting glucose concentration, a history of gestational diabetes, or a first-degree relative with diabetes should be evaluated with an oral glucose tolerance test. An abnormal glucose tolerance test result is a contraindication to donation. Patients often lose weight and otherwise change their lifestyle (exercise, diet), leading to an improvement in their results and eventual acceptance as donors. It is important that these lifestyle and risk modifications be sustained after donation occurs.

Renal Abnormalities in the Living Donor

As well as factors identified in the history (e.g., previous calculi, urinary tract infections, prostatic disease), a variety of previously unidentified renal abnormalities can be encountered in prospective donors during their assessment. These include microhematuria, renal scarring (e.g., polar distortion suggesting reflux nephropathy), renovascular abnormalities, and renal masses and cysts.

Isolated hematuria in a prospective donor necessitates consideration of thin basement membrane nephropathy, Alport syndrome (carrier status in women may cause minor or moderate abnormalities), and IgA nephropathy as well as urinary tract infection, malignant disease, and nephrolithiasis. Microhematuria is a relatively common problem, with persistent microhematuria evident in approximately 3% of the general population.[51] Among the possible disorders, IgA nephropathy is generally a contraindication to live donation, whereas thin basement membrane nephropathy may not necessarily be so.[52] The implications of isolated mesangial IgA without other manifestations of glomerulonephritis require further study, and donation should be decided in the context of family history, absolute renal function, presence of interstitial disease, and age. If persistent isolated asymptomatic microhematuria is detected during living donor evaluation, a workup should include cystoscopy and urinary cytology if the hematuria is not clearly glomerular in origin. A renal biopsy should be considered when there is glomerular hematuria or the possibility of familial disease (e.g., Alport syndrome, IgA nephropathy) because this aids the decision-making process by clarifying the prospective donor's future risk of progressive renal disease.[53]

Those with a history of bilateral or recurrent stones and those with systemic conditions associated with recurrent stone disease should not donate. An asymptomatic potential donor with a current single stone is suitable if the donor does not have a high risk of recurrence, if the stone is smaller than 1.5 cm, and especially if the stone is potentially removable during transplantation.[47] The evaluation of an asymptomatic donor with a single prior episode of nephrolithiasis should include evaluation of serum calcium, creatinine, albumin, and parathyroid hormone levels; spot urine for cystine; urinalysis and urine culture; spiral computed tomographic scan; chemical analysis of the stone, if available; and 24-hour urine measurement of oxalate, uric acid, and creatinine.

Atherosclerotic renal vascular disease is a relative contraindication to living donation. If it is discovered, the donor should be normotensive, have normal renal function, and have only unilateral disease.[54] Careful evaluation for coronary heart disease and peripheral vascular disease should be undertaken, given the significant association of renovascular disease with atherosclerosis elsewhere. Fibromuscular dysplasia is found in 2% to 4% of prospective donors. Donors with severe and diffuse disease should not be accepted for donation. The age of the prospective donor should also be considered, with the outcome in donors older than 50 years more predictable and benign than in younger donors.[55]

Malignant Disease

A past history of certain malignant neoplasms is considered a contraindication to live kidney donation. These include melanoma, testicular cancer, renal cell carcinoma, bronchial and breast cancer, choriocarcinoma, hematologic malignant neoplasm, and multiple myeloma.[47] A history of malignant disease may be acceptable for donation if prior treatment of the malignant neoplasm does not decrease renal reserve or place the donor at increased risk of renal disease and prior treatment of malignant disease does not increase the operative risk of nephrectomy. A history of malignant disease may be acceptable if the specific cancer is curable and transmission of the cancer can reasonably be excluded; consultation with an oncologist may be required. Examples of cancers considered to have low risk for transmission include early prostatic and early low-grade bladder and cervical malignancies. Consent to receive a renal transplant must include a discussion with the donor and the recipient regarding the fact that risk of transmission of malignant disease cannot be completely excluded.

Cardiovascular and Pulmonary Disease

In prospective donors, the cardiac assessment should be based on the history, risk factors, examination, and electrocardiographic findings. An exercise or pharmacologic stress test and echocardiography may be warranted in certain circumstances. Individuals with myocardial dysfunction or coronary ischemia are at increased anesthetic risk and should generally not donate. Pulmonary contraindications to donation include chronic lung diseases that significantly increase the anesthetic risk. If indicated by history and examination, pulmonary function testing, echocardiography, or sleep studies should be performed. In all cases, donors should cease smoking for at least 8 to 12 weeks before surgery to minimize the risk of postoperative pneumonia.

COMPATIBILITY AND IMMUNOLOGIC CONSIDERATIONS

Blood Group Compatibility

Traditionally, transplantation across incompatible blood groups has been avoided because of the risk of hyperacute rejection mediated by preformed anti-A or anti-B antibodies to the carbohydrate blood group antigens, expressed by endothelial cells as well as by red blood cells. In recent years, ABO-incompatible transplantation has become more widespread, largely on the basis of excellent outcomes described initially by Japanese centers.[56] "Desensitizing" the recipient can avert hyperacute rejection. This involves removal of blood group antibodies by plasma exchange or immunoadsorption to achieve target titers. Preemptive splenectomy or rituximab administration (anti-CD20 monoclonal antibody) is often also used; however, the need for these measures is not clear.[57] Rejection is predicted by high initial antibody titers and high rebound titers early after transplantation.[58] A further period of plasma exchange or immunoadsorption after transplantation is commonly instituted, whereas other centers determine the need for these therapies preemptively based on post-transplantation antibody titers. With use of this protocol, patient and graft survival appears to be equivalent to that of blood group–compatible transplantation for the short to medium term (up to 9 years).[56] Longer-term results are awaited. A comprehensive overview and summary of current approaches relating to

antibody-incompatible transplants is available at the British Transplantation Society website, www.bts.org.uk.

Human Leukocyte Antigen Compatibility

"Tissue typing" of recipient and donor determines their HLA match. HLA antigens are coded on chromosome 6, with half (one haplotype) inherited from each parent. The major histocompatibility class I HLA-A and HLA-B and class II HLA-DR antigens are routinely determined, because rejection responses are thought to most commonly stem from mismatches at these alleles. There is an increasing awareness of the importance of immune responses to other HLA antigens, and many centers now look for the presence of antibodies to HLA-C, HLA-DQ, and HLA-DP. A six-antigen (HLA-A, HLA-B, and HLA-DR) match confers a graft survival advantage compared with 0 antigen matches for both cadaveric and living donor transplantation of 10% at 10 years.[59,60] In addition to determination of the HLA compatibility, crossmatching and screening for anti-HLA antibodies are performed to assess the risk of rejection.

Assessing Human Leukocyte Antigen Sensitization

The principle of screening for antibodies against HLA antigens using panel reactivity is shown in Figure 102-4. IgG antibodies against class I (HLA-A and HLA-B) antigens are highly associated with acute rejection and are a contraindication to transplantation. IgM antibodies against HLA antigens may also predict rejection if they are present in current but not past sera; however, they may also be falsely positive. Prior treatment of sera with dithiothreitol can remove IgM antibodies and aid in the interpretation of the test (Table 102-4). Autoantibodies (such as may occur in lupus) may also give false-positive results and can be determined by prior absorption with autologous lymphocytes.

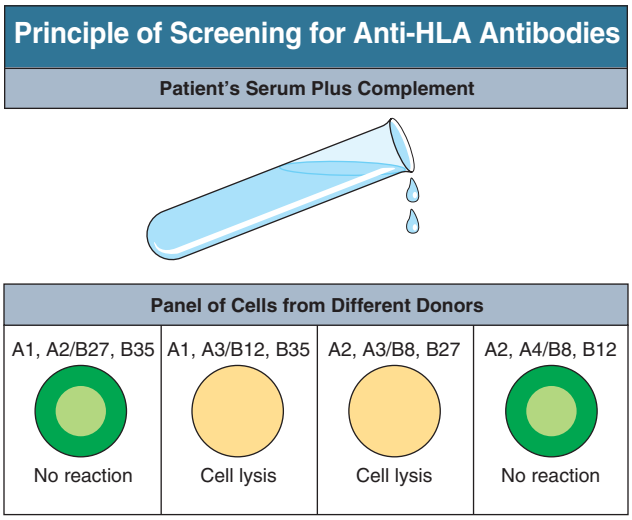

Figure 102-4 Principle of screening for anti–human leukocyte antigen (HLA) antibodies. The patient's serum is tested with a panel of cells of known HLA types. The most common HLA antigens are represented in such panels. In this example, the A3 antigen is the only antigen present in the two lysed cell populations and absent from the nonlysed samples. Therefore the patient's serum contains anti-HLA A3 antibodies.

Sensitization to HLA antigens generally occurs through blood transfusion, pregnancy, or prior transplantation. Presence in the recipient of antibodies to donor-specific HLA antigens can result in hyperacute rejection. Crossmatching of donor lymphocytes with recipient serum allows screening for this possibility. Terasaki and coworkers pioneered the complement-dependent cytotoxicity (CDC) crossmatch.[61] This assay determines the presence of antibodies thought to be of clinical significance by mixing donor T or B lymphocytes with recipient serum in the presence of complement. The sensitivity of the assay can be augmented by the addition of anti–human globulin. Presence of a positive T cell CDC crossmatch to the donor is highly predictive of hyperacute rejection,[61,62] whereas a B cell CDC crossmatch is more subject to false-positive results but should prompt a search for donor-specific antibodies.[63] A positive T cell crossmatch is an absolute contraindication to transplantation.

The flow crossmatch is more sensitive than the CDC in detecting antibody capable of binding to donor T or B lymphocytes. Binding of antibody from donor serum is detected by flow cytometry after probing with a fluorescein-labeled anti-immunoglobulin antibody. The predictive value of a positive flow crossmatch for rejection is less than that of a CDC crossmatch because of its increased sensitivity, and it does not assess the ability of the antibody to fix complement. In most centers, it is not routinely performed before deceased donor transplants, but it is commonly performed in a living donor transplant workup. A positive flow crossmatch (with a negative CDC crossmatch) is not an absolute contraindication to proceeding; however, it may lead to alteration of the immunosuppressive regimen (e.g., use of a desensitization protocol) to decrease the risk or severity of antibody-mediated rejection.

Determination of the presence of anti-HLA antibodies in the recipient's serum is increasingly used as a means of predicting rejection. This virtual crossmatch compares the specificity of the antibodies identified with the prospective donor's HLA typing. Donor-specific anti-HLA antibodies are correlated with worse graft survival even in the setting of a negative crossmatch.[64] Antibodies can be detected through panel reactive antibody testing, by enzyme-linked immunosorbent assay, or with more sensitive antigen-coated bead techniques. Beads are coated with a single HLA antigen and are mixed with recipient serum and probed with a fluorescein-labeled

Interpretation of the Crossmatch Test

Antibody to MHC Class	Crossmatch (Normal Procedure)		Crossmatch (Dithiothreitol)		Risk of Antibody-Mediated Graft Damage
	T Cells	B Cells	T Cells	B Cells	
IgG against class I	+	+	+	+	Yes
IgM against class I	+	+	–	–	Yes; IgM class I antibodies may be harmless if present in old sera only but not in the current serum
IgG against class II	–	+	–	+	Yes
IgM against class II	–	+	–	–	Unknown
IgM autoantibodies	+	+	–	–	No

Table 102-4 Interpretation of the crossmatch test. *MHC,* Major histocompatibility complex.

anti-immunoglobulin antibody. Beads that bind antibody are therefore identified by fluorescence. The decision on whether to proceed with transplantation in the context of this information is complex. Recommendations for detection and characterization of clinically relevant antibodies in solid organ transplantation are summarized by the British Society of Histocompatibility and British Transplantation Society and are available at www.bts.org.uk. A more recent set of guidelines was also published after a Consensus Conference on Antibodies in Transplantation, held in 2012.[66]

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CHAPTER 103

Kidney Transplantation Surgery

Adam D. Barlow and Michael L. Nicholson

SOURCES OF KIDNEYS FOR TRANSPLANTATION

The usual and most frequent source of kidneys for transplantation has been donation after brain death (DBD), formerly known as donation from a heart-beating cadaveric donor. The increasing worldwide discrepancy between the availability of and the need for renal allografts[1] has led to the increasing use of alternative sources of organs, including donation after cardiac death (DCD) donors (previously known as non–heart-beating donors) and living donors. The evaluation and selection of donors are discussed in Chapter 102. Here we discuss surgical aspects of retrieval and transplantation of kidneys.

DONATION BEFORE CARDIAC DEATH DONORS

The potential DBD donor is maintained by artificial ventilation in a critical care setting until death has been diagnosed by brainstem death criteria,[2] the consent of the next of kin for donation has been given, and the necessary legal and institutional approvals have been obtained.

In the operating room the initial step is cannulation of the aorta and inferior vena cava while the heart is still beating. This allows perfusion of the organs with cold preservative solution immediately before cardiac arrest, minimizing warm ischemia. The priorities of the organ retrieval team are influenced by the range of organs being donated. Heart, lung, and liver retrieval take priority over kidney retrieval, which may significantly lengthen the ischemic time. The kidneys are removed *en bloc,* and typically the artery is retrieved with a cuff of aorta (Carrel patch), with the maximum achievable length of renal vein, and 10 to 15 cm of ureter. The length of the right renal vein may be maximized by including a portion of inferior vena cava in continuity. Care is taken to avoid damage to polar and other accessory arteries, especially the lower pole artery, which may supply the ureter; stripping of adventitial tissue from the ureter must also be avoided, because this may also compromise its blood supply.

The kidneys are flushed with ice cold preservation fluid until the effluent is clear and then are stored for transport in crushed ice or on a perfusion machine (see the discussion of renal preservation).

DONATION AFTER CARDIAC DEATH DONORS

Before consensus was reached regarding the definition of brainstem death, DCD donors were the main source of transplant organs. These donors were intensive care unit based and had suffered head injuries or cerebrovascular accidents deemed irrecoverable, but organ retrieval could proceed only after cardiorespiratory death. This changed with the introduction of brainstem death legislation, but the use of DCD kidneys has recently increased again in response to the shortage of suitable organs for transplantation. An international consensus has defined categories of DCD donors[3] to facilitate legal and ethical discussion and to highlight possible differences in organ viability (see Box 102-3). DCD kidneys sustain a period of warm ischemia, the period between cardiac arrest and the time that *in situ* cold perfusion is started. The duration of ischemia correlates with rates of primary nonfunction, delayed graft function, acute rejection, allograft, and patient survival. The main requirement of organ procurement from DCD donors is therefore to achieve rapid *in situ* perfusion of the kidneys to limit warm ischemia. This requires an emergency response team of surgeons and transplant coordinators, with considerable on-call and logistic commitments.

Donation after cardiac death donors may be either uncontrolled (Maastricht categories I and II) or controlled (Maastricht categories III through V). In controlled donors, cardiac arrest is expected, and it is therefore possible to reduce the warm ischemia time to only a few minutes because the surgical retrieval team will be on standby. Unexpected donor cardiac arrest may result in prolonged warm ischemia times. The duration of reversible warm ischemia time that the human kidney can sustain is unknown, but DCD kidneys with warm ischemia exceeding 60 minutes are considered by many to be of marginal suitability.

Donation After Cardiac Death Protocol

Centers involved with DCD donation should adhere to the Maastricht protocol,[4] which includes the following principles:

- Approval by the local medical ethics committee
- Diagnosis of death by doctors who are independent of the transplantation team
- 10-minute rule (after declaration of cardiac death, the body is left untouched for a period of 10 minutes before intervention)
- Rapid *in situ* cooling with use of a catheter inserted into the aorta
- Organ retrieval by standard surgical techniques

Uncontrolled DCD Donors

After a period of unsuccessful resuscitation, confirmation of cardiac death, and observation of the 10-minute rule, cardiac massage and ventilation with 100% oxygen are recommenced in an attempt to deliver oxygenated blood to the kidneys. A mechanical resuscitation device may be used. *In situ* renal cooling is effected by placing a double-balloon, triple-lumen perfusion catheter into the aorta via a femoral artery cut-down (Fig. 103-1), with instillation of preservation solution. Alternatively, the donor can be moved to an operating room as soon as death has occurred, and the aortic perfusion catheter is placed directly at laparotomy rather than via a femoral artery cut-down.

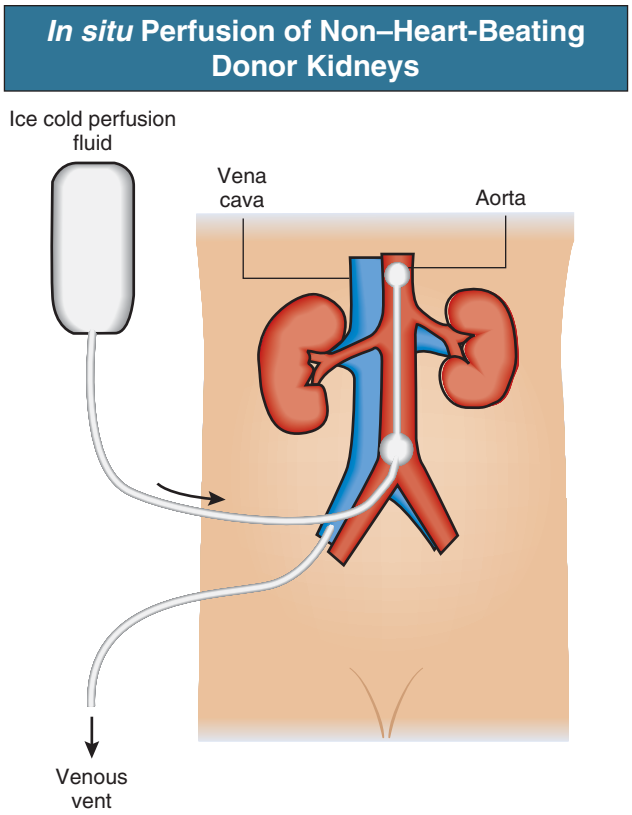

Figure 103-1 Technique for *in situ* perfusion of donation after cardiac death kidneys. A double-lumen, double-balloon arterial catheter is introduced through the femoral artery and the lower balloon inflated at the aortic bifurcation and the upper balloon above the renal arteries. Ice-cold perfusion fluid is introduced and vented through the femoral vein until the effluent becomes clear.

Controlled DCD Donors

For controlled DCD donors, the transplantation team awaits cardiac arrest; after confirmation of death, the 10-minute rule is observed, and then the perfusion catheter is inserted via the femoral artery. Alternatively, the patient can be taken to the operating room before cardiac death if the next of kin gives consent.

LIVING KIDNEY DONORS

In the United States in 2011, 32% of renal transplants were from living donors,[5] compared with 40% in the United Kingdom.[6] After a rapid increase in living donor transplantation at the beginning of this decade, rates have become more static. Superior recipient post-transplantation outcome compared with use of kidneys from deceased donors,[7] the potential for preemptive transplantation before dialysis, and the ability to plan the procedure (allowing optimization of recipient condition) are major advantages and justify continued efforts to expand use of living donors. The medical evaluation of the living donor is discussed in Chapter 102 (see Boxes 102-5 and 102-6).

Preoperative Imaging

Preoperative imaging of living donors confirms the presence of two functioning kidneys, indicates pathology that would preclude donation, and provides anatomic information necessary for planning the procedure. Imaging assumes paramount importance before minimal access donor nephrectomy because of the reduced operative exposure and particular difficulties in the identification of complex renal vein tributaries. The location, size, and number of renal veins and tributaries needs to be accurately described preoperatively. Angiography combined with excretion urography is now obsolete. For preoperative description of the main renal artery and vein anatomy, magnetic resonance angiography and computed tomographic angiography are comparable,[8] but computed tomographic angiography is more sensitive and specific for complex vascular anatomy and provides excellent correlation between imaging and surgical findings[9] (Fig. 103-2).

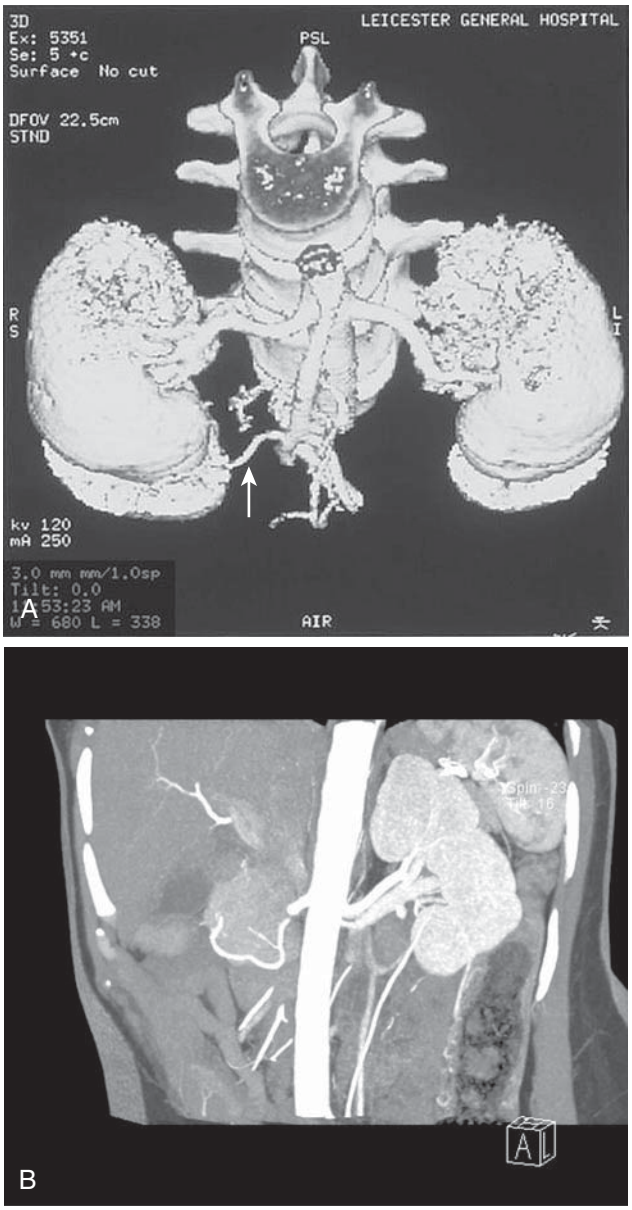

Figure 103-2 Living donor preoperative computed tomographic angiogram. A, Three-dimensional reconstruction of arterial supply. Note the lower pole artery to the right kidney *(arrow),* which may supply the ureter as well as the lower pole parenchyma. **B,** Conventional image showing single artery and vein to the left kidney.

Minimal Access (Laparoscopic) Donor Nephrectomy

Living donor nephrectomy has traditionally been performed through an open incision, necessitating a prolonged period of recovery. This

Figure 103-3 Flank wound from open nephrectomy.

Donor Benefits of Minimally Invasive Donor Nephrectomy
• Shorter incisions • Less pain • Shorter hospital stay • Shorter recovery • Better cosmetic appearance

Box 103-1 Donor benefits of minimally invasive donor nephrectomy.

and the cosmetic implications of a large flank wound may discourage potential donors (Fig. 103-3). To reduce such disincentives, there has been a move toward minimally invasive donor nephrectomy, first performed as a transperitoneal laparoscopic procedure (laparoscopic donor nephrectomy [LapDN]).[10] LapDN is associated with decreased severity and duration of postoperative pain, shorter in-patient stay, quicker return to work and normal activities, and improved cosmetic result when compared with open donor nephrectomy[11] (Box 103-1). Furthermore, the overall societal cost of LapDN is lower,[12] and recipient quality-of-life scores are higher.[13] The procedure is, however, technically demanding, and there is potential for damage to the renal parenchyma, vessels, and ureter during dissection. It takes longer than open nephrectomy and exposes the allograft to a longer period of warm ischemia.[11]

Nevertheless, retrospective data suggest that minimal access donor nephrectomy not only offers postoperative advantages to the donor, but also increases the number of transplants performed by reducing donor disincentives; estimates range from a 25% to a 100%[14] increase in transplantation activity. The widespread introduction of LapDN at the beginning of this decade saw an initial dramatic increase in the number of live kidney donors. However, rates have been static in both the United States and the United Kingdom over the last 5 years, suggesting that we may have seen the maximum benefits of this effect. Three minimal access approaches have been described: transperitoneal, extraperitoneal, and hand-assisted living donor nephrectomy.

Transperitoneal Laparoscopic Donor Nephrectomy

Pneumoperitoneum is established and four laparoscopic ports are usually required (Fig. 103-4). After laparoscopic dissection a

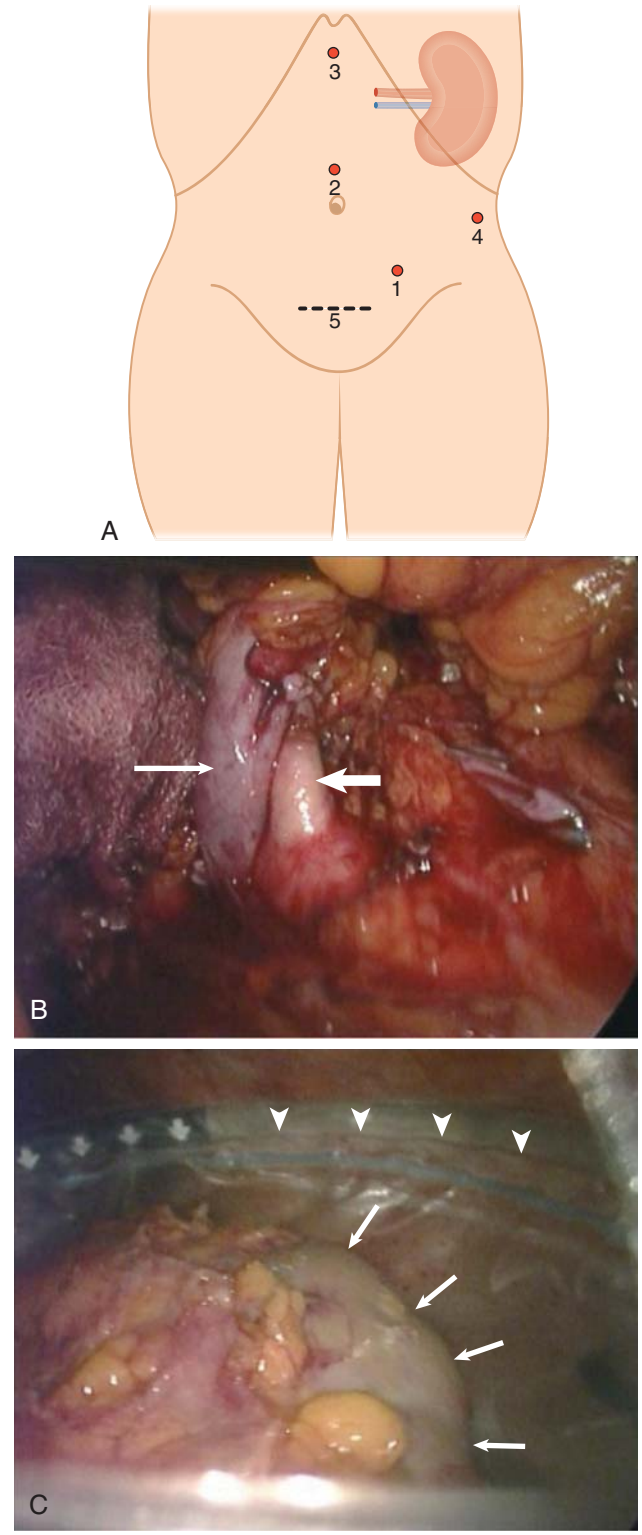

Figure 103-4 Technique for laparoscopic donor nephrectomy. **A,** Positions for four laparoscopic ports (*1* to *4*) and Pfannenstiel incision *(5)* through which the kidney is removed. **B,** Intraoperative view showing left renal artery *(short arrow)* and vein *(long arrow)* prepared for control and division. **C,** Intraoperative view showing the kidney (*arrows* mark lateral margin) placed in the endoscopic retrieval bag *(arrowheads mark the edge of the bag).*

Pfannenstiel incision is made through which the kidney is brought out within an endoscopy retrieval bag after control and division of the artery vein and ureter.

Hand-Assisted Laparoscopic Donor Nephrectomy

The hand-assisted technique allows tactile sense to facilitate dissection, retraction, and exposure. It is said to be easier to learn and can be safely and efficiently performed by surgeons with less laparoscopic experience. The hand-assist device allows the operator's nondominant hand to enter the abdomen through an airtight system.

Retroperitoneoscopic Operative Technique

The retroperitoneal approach avoids breaching the peritoneum, displays the renal anatomy in a very different manner, and may be easier for retrieving the full length of the vessels, especially on the right side. The disadvantage is that a more limited operating space is available than with the transperitoneal or hand-assisted laparoscopic techniques.

Contraindications to Minimal Access Donor Nephrectomy

There are no absolute contraindications other than those applying to the open operation. The relative contraindications are dictated by donor factors and the experience of the surgeon. The donor must be fit for anesthesia, including the physiologic stress of pneumoperitoneum. Obesity is a relative contraindication for both open and laparoscopic surgery, and the hand-assisted approach may be better suited in such patients. Previous abdominal surgery is a further relative contraindication because of the potential for adhesions. Multiplicity of renal vessels should not hinder LapDN.

Effect of Pneumoperitoneum

Transient intraoperative oliguria secondary to decreased renal blood flow is a frequent occurrence during laparoscopic procedures. Proposed mechanisms include decreased cardiac output, renal vein compression, ureteral obstruction, renal parenchymal compression, and systemic hormonal effects. Intracranial pressure increases during pneumoperitoneum, with release of vasoconstrictor agents that decrease renal blood flow. Use of a lower pressure reduces the adverse effects of pneumoperitoneum on renal perfusion. In donor nephrectomy, impaired renal blood flow may compromise early allograft function and compound the damaging effects of warm and cold ischemia and operative manipulation of the kidney. Laparoscopically derived donor kidneys have higher serum creatinine up to 1 month post-transplantation compared with open surgery, but thereafter graft function is equivalent.[15] The pioneers of LapDN used high volumes of crystalloid preoperatively and intraoperatively to maintain renal perfusion in the presence of pneumoperitoneum. The authors have seen two episodes of unilateral pulmonary edema in the dependent lung, and we now recommend volume loading the donor with 2 liters of crystalloid the night before surgery and only using replacement fluid during surgery. This protocol has led to no apparent detriment to graft function.

Graft Function and Acute Rejection

There is no consistent evidence that graft function differs among kidneys retrieved by open, laparoscopic, or hand-assisted donor nephrectomy. The exception is that rates of delayed graft function and acute rejection may be higher in pediatric recipients, especially the 0- to 5-year age group.

Pretransplantation ischemia could, in theory, render the donor kidney more immunogenic by inducing major histocompatibility complex (MHC) class II expression. However, despite the longer warm ischemia time, acute rejection rates and severity of rejection are not higher in laparoscopic than in openly retrieved living donor kidneys.

Technical Issues

Ureteral ischemia was more common in early experience of LapDN but can be avoided if care is taken to ensure that sufficient periureteral tissue is taken and that the dissection does not occur too close to the renal pelvis.

Multiple arteries need not be a barrier to successful use of grafts from laparoscopic donors. In open donor nephrectomy, the right kidney is retrieved in 20% to 30% of procedures, whereas LapDN uses the right kidney in less than 10%,[16] reflecting concern over the operative safety of the right-sided laparoscopic operation, principally the difficulties involved in obtaining an adequate length of renal vein. It has been argued that this practice has led to compromise of the principle that the better kidney should remain with the donor.

Postoperative Recovery

After uneventful open nephrectomy, the donor can expect to be discharged from the hospital in 5 to 6 days and is able to return to work after 3 to 6 weeks, although return to work has been shown to be 2 to 3 weeks later in open nephrectomy compared with LapDN.[11] After LapDN the donor usually leaves hospital in 2 to 4 days and can return to work in 3 to 6 weeks.

Choice of Donor Operative Technique

The choice of operative procedure depends on the local expertise of the surgeons. There is accumulating evidence that the laparoscopic operation removes some of the disincentives to donation, and this approach is likely to be adopted widely in the future.

RENAL PRESERVATION

Preservation of deceased donor organs is crucial to allow time for matching, sharing of organs, and preparation of the recipient. Damage from hypothermia and reperfusion must be minimized. There is little standardization of the type of preservation solution used. Marshall's hyperosmolar citrate solution and histidine-tryptophan-ketoglutarate are popular choices in Europe, but University of Wisconsin (UW) solution is more commonly used in the United States because extended preservation times are more often required.

Organs can be preserved by cold storage (kept in crushed ice after flushing with preservation solution) or by machine-driven pulsatile perfusion. The proposed benefits of machine perfusion come from allowing aerobic function through provision of oxygen and substrate and removal of metabolic end products. Although machine perfusion has been used for many years, there is still no consensus about its superiority to cold storage nor about the best perfusion parameters. Recent randomized trials have yielded conflicting results; a U.K. trial of DCD kidneys showed no benefit,[17] whereas a European trial demonstrated reduced delayed graft function in deceased donor transplants after machine perfusion.[18]

A novel approach to kidney preservation, only recently introduced into clinical practice, is *ex vivo* normothermic perfusion. Early results are promising,[19] but the technique needs to be studied in larger clinical trials.

Decisions on the use of a kidney from a marginal donor can be supported by data from machine or normothermic perfusion; high

perfusion pressures are associated with primary nonfunction and delayed graft function.

RENAL TRANSPLANTATION PROCEDURE

The transplanted kidney is placed heterotopically in one or other iliac fossa. The inferior epigastric vessels are ligated, as is the round ligament of the uterus in female patients. Occasionally the inferior epigastric artery may be preserved and used for revascularization of small polar arteries. In male patients the spermatic cord is mobilized and preserved. The peritoneum should not be breached, but instead swept superiorly to reveal the extraperitoneal bed into which the transplanted kidney will be placed. The iliac blood vessels are then mobilized, with care taken to meticulously ligate all the associated lymphatic channels to reduce the risk of post-transplantation lymphatic leak.

Vascular Anastomosis

The renal vein is anastomosed end to side to the external iliac vein. The arterial anastomosis can be performed either end to side to the external iliac artery or end to end to the divided internal iliac artery (Fig. 103-5). The end-to-side anastomosis is technically easier and is the usual method used in cadaveric transplantation, where it is possible to include a Carrel aortic patch with the renal artery.

With living donor kidneys it is not possible to include a Carrel patch, and occasionally a cadaveric kidney may be provided without a useable patch. In these circumstances the options are to anastomose the renal artery end to end to the divided internal iliac artery or end to side to the external iliac artery. Use of an aortic punch to create a circular arteriotomy may facilitate the latter technique. For living donor kidneys most surgeons use the external iliac artery. It is the authors' experience that positioning the kidney is often easier if the internal iliac artery has been used for the anastomosis, but this does risk buttock claudication and increases the risk of erectile dysfunction.

After completion of the vascular anastomoses, the kidney must sit in such a position that the renal vessels are not kinked. The transplanted kidney can be placed laterally in the iliac fossa or may be placed in a subrectus pouch fashioned specifically for the purpose.[20] In the latter case the renal vessels run laterally from the kidney, and this needs to be noted when a post-transplantation biopsy is performed. An operative diagram of the position of the kidney and vessels is therefore an important component of the clinical notes.

If there are multiple renal vessels, the number of anastomoses should be minimized. This can usually be achieved by careful bench surgery before implantation. If there are two or more renal arteries, their aortic patches are joined in such a way that a single arterial anastomosis is required. If necessary, recipient iliac artery or saphenous vein is used to facilitate reconstruction. Occasionally, small polar arteries will be recognized only after a kidney has been retrieved, and it is particularly important to reanastomose lower polar arteries accurately because these may provide all the ureteral blood supply. In the case of double renal veins, the most common course of action is simply to ligate the smaller vein; the larger one is usually sufficient to drain the whole kidney. If there are two equally sized veins, both may need to be anastomosed separately to the external iliac vein.

Urinary Drainage

The traditional method of ureteral anastomosis is the Politano-Leadbetter technique, involving a transvesical ureteroneocystostomy

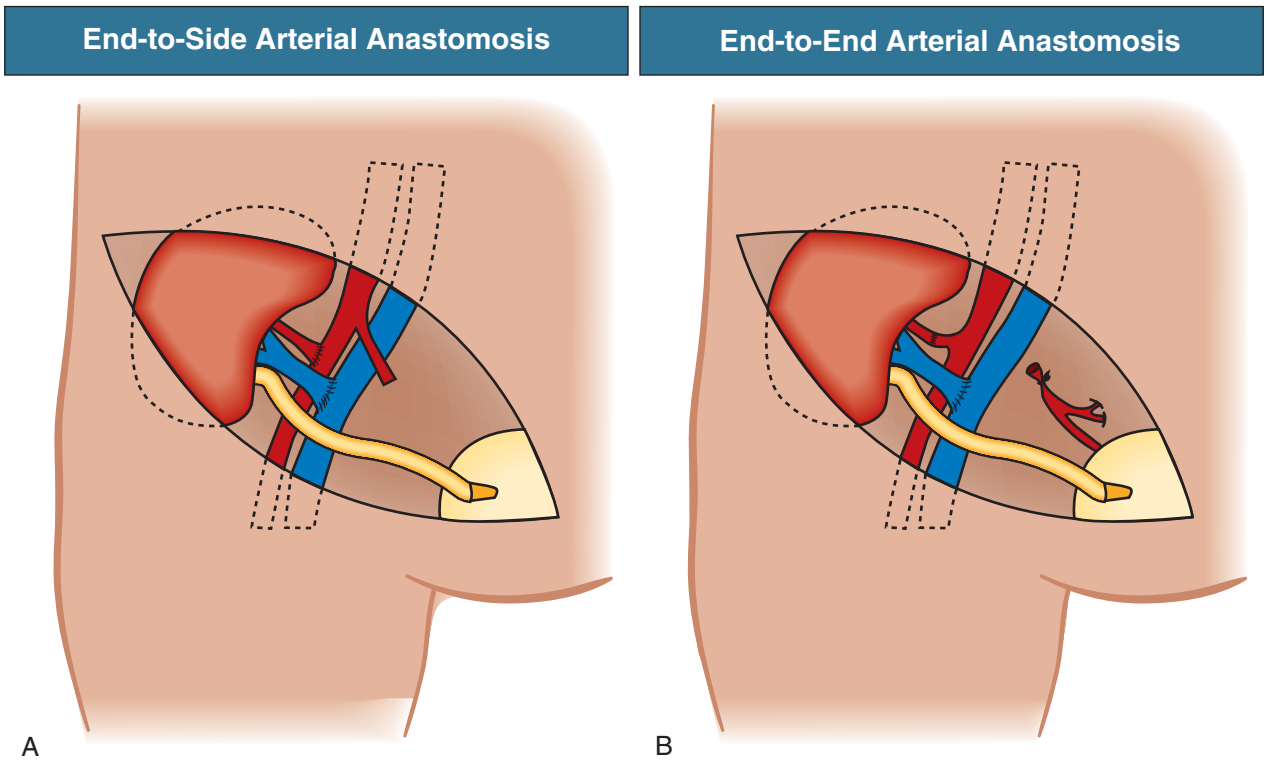

Figure 103-5 Vascular anastomosis techniques for renal transplantation. A, End-to-side anastomosis to the external iliac artery. **B,** End-to-end anastomosis to the divided internal iliac artery, suitable for living donor transplantation in which no aortic patch is available.

with creation of a submucosal antireflux tunnel. The end of the transplanted ureter is drawn through a submucosal tunnel from outside to inside and sutured to the bladder mucosa. The majority of surgeons now prefer the technically simpler extravesical ureteroneocystostomy onlay in which the spatulated end of the ureter is anastomosed to the cystostomy and the divided muscle layer is then resutured over the ureter to create a short antireflux muscle tunnel. The onlay method has the advantage of being possible with only a short length of ureter. The shorter the ureter, the less likely it is that there will be an inadequate blood supply to the distal end, thereby reducing the risks of ischemic ureteral leaks or stenosis. A temporary double-J ureteral stent is usually placed. Stents reduce the impact of small technical errors while the ureter is leaking, and reduce major urologic complications to an incidence of 1.5%.[21] However, they are a potential source of urinary infection, can become encrusted or blocked by debris, and can migrate or fragment. Nevertheless, antibiotic prophylaxis is not justified because it increases the risk of infection with multiresistant organisms. A further danger is the forgotten stent that has not been removed, which should always be considered in patients with unexplained and persistent lower urinary tract symptoms after transplantation. Stents are usually removed 4 to 6 weeks post-transplantation, and this can be performed without general anesthesia with use of a flexible cystoscope.

Alternative Techniques of Urinary Reconstruction

Renal transplantation is quite commonly performed in patients who have abnormal bladders. In many patients it is possible to anastomose the transplanted ureter to the bladder in the hope that the bladder can be rehabilitated, if necessary, with use of post-transplantation intermittent self-catheterization. Nonetheless, some patients require urinary diversion with an ileal conduit. The conduit should be fashioned at least 6 weeks before transplantation, but it may have been present for many years. If so, a contrast study (a conduitogram) should be performed before transplantation to exclude the development of conduit stenosis, although this is rare. The transplanted kidney is best placed in the ipsilateral iliac fossa to avoid tension in the ureter, and it may be preferable to deliberately place the transplanted kidney upside down so that the ureter runs cranially and has a more direct route to the conduit. After revascularization, the peritoneum is opened and the ureter is anastomosed to the conduit over a double-J stent. Excellent long-term results have been achieved with this technique.[22]

Drainage and Wound Closure

Both the transplant bed and the subcutaneous tissues may be drained to prevent the accumulation of serosanguineous fluid or lymph around the transplanted kidney, although many surgeons no longer routinely place drains. The skin is best closed with a subcuticular absorbable suture and then dressed with a clear adhesive dressing so that ultrasound scanning can be performed early without disturbing the wound. For this reason, metal clips are never used for the skin.

Postoperative Course

The recipient is nursed in a general ward with standard precautions and no need for reverse barrier nursing. There is no benefit to continuing prophylactic antibiotics beyond a single dose given at induction of anesthesia. Prophylaxis against thromboembolic disease is in the form of thromboembolic deterrent (TED) stockings and low-molecular-weight heparin is continued until discharge. Oral fluids and diet are commenced as tolerated immediately after surgery. Maintenance immunosuppressive agents are given orally, except in the presence of a prolonged postoperative ileus with high volumes of nasogastric drainage, when they should be administered intravenously. If recovery is straightforward, the bladder catheter and wound drains are usually removed by day 5, and the recipient is fit for discharge after 7 to 10 days to be kept under close outpatient monitoring.

SURGICAL COMPLICATIONS OF RENAL TRANSPLANTATION

There is a small but significant incidence of technical complications, which can be minimized by avoiding damage to the kidneys at the time of the retrieval. Nonetheless, the presence of multiple renal vessels and donor atherosclerotic disease does increase the likelihood of technical problems in the recipient, as do recipient obesity, atherosclerosis, and previous transplantation. Algorithms to aid in the management of complications in the early post-transplant period can be found in Figures 103-6 and 103-7.

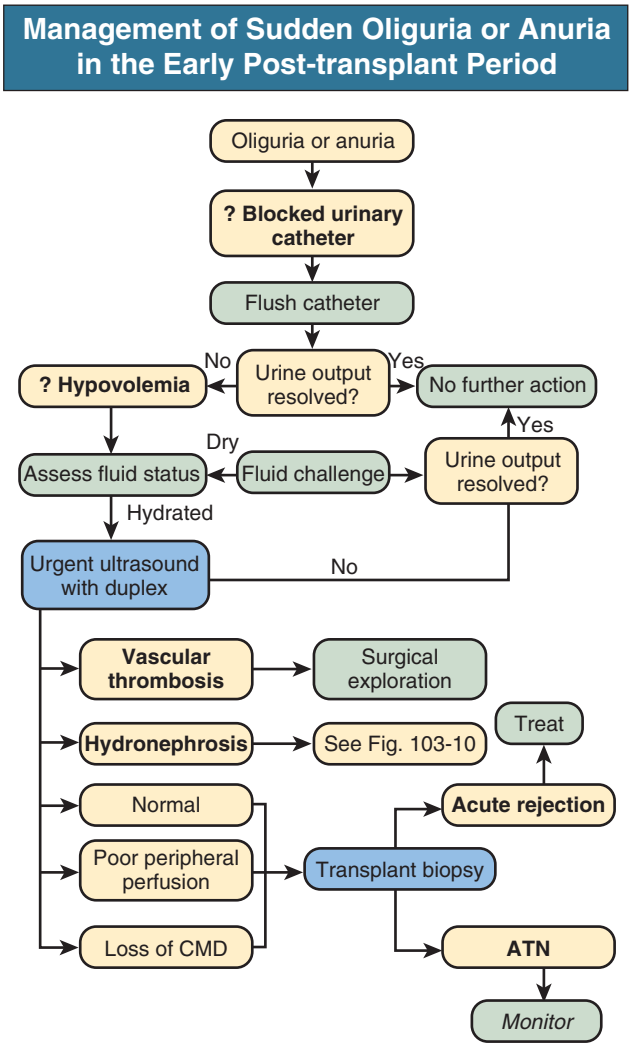

Figure 103-6 Management of sudden oliguria or anuria in the early post-transplant period. *ATN,* Acute tubular necrosis; *CMD,* corticomedullary differentiation.

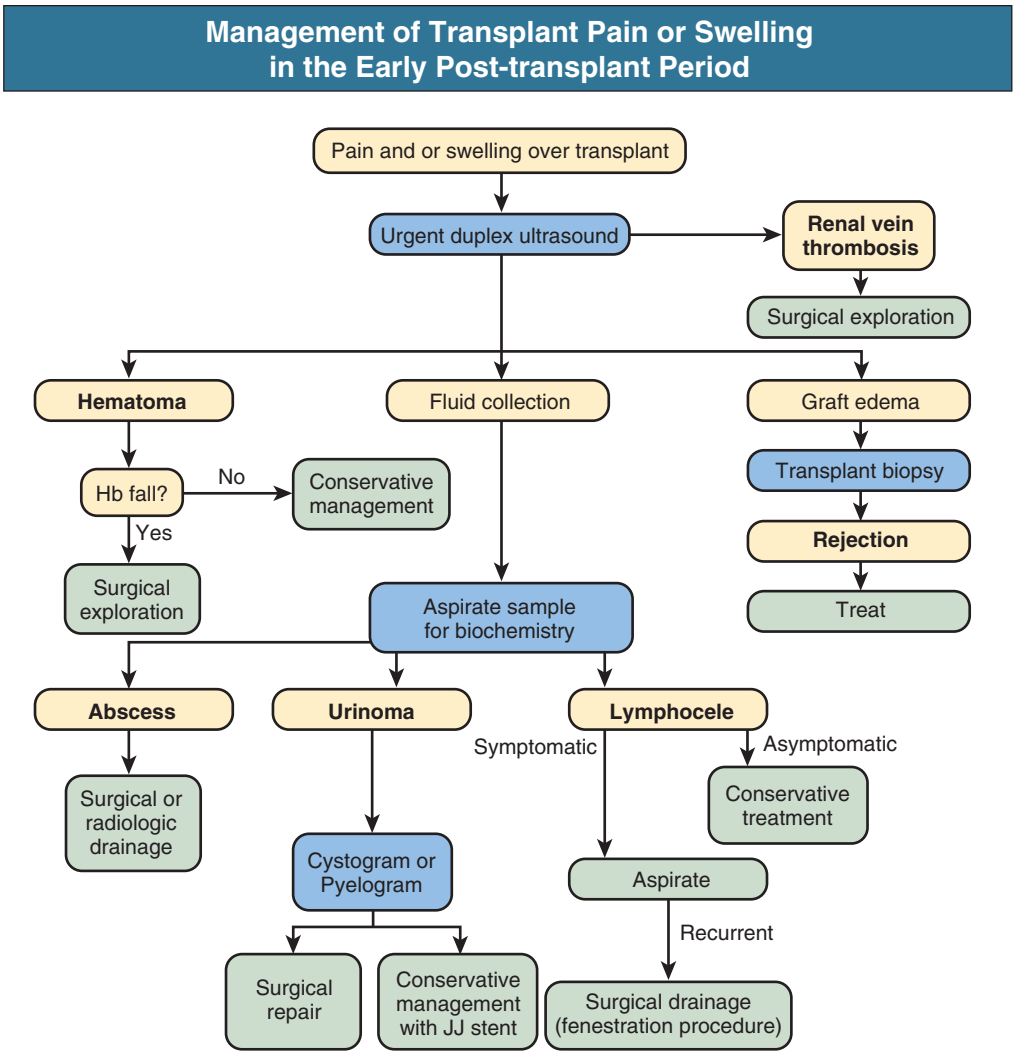

Figure 103-7 Management of transplant pain or swelling in the early post-transplant period. *Hb,* Hemoglobin.

Wound Infection

The use of preoperative prophylactic antibiotics, commonly amoxacillin-clavulanic acid, has reduced the incidence of wound infection to less than 1%. If a wound infection does occur, treatment is with antibiotics, guided by microbiologic wound swabs, and drainage of collections as necessary.

Wound Dehiscence

The risk of wound dehiscence is increased in obese and diabetic patients and those receiving sirolimus. Identification and treatment of any infection are mandatory. Resuturing of the wound is rarely justified. Large areas of dehiscence often benefit from vacuum-assisted closure, but the majority require only frequent dressing.

Vascular Complications

Transplant vascular thrombosis is a feared complication that may cause early and irreversible graft failure. Although there are also significant hemorrhagic risks, routine perioperative prophylaxis should be given with subcutaneous low-molecular-weight heparin, and some units prescribe aspirin for the first few postoperative months.

Bleeding from Vessels in the Renal Hilum

Careful postoperative observation and regular hemoglobin and hematocrit measurements are crucial for the early detection of bleeding. Output from the transplant drains may give an early indication of heavy blood loss. Unsecured small vessels in the renal hilum may not be obvious during surgery, but they may start bleeding postoperatively. This form of blood loss can be slow, persistent, and serious. If the patient's condition allows, urgent imaging may be performed to secure a diagnosis, but the best course of action is usually emergency exploration of the transplant under general anesthesia.

Anastomotic Hemorrhage

Anastomotic hemorrhage is a rare occurrence, usually caused by a technical surgical error, and is more common with multiple arteries and the use of antiplatelet agents.[23,24] Early after transplantation, the patient may report pain over the graft. This symptom should always be taken seriously. There may also be pain in the back or the rectum caused by a tension hematoma in the retroperitoneum or pelvis. Significant hemorrhage will be attended by circulatory collapse, with tachycardia and hypotension. There will be a decrease in the hemoglobin and hematocrit, sometimes to alarmingly low levels. The patient must be returned to the operating room immediately and the transplant reexplored.

Hemorrhage can also occur some weeks after transplantation because of the development of a mycotic aneurysm of the renal artery. In the rare case of a ruptured mycotic aneurysm, an immediate graft nephrectomy is required, but the mortality is high.

Renal Artery Thrombosis

Renal artery thrombosis is a rare event, occurring in less than 1% of transplants. The usual outcome is loss of the kidney. Acute arterial thrombosis may occur intraoperatively or during the first days or weeks post-transplantation. Potential causes include hyperacute rejection or a procoagulant state, but most cases are caused by a technical error during the anastomosis of small or atheromatous vessels.[24] Successful vascular anastomosis requires that the vessels are not under tension and that there is a smooth transition between the two endothelial surfaces; sutures must be placed through all layers of the vessel walls so that an intimal flap is avoided. Vascular adventitia is thrombogenic and must be excluded from the lumen of the anastomosis. The risk of renal artery thrombosis is increased in the presence of atherosclerosis, persistent hypotension, volume depletion (e.g., diarrhea, excessive preoperative dialysis), and prothrombotic states, including diabetes.

Renal arterial thrombosis presents with sudden anuria, the differential diagnoses being a blocked urinary catheter, dehydration, acute tubular necrosis, or a urologic complication. A high index of suspicion is required to make this diagnosis, particularly in the immediate postoperative period. The only worthwhile investigation is an urgent duplex ultrasound scan, but if the diagnosis is seriously entertained, then the only hope of saving the transplant is to reexplore it immediately in the hope that a correctable cause can be found. The reality is that unless the acute arterial thrombosis occurs during surgery, there is little chance of saving the transplanted kidney. Acutely thrombosed grafts must nevertheless be explored and removed to avoid the development of sepsis in a necrotic graft, a potentially fatal complication.

Renal Vein Thrombosis

Renal vein thrombosis is more common than arterial thrombosis and occurs in 1% to 6% of renal transplants.[24,25] Although it may result from a technical error at the time of surgery, its cause is usually less certain. The renal vein can certainly be twisted or kinked if it is not correctly placed after completion of the vascular and ureteral anastomoses. The peak incidence of renal vein thrombosis is 3 to 9 days post-transplantation[26]; a transplant patients with good initial graft function will have a sudden loss of urine output, which is often markedly blood stained, associated with severe pain arising from swelling and (very rarely) rupture of the allograft. The ipsilateral leg may also swell if there is involvement of the iliac venous system. Renal vein thrombosis may also be occult and is one differential diagnosis of delayed graft function. Duplex ultrasound scanning is the best investigation. In an established renal vein thrombosis this may show an obviously swollen allograft with surrounding hematoma and an absence of renal perfusion. Lesser degrees of thrombosis, or indeed incipient thrombosis, may be highlighted by an absence of arterial flow in diastole. An even later development is a reversal of flow in diastole.

As with arterial thrombosis, if this diagnosis is entertained, then the best course of action is to reexplore the transplant as an emergency. The renal vein anastomosis can be opened to allow clot to be extracted, and the venotomy is then closed and the kidney observed for improvement. A more radical alternative is to immediately explant the kidney by taking down the arterial, venous, and ureteral anastomoses. The kidney can then be reflushed with cold perfusion fluid on the back table and held in preservation fluid at 4° C. This allows much more time to assess the cause of the venous thrombosis, and if the kidney remains viable, the transplant operation can then be repeated. If the transplant is already infarcted or cannot be adequately flushed with preservation fluid, then the organ will need to be discarded anyway and nothing is lost by immediate explantation. Successful emergency surgical exploration with subsequent long-term function is rare. Interventional radiographic techniques offer an alternative to surgery. The renal vein can be selectively catheterized via the ipsilateral femoral vein, and graft thrombolysis may then be attempted. This technique is particularly useful when renal vein thrombosis occurs late after transplant and the risk of systemic anticoagulation is low. The use of various thrombolytic agents has been reported, including heparin, urokinase, streptokinase, and tissue plasminogen activator (tPA), with no consensus as to which is the most appropriate.

Transplant Renal Artery Stenosis

Transplant renal artery stenosis is a later complication occurring 3 to 48 months after transplantation. Not all stenoses are of functional or clinical significance, as shown by studies in which all functioning transplants have undergone angiography.[27] Causal factors include donor and recipient atherosclerosis, factors associated with surgical technique, and severe acute rejection.[28] The presentation and management of transplant renal artery stenosis are discussed in Chapter 66.

Lymphocele

Small, clinically insignificant lymphatic collections can be demonstrated by ultrasound scan in up to 50% of renal transplants.[29] Larger lymphoceles that cause complications or require treatment occur in 2% to 10% of patients.[30] The source of peritransplant lymph leaks is the lymphatic channels around the iliac arterial system rather than the lymphatics of the transplanted kidney itself.[31] Therefore, during the dissection of the iliac arterial system, all the surrounding lymphatic channels must be meticulously secured with nonabsorbable ligatures or metals clips. Wound suction drains should not be removed postoperatively until less than 30 ml of fluid is produced on 2 consecutive days. It is safe to leave drains in place for several weeks post-transplantation to allow a low-volume lymphatic leak to seal by gradual fibrosis. Despite the theoretical risk of infection, this does not seem to be a problem in practice. If necessary, the patient can be discharged from the hospital with the drain *in situ.*

Compression of the transplanted ureter leading to renal dysfunction is produced only by very large lymphoceles (volume >300 ml). The peak incidence is at 6 weeks, but a lymphatic collection may present 2 weeks to 6 months after transplantation.[29] Most lymphatic collections are found anterior to the iliac vessels and lying between the transplant and the bladder (Fig. 103-8). Presenting features may include wound or ipsilateral thigh swelling in association with suprapubic discomfort and urinary frequency caused by bladder compression. Other presentations include pain over the transplanted kidney sometimes associated with fever, ureteral obstruction with graft dysfunction, and ipsilateral thrombophlebitis. However, the vast majority are asymptomatic and present as an incidental finding during an ultrasound scan being performed for another reason. It is important to aspirate all peritransplant fluid collections under ultrasound control to aid diagnosis. Macroscopic findings are usually sufficient to differentiate infected from noninfected lymph, and biochemical analysis of the fluid allows a urine leak to be excluded. Computed tomography or magnetic resonance imaging is an essential investigation if surgery is being contemplated, particularly if a laparoscopic procedure is planned. This allows accurate definition of

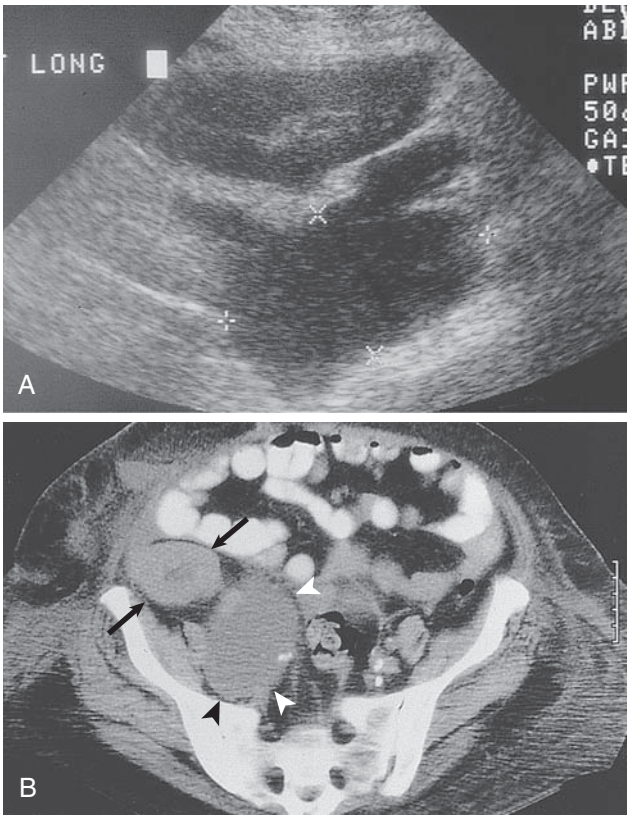

Figure 103-8 Post-transplantation lymphocele. A, Ultrasound appearance. A large echolucent lymphocele can be seen inferior to the transplanted (marked by *crosses*). **B,** Computed tomography appearance. A 5- × 5-cm lymphocele *(arrowheads)* is present under the transplanted kidney *(arrows)*.

the relationship between the lymphocele and the transplanted ureter. If the ureter is bow-strung across the superior surface of the lymphocele, then it could be damaged during a laparoscopic fenestration procedure.

Many small lymphoceles are asymptomatic and will resolve spontaneously given enough time. If action is deemed necessary, first-line treatment is aspiration under ultrasound control. If there is a recurrence, further aspirations can be performed or an external drain can be placed with ultrasound guidance. If these simple measures fail, then open or laparoscopic surgical drainage may be required. A 5-cm diameter disk of the lymphocele wall is removed to create a large opening into the peritoneal cavity, allowing reabsorption of the lymph through the abdominal lymphatic drainage system. These peritoneal fenestrations have a tendency to heal before the lymphocele is completely reabsorbed, leading to early recurrence; a metal or omental plug may prevent this.

Urologic Complications

Urinary tract complications are relatively common after renal transplantation, with an incidence of 5% to 14%.[32] Although they can be difficult to manage, they only rarely cause graft loss or mortality. The relatively high incidence of urologic problems is a consequence of the tenuous blood supply of the transplanted ureter. After kidney retrieval, the only ureteral blood supply that is preserved is derived from the renal artery near the hilum of the kidney, and this can be easily damaged during retrieval.

Urinary Leaks

Urinary leaks most commonly occur because of ischemic necrosis in any part of the transplanted urinary collecting system. The distal ureter has the poorest blood supply and is therefore the most common site. Less commonly, leaks occur from the renal pelvis or the midportion of the ureter, which may be a result of unrecognized direct damage to the ureter during organ retrieval. Urinary leaks tend to occur in the first few days after transplantation but can present much later. The usual presentation is with straw-colored fluid leaking directly from the transplant wound or accumulating in the drains in association with oliguria. Alternatively, extravasating urine may accumulate as a peritransplant fluid collection. This presents as a painful swelling of the wound, and the patient may have a fever. In either case, the extravasated fluid must be differentiated from lymph by biochemical analysis of the fluid and a simultaneous serum sample. Urine will have markedly elevated urea and creatinine levels compared with the patient's serum, whereas lymph will have a similar biochemical profile.

The presence of a urinary fistula should be confirmed by antegrade or retrograde pyelography. Both of these techniques present challenges. Antegrade puncture of a nondilated pelvicaliceal system is technically difficult but usually possible. Retrograde cannulation of the transplanted ureteral orifice can be attempted with a flexible cystoscope. This is also a difficult maneuver because the transplanted ureter is implanted into the dome of the bladder rather than at its base. If the urine leak is contained as a urinoma, ultrasound will demonstrate a fluid collection between the transplanted kidney and the bladder, which can be sampled by needling or drained by the placement of a suitable percutaneous catheter.

The management of urinary leaks has changed significantly in recent years. The former practice of early reexploration and surgical reconstruction[33] is no longer always necessary. Interventional radiographic techniques offer an alternative, at least for initial treatment. The aim is to place a double-J (pigtail) ureteral stent across the region of damage via an antegrade nephrostomy; this may allow time for the urinary fistula to heal.[34] This technique, however, is unlikely to be successful if there is significant ischemic necrosis of the ureter, in which case, surgery still has a role. Reexploration of kidney transplants is straightforward in the early postoperative period but may be a considerable challenge later because of the development of an intense peritransplant fibrotic reaction. The choice of operative procedure for a necrotic distal ureter depends on the length of remaining viable ureter. If there is sufficient length after excision of the necrotic distal portion, the transplanted ureter may simply be reimplanted into the bladder. If this is not possible, the urinary tract should be reconstructed with use of the patient's native ureter. Depending on length of viable transplanted ureter, there is a choice between anastomosing the native ureter to the transplanted ureter proximal to the ischemic segment (ureteroureterostomy) or to the transplanted renal pelvis (ureteropyelostomy; Fig. 103-9). Whichever technique is chosen, the anastomosis should be protected with a double-J stent. Although these techniques require the native ureter to be ligated proximally, there is usually no need to perform an ipsilateral nephrectomy.[35] Postoperatively, the antegrade nephrostomy can be left *in situ* so that a contrast study can be performed after 7 to 10 days to confirm healing of the new anastomosis. If the transplant recipient has undergone an ipsilateral nephrectomy in the past or the native ureter is too diseased to be used for reconstruction, a Boari bladder flap can be used to reconstruct the urinary tract.

Ureteral Obstruction

Obstruction of the transplanted ureter may occur at any time after transplantation. It should always be considered in the differential

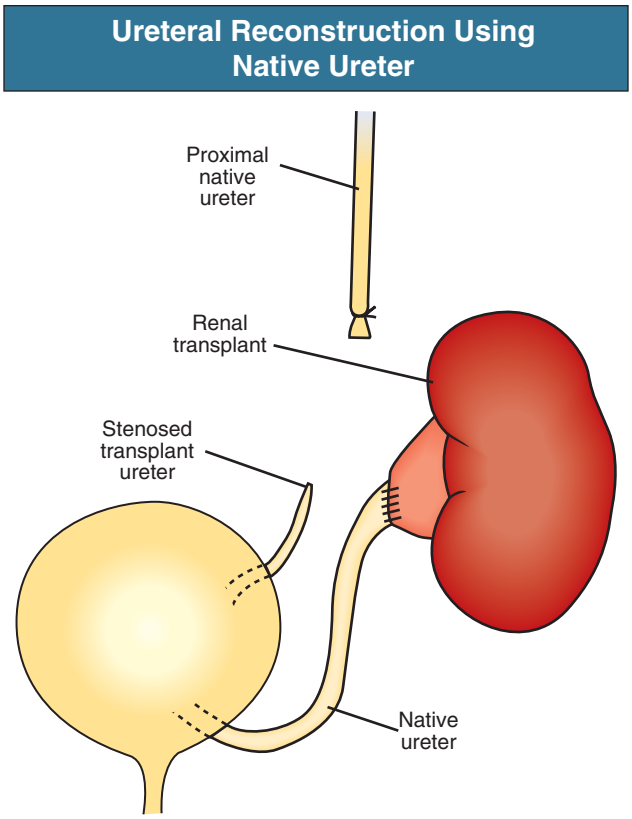

Figure 103-9 **Ureteral reconstruction using native ureter.**

diagnosis of acute transplant dysfunction and excluded by ultrasound examination. The management of transplant ureteral obstruction is summarized in Figure 103-10. Early obstruction is uncommon and suggestive of a technical error, such as creating a submucosal bladder tunnel that is too tight, kinking of a redundant length of ureter, and incorrect suture placement during anastomosis. Early obstruction may also be caused by blood clot in the ureter, bladder, or catheter. Bleeding may occur from the ureterovesical anastomosis or cystostomy or after a transplant biopsy. It is common practice to drain the urinary bladder using a three-way irrigating catheter because small-diameter two-way Foley catheters are easily blocked by blood clot.

Late ureteral obstruction may occur at the vesicoureteral or pelviureteral junctions. Ischemia that is not severe enough to cause necrosis is presumed to be the cause of most vesicoureteral obstructions.[36] Renal transplants invariably excite a pronounced perigraft fibrotic response, and this is more likely to be the cause of an obstruction at the level of the pelviureteral junction. It is also possible that acute rejection episodes contribute to subsequent fibrosis.[34] BK polyoma virus can also cause late ureteric obstruction because of hypertrophy of ureteric epithelial cells in combination with infiltration of inflammatory cells.

An ultrasound scan will demonstrate a dilated pelvicaliceal system. However, longstanding kidney transplants may have quite marked pelvicaliceal dilation without being obstructed. This most commonly causes uncertainty in assessment of whether obstruction may be contributing to chronic allograft dysfunction in a patient with biopsy-proven chronic allograft nephropathy. Further investigation is needed to confirm or refute the presence of obstruction and

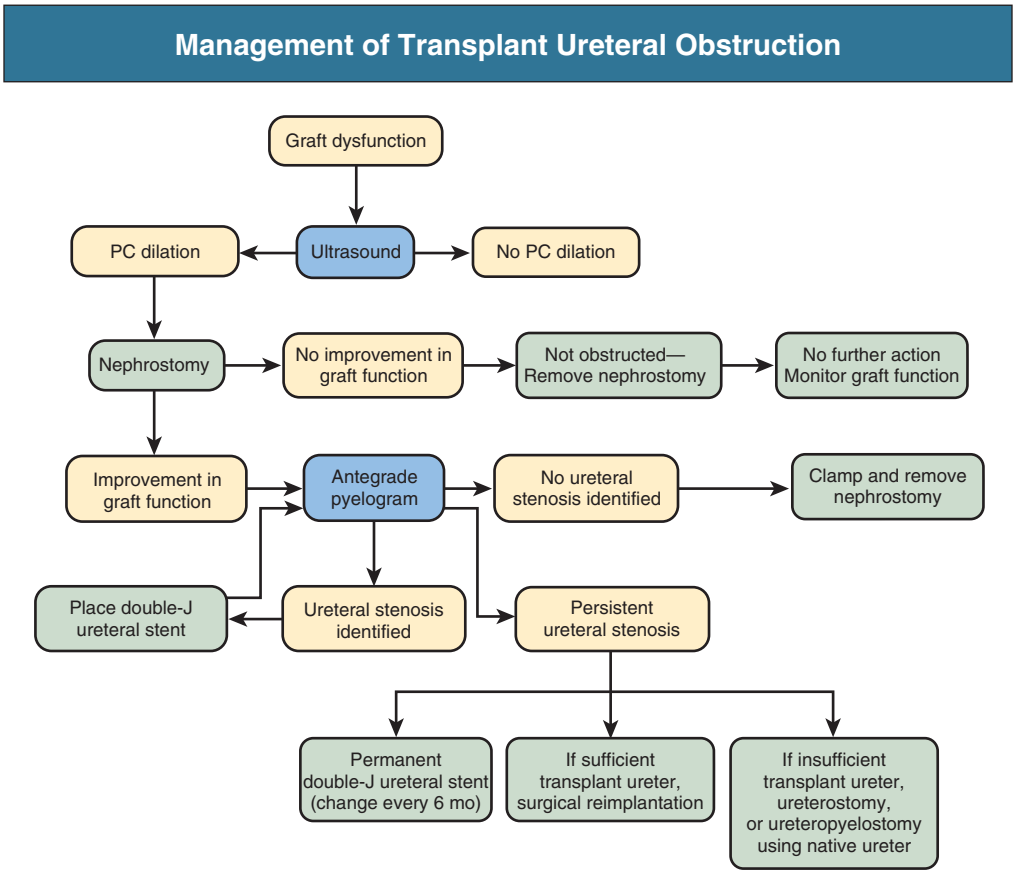

Figure 103-10 **Management of transplant ureteral obstruction.** *PC,* Pelvicaliceal.

to define its anatomy. Retrograde pyelography has a low success rate because of the difficulty of catheterizing the transplanted ureteral orifice at cystoscopy. Therefore, percutaneous nephrostomy followed by antegrade pyelography is the investigation of choice in suspected transplant ureteral obstruction. The nephrostomy is performed under antibiotic cover using ultrasound control, and the nephrostomy tube should be left in place for a few days. If serum creatinine decreases during this period, then obstruction is confirmed. If there is no improvement in renal function, significant obstruction can be confidently excluded. This simple observation avoids the need for an antegrade pressure study (Whittaker test), which may be difficult to interpret in transplanted kidneys. After external decompression of the transplanted kidney for a few days, an antegrade pyelogram is obtained to accurately define the anatomy of the obstructing lesion.

Nonoperative approaches for the treatment of transplant ureteral stricture are often preferred.[37] The simplest approach is to place a double-J stent across the stricture via a percutaneous nephrostomy. This may require initial balloon dilation.[38] The stent can be removed after 6 weeks, but the restenosis rate is high. An alternative is long-term stenting, changing the stent every 6 months. The disadvantage of this method is a high incidence of urinary tract infection, with potential severe consequences for immunosuppressed patients, and long-term antibiotic prophylaxis is a sensible precaution. Open surgical management still has a place in the management of ureteral obstruction. The operation performed depends on the site of obstruction and the remaining length of healthy transplanted ureter proximal to the obstruction (see the discussion of urinary leaks). Not all cases of obstruction require intervention. When there is a mild degree of obstruction not associated with urinary tract infection and in a longstanding kidney that is affected by chronic allograft nephropathy, it may be better to simply monitor transplant function, reserving intervention for a later date should it become necessary.

Complications in the Transplant Bed

A number of nerves may be encountered in the retroperitoneal dissection required for kidney transplantation. These include the lateral femoral cutaneous nerve and the femoral, obturator, and sacral nerves. Each of these may be damaged by a traction injury, particularly when modern fixed wound retraction systems are used, because these can exert a great deal of pressure on the surrounding tissues. Patients with such neurapraxias should recover completely, but this may take some months, and the condition can be very disabling.

In male transplant recipients, the spermatic cord must be mobilized during the dissection to gain access to the retroperitoneal space. Damage to the testicular artery in the cord can result in testicular atrophy.

TRANSPLANT NEPHRECTOMY

The optimal management strategy for patients with a failed renal transplant remains unclear, with a lack of good-quality evidence. Transplant nephrectomy is mandatory for early graft failure caused by vascular thrombosis, capsular rupture, and irreversible rejection. However, the management of a renal transplant that has chronically failed is more challenging. The options are transplant nephrectomy or leaving the graft *in situ,* with or without continuation of immunosuppression. Mortality from both infection and cardiovascular disease have been shown to be higher in patients with failed grafts continuing immunosuppression.[39] However, weaning and discontinuation of immunosuppression have also been shown to increase the risk of transplant nephrectomy and allosensitization.[40]

If the graft remains *in situ* without immunosuppression, signs and symptoms such as pain, fever, hematuria, and thrombocytopenia may prompt transplant nephrectomy, although the patient can also be treated initially with corticosteroids.

Historically, transplant nephrectomy was advocated to remove antigenic stimulation for anti–human leukocyte antigen (HLA) antibody production, which might adversely affect the possibility of retransplantation. However, there is some evidence that transplant nephrectomy, particularly late after transplantation, may actually increase allosensitization.[41] The suggestion is that the graft may act as an "immunologic sponge" to absorb antibody or may regulate the production of antidonor antibody by the recipient's immune system.

Early graft nephrectomy is straightforward, but after the first few weeks kidney transplants usually develop quite intense perigraft fibrosis, and this can make late allograft nephrectomy a difficult technical challenge. A subcapsular dissection is preferred, and after removal of the kidney, the hilum is sutured, leaving a cuff of donor vessels in place. Careful hemostasis is required, and the whole raw capsular bed should be cauterized. The wound is usually closed without drains.

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CHAPTER 104

Prophylaxis and Treatment of Kidney Transplant Rejection

Alexander C. Wiseman and James E. Cooper

The clinical presentation of the immune response to transplanted tissue, referred to as *rejection,* became apparent in 1960 when, after successful proof-of-principle kidney transplants were performed in identical twins, kidney transplantation was attempted between immunologically dissimilar individuals.[1] Eleven patients underwent lymphoid irradiation to prevent rejection after kidney transplant from nonidentical donors. Although 10 of the 11 died of overwhelming infection, illustrating the potential consequences of immunosuppression, the lone surviving patient from this series subsequently underwent two episodes of acute rejection, both of which were successfully treated with corticosteroids with successful graft function. Thus began the development of immunosuppressive agents that could prevent and treat rejection while not inducing severe life-threatening side effects, and the characterization of the histologic patterns of injury that quantify the type and severity of rejection. The occurrence of acute rejection in the first year after transplant has significantly diminished from a near-universal occurrence of rejection in earlier eras to present-day rates of 10% to 15%,[2] primarily because of the development of newer immunosuppression medications. Although the incidence of acute rejection has diminished, the management of chronic rejection has remained a challenge, with continued attempts to better define the nature of injury and methods to prevent or reverse this process (Fig. 104-1). However, as attention shifts to limiting the toxicity of immunosuppression medications in corticosteroid-withdrawal and calcineurin inhibitor (CNI)–withdrawal protocols and to attempting to increase access to transplant by performing transplants across human leukocyte antigen (HLA) and blood type barriers, management of acute rejection continues to be an important clinical issue.

DEFINITION

Rejection (both acute and chronic) is defined by histologic findings after kidney transplant biopsy. A biopsy considered adequate for analysis involves sampling of at least 10 glomeruli and two small arteries, stained with hematoxylin-eosin (HE), periodic acid–Schiff (PAS) or silver, and trichrome stains; a biopsy with seven to nine glomeruli and one artery is considered of marginal adequacy. When biopsy is performed for clinical indications (renal dysfunction), two separates cores should be obtained because the findings of rejection are often patchy in distribution (Fig. 104-2).[3] There is not a consensus of opinion regarding the number of cores required when biopsies are performed for nonclinical indications (e.g., in protocol-driven practice), although adequate tissue sampling defined by the previously described criteria is preferable if performed.

The Banff Working Classification of Renal Allograft Pathology forms the basis of the histologic definition of rejection and is continually reviewed and updated on a biannual basis. First developed in 1993 with a primary focus on T cell–mediated acute inflammatory infiltrates to classify the degree of rejection, a more recent (2007) classification now differentiates a humoral (antibody-mediated) response from the T cell response and further distinguishes a chronic humoral form of injury previously included within the term "chronic allograft nephropathy" (see Chapter 107)[4] (Box 104-1). This was based on the indirect identification of antibody-mediated injury via evidence of complement (C4d) deposition. C4d is a fragment of C4b that is generated on IgG and IgM deposition and activation of the classical complement pathway. C4b/C4d forms a covalent bond with proteins on tissue such as capillary endothelial cells via a sulfhydryl group, and persists bound to tissue after immunoglobulin and other complement products have been released.[5] Staining for C4d, either by immunohistochemistry or immunofluorescence, is often performed on allograft biopsy specimens to aid in identifying if an antibody-mediated process may be involved in patients with graft dysfunction. Although issues of standardization and reliability of staining exist, C4d staining remains an important marker of antibody-mediated injury and should be performed in any biopsy from which a change in immunosuppression may be entertained.

Antibody-Mediated Rejection

Acute antibody-mediated (humoral) rejection (AHR) is estimated to occur in 3% to 10% of all transplants and is present in 20% to 30% of episodes of acute rejection,[6] occurring typically within the first few weeks of transplantation or in association with a change in immunosuppression. Although patients who have pre-existing donor-specific HLA alloantibodies ("donor-specific antibodies") are at higher risk for the development of acute humoral rejection, the identification of *de novo* donor-specific antibodies at the time of graft dysfunction is common. The diagnosis of acute humoral rejection requires (a) evidence of circulating donor-specific antibodies, (b) C4d deposition in peritubular capillaries, and (c) evidence of tissue injury (Fig. 104-3). Patterns of injury associated with acute humoral rejection range from acute tubular cell injury suggestive of acute tubular necrosis to thrombotic microangiopathy (TMA), but typically will be associated with neutrophils and/or macrophages in peritubular capillaries. Staining for C4d is considered a sensitive marker for acute antibody-mediated injury and should be routinely performed on renal allograft biopsy specimens when this process is being considered in the differential diagnosis.

Chronic active antibody-mediated rejection has been identified as a leading cause of late allograft loss,[7,8] and accurately diagnosing this condition has been a subject of interest. Chronic active antibody-mediated rejection is likely the result of an indolent alloimmune response that can result in transplant glomerulopathy and microcirculatory inflammation (Fig. 104-4). Although transplant glomerulopathy is often associated with circulating donor-specific antibodies

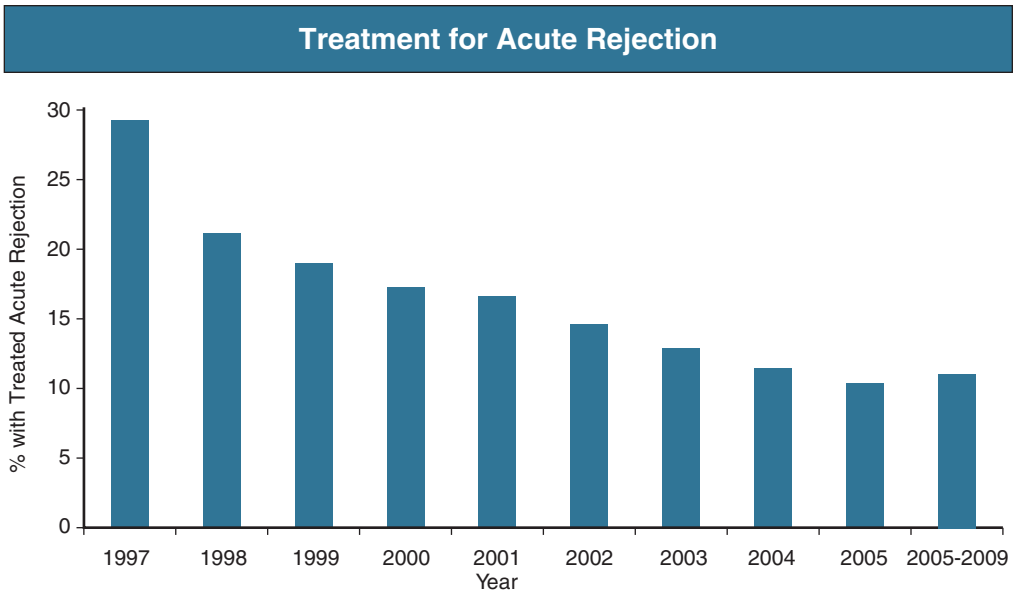

Figure 104-1 Treatment for acute rejection for all kidney transplants in the United States, 1997-2005. (As reported to the Scientific Registry of Transplant Recipients, SRTR reports 2007 and 2012.)

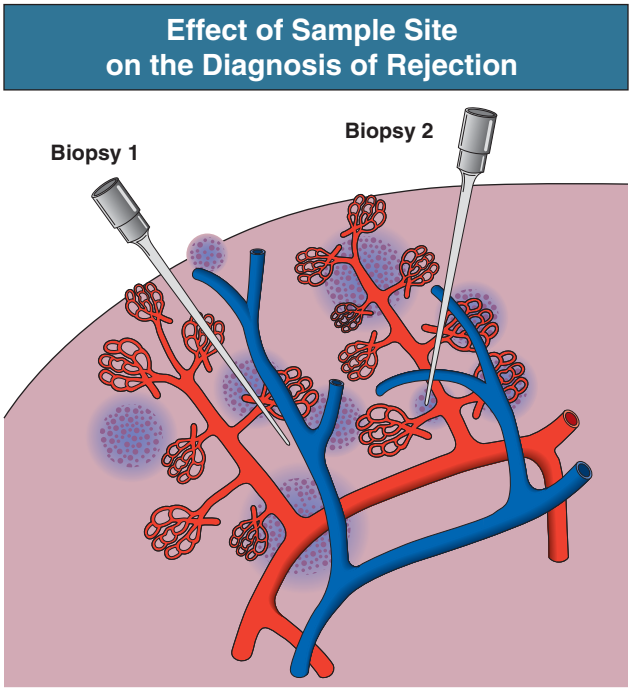

Figure 104-2 Effect of sample site on the diagnosis of rejection. Acute rejection begins as patchy, focal infiltrates and becomes homogeneous only in advanced stages. The intensity of mononuclear infiltrate seen on biopsy would differ between core 1 and core 2. Routinely taking two core biopsy samples can help decrease the sampling errors, which can affect the histologic interpretation of rejection.

BANFF Classification of Rejection

Antibody Mediated

Acute

C4d$^+$, presence of circulating antidonor antibodies and acute tissue injury

I. ATN-like (minimal inflammation)

II. Capillary and/or glomerular inflammation and/or thromboses

III. Arterial inflammation

Chronic

C4d$^+$, presence of circulating antidonor antibodies and chronic tissue injury
(1) Glomerular double contours, (2) peritubular capillary basement membrane multilayering, (3) tubular atrophy or interstitial fibrosis, and/or (4) fibrous intimal thickening in arteries

T Cell Mediated

Acute

Mononuclear cell interstitial inflammation and tubulitis and/or arteritis

IA: More than 25% interstitial infiltration, 4 to 10 mononuclear cells/tubular cross section

IB: More than 25% interstitial infiltration, >10 mononuclear cells/tubular cross section

IIA: Intimal arteritis, mild to moderate (0% to 25% of luminal area)

IIB: Intimal arteritis, severe (>25% of luminal area)

III: Transmural arteritis and/or fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocyte inflammation

Chronic

Arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neointima

Borderline

Presence of 10% to 25% interstitial infiltration, <4 mononuclear cells/tubular cross section

Box 104-1 Classification of rejection. *ATN,* Acute tubular necrosis. *(Modified from reference 4.)*

and C4d deposition, 30% to 50% of cases will be identified in the absence of these diagnostic markers.[9] This suggests that either these lesions are not solely caused by a humoral response or the lack of a temporal relationship of donor-specific antibodies or C4d deposition to biopsy findings is related to phenomena such as non–complement fixing antibodies and/or the waxing-waning nature of the humoral response.

The current Banff diagnostic criteria for chronic humoral rejection require (1) evidence of donor-specific antibodies, (2) C4d deposition in peritubular capillaries, and (3) evidence of chronic tissue

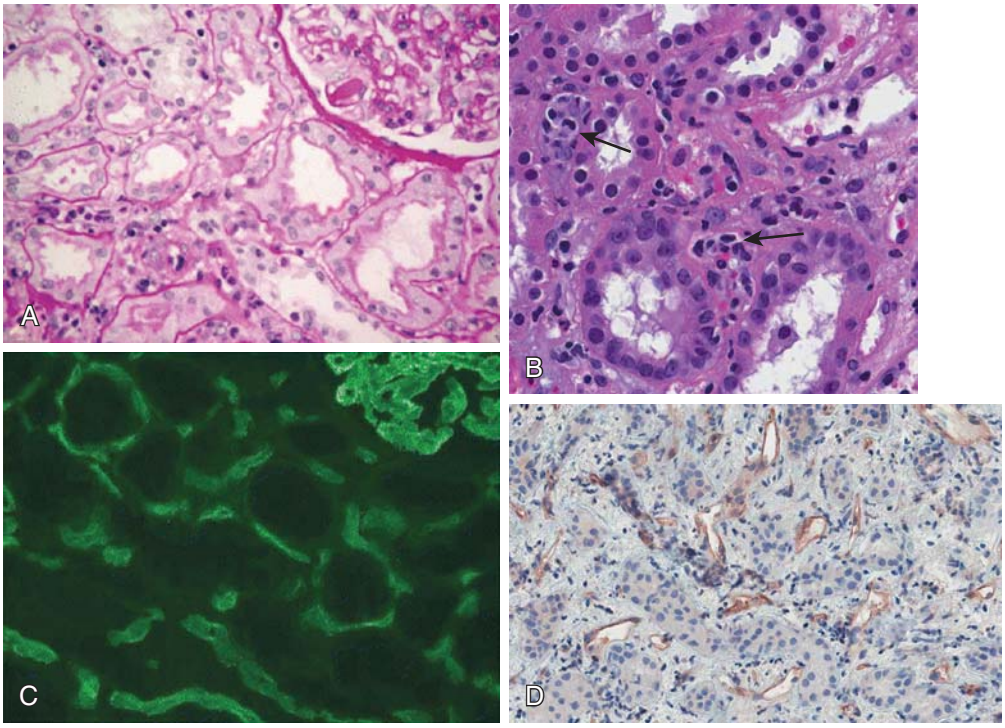

Figure 104-3 Acute antibody-mediated rejection. A, Peritubular and glomerular capillaries contain numerous polymorphonuclear leukocytes and mononuclear cells. **B,** Numerous polymorphonuclear leukocytes are observed in a peritubular capillary *(arrows)*. Interstitial edema is noted. (Periodic acid–Schiff; magnification ×200.) **C,** Immunofluorescence staining of peritubular capillaries with C4d. (Fresh frozen tissue sample; magnification ×250.) **D,** Immunohistochemistry demonstrating peritubular capillary staining of C4d. (Paraffin-embedded tissue; magnification ×480.) *(From reference 66.)*

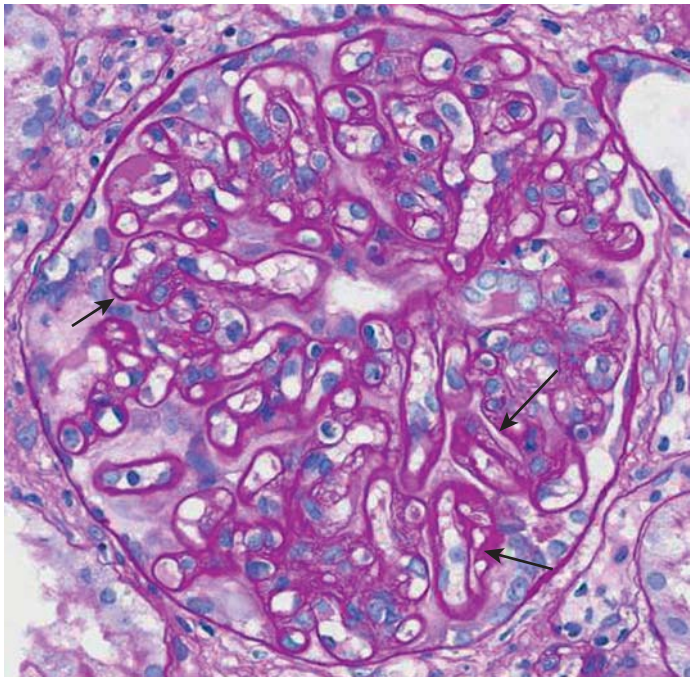

Figure 104-4 Transplant glomerulopathy. Light microscopy showing typical membranoproliferative changes, including glomerular basement membrane duplication and thickening *(arrows)*.

injury. The forms of chronic tissue injury may include duplication of the glomerular basement membrane, multilamination of the peritubular capillary basement membrane, arterial intimal fibrosis without elastosis, and/or interstitial fibrosis with tubular atrophy. Although the Banff classification still recognizes diffuse peritubular capillary C4d deposition as a diagnostic criterion for chronic active antibody-mediated rejection, recent evidence questions the sensitivity of C4d in detecting humoral graft damage and suggests that microcirculatory injury (peritubular capillaritis, glomerulitis) may be a more important indicator of this process.[7,10] Recent molecular studies show upregulated endothelial gene expression in combination with circulating donor-specific antibodies to be indicative of antibody-mediated graft damage (termed *C4d-negative antibody-mediated rejection*) and a more sensitive indicator of graft loss than C4d deposition.[11] A report from the 2011 Banff meeting recognizes the existence of C4d-negative antibody-mediated rejection and has aimed to define diagnostic criteria for this entity.[12]

T Cell–Mediated Rejection

The classical pathologic description of rejection is now referred to as *T cell–mediated rejection.* The classification of acute T cell–mediated rejection (acute cellular rejection [ACR]) is based on the degree and location of mononuclear cell inflammation. Because interstitial inflammation and tubulitis are frequently present immediately beneath the renal capsule (subcapsular inflammation) in stable allografts, this histology is not taken into account in interpreting an allograft biopsy for the presence of rejection. When severe, interstitial inflammation may extend into tubules via injury to the tubular basement membrane (tubulitis). The predominant phenotype of these infiltrates is a mixture of $CD4^+$ and $CD8^+$ T cells; however, B cells, eosinophils, and macrophages may also be present. Less commonly, endarteritis (endothelialitis) may be present: T cells and macrophages extend under the arterial endothelium, a phenomenon that may or may not be accompanied by interstitial inflammation or tubulitis. The finding of interstitial infiltrates and tubulitis in a kidney transplant biopsy specimen is not specific to ACR, and other causes such as viral nephropathy (BK virus, less commonly cytomegalovirus [CMV]), pyelonephritis, or post-transplant lymphoproliferative disease should be considered based on the clinical presentation. In contrast, the histologic finding of endothelialitis is pathognomonic of ACR.

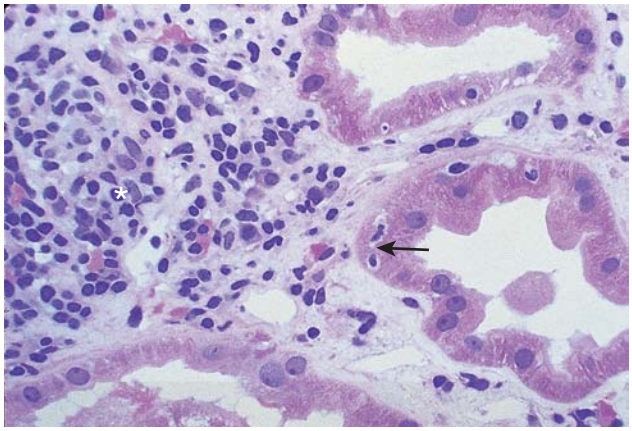

Figure 104-5 Type I acute cellular rejection. Type I acute rejection manifests with interstitial mononuclear cell infiltration *(asterisk)* with invasion of the tubules *(arrow).* (Periodic acid–Schiff; magnification ×200.)

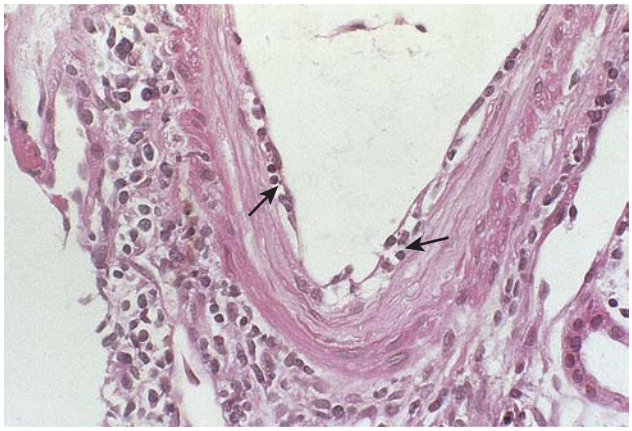

Figure 104-6 Type II acute cellular rejection. Type II rejection, called *acute vascular rejection,* manifests with endothelialitis with mononuclear cell infiltration *(arrows)* beneath the arterial endothelium. (Periodic acid–Schiff; magnification ×200.) *(Courtesy Dr. Agnes Fogo, Vanderbilt University, Nashville, Tennessee.)*

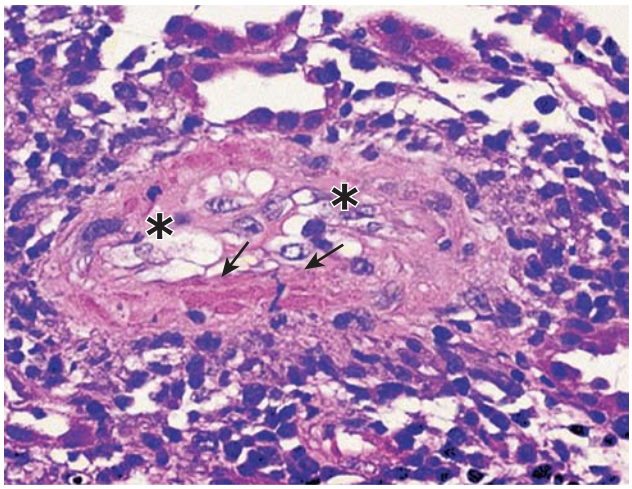

Figure 104-7 Type III acute cellular rejection. Severe small-vessel vasculitis with transmural mononuclear cell infiltration, fibrinoid necrosis *(arrows),* and very swollen endothelial cells *(asterisks).* (Periodic acid–Schiff; magnification ×400.) *(From reference 67.)*

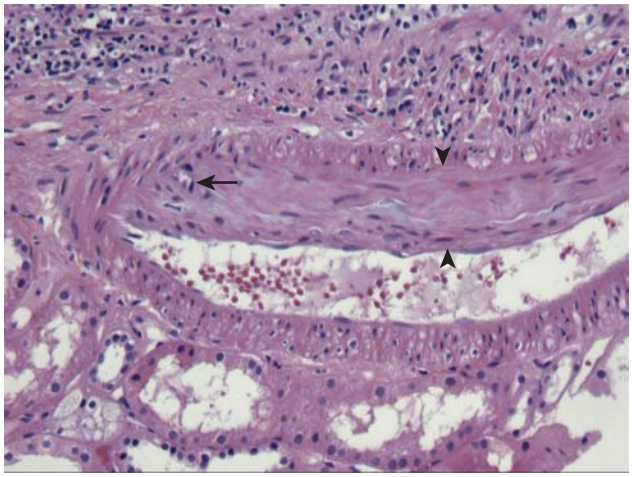

Figure 104-8 Chronic active T cell–mediated rejection. Chronic allograft arteriopathy with the formation of a fibrous neointima *(between arrowheads)* and embedded mononuclear cell infiltration *(arrow).* (Hematoxylin-eosin stain; magnification ×200.) *(Photomicrographs courtesy Dr. Maxwell Smith, University of Colorado, Denver, Colorado.)*

Acute T cell–mediated rejection is histologically classified in the Banff criteria based on the presence or absence of endothelialitis, the degree of interstitial inflammation, and the quantity of infiltrating cells into tubules. Type I ACR is characterized by the absence of endothelialitis, with interstitial inflammation of at least 25% of the parenchyma, and tubulitis (type IA requires 4 to 10 mononuclear cells/tubular cross section, whereas type IB requires >10 mononuclear cells/tubular cross section) (Fig. 104-5). Type II ACR is characterized by vascular involvement or endothelialitis (IIA requires mild to moderate intimal arteritis, and IIB requires arteritis with at least 25% of the luminal area lost in at least one arterial cross section) (Fig. 104-6). Type III ACR is characterized by vascular inflammation that extends to the media ("transmural") and may be accompanied by fibrinoid change and necrosis of the smooth muscle cells (Fig. 104-7). Type II and III ACR may or may not be associated with elements of type I ACR; therefore the pathologic description of rejection should not be viewed as a pathogenic continuum. However, type II and III ACR appear to require different therapeutic interventions and carry different prognostic implications than type I ACR (see later sections).

Chronic active T cell–mediated rejection is a histologic diagnosis that refers to arterial intimal fibrosis specifically with evidence of mononuclear cell infiltration and formation of neointima (Fig. 104-8). This is distinguished from chronic humoral rejection by the location of vascular injury and lack of evidence of pathogenic antibody, and is distinguished from other nonimmunologic processes that may lead to vascular and interstitial fibrosis by the presence of persistent infiltrating cells within vessels. This is covered in greater detail in Chapter 107.

Borderline Rejection

The finding of inflammation in 10% to 25% of the interstitium with tubulitis of less than four mononuclear cells per tubular cross section is classified as borderline rejection. This currently remains a pathologic definition without clear clinical significance. When borderline rejection is identified in the setting of graft dysfunction or with other findings such as glomerulitis, the risk of progression to clinical rejection on subsequent biopsies is increased and therefore treatment may be considered.[13]

Differential Diagnosis of Renal Allograft Dysfunction

Week 1 Post-Transplantation
Acute tubular necrosis
Hyperacute or accelerated rejection
Urologic
  Obstruction
  Urine leak
Vascular thrombosis
  Renal artery
  Renal vein
Volume contraction

<12 Weeks After Transplantation
Acute rejection
Calcineurin inhibitor toxicity
Volume contraction
Urologic
  Obstruction
Infection
  Bacterial pyelonephritis
  Viral infections
Interstitial nephritis
Recurrent disease

>12 Weeks After Transplantation
Acute rejection
Volume contraction
Calcineurin inhibitor toxicity
Urologic
  Obstruction
Infection
  Bacterial pyelonephritis
  Viral infections
Chronic allograft nephropathy
Recurrent disease
Renal artery stenosis
Post-transplantation lymphoproliferative disorder

Box 104-2 Differential diagnosis of renal allograft dysfunction.

CLINICAL MANIFESTATIONS

The clinical presentation of acute rejection is common to both T cell and antibody-mediated rejection. Patients typically present with a rapid rise in serum creatinine, and in severe cases may have a decreasing urine output, weight gain, fever, or graft tenderness. The clinical findings are commonly nonspecific, and other causes of graft dysfunction are often considered at the time of presentation in the context of an individual's risk for the development of acute rejection (Boxes 104-2 and 104-3). Because of the increase in presensitized patients undergoing transplantation, patients with known donor-specific antibody in desensitization protocols, and ABO-incompatible transplants, approximately 25% of acute rejection episodes now have a humoral component. In acute humoral rejection there may be features of TMA with microangiopathic anemia and thrombocytopenia. If there is immediate cyanosis of the graft on revascularization (hyperacute rejection) or an abrupt decline in urine output and graft tenderness 3 to 14 days post-transplant (delayed hyperacute or accelerated rejection), donor-specific antibody is implicated. Typically there is type III AHR and interstitial hemorrhage on biopsy.

Risk Factors for Acute Rejection

High Risk
Sensitization (high panel reactive antibody percentage)
  Previous transplantation
  Pregnancy
  Transfusion
Delayed graft function
  Deceased donor source
  Increased donor age
  Prolonged ischemic time
  Donor brain death
  Donor acute renal dysfunction
HLA mismatching
Positive pretransplantation B cell crossmatch
ABO incompatibility
Corticosteroid minimization
Infection
  Bacterial pyelonephritis
  Cytomegalovirus
Adolescent recipient
African American recipient
Previous rejection episode

Low Risk
Zero HLA mismatch
Elderly recipient of young donor kidney
Preemptive transplantation
Living donor source
First transplant

Box 104-3 Risk factors for acute rejection. *HLA,* Human leukocyte antigen.

PROPHYLAXIS AND PREVENTION

Prophylaxis

The primary goal of transplant management is prevention of immunologic graft loss in the early period after transplant. Over time, the risk for acute rejection diminishes and goals of immunosuppression therapy shift toward considerations of side effects of medications and risks for other events such as cardiovascular disease and malignancy. Therefore, current clinical practice follows a general strategy of intensive immunosuppression and monitoring in the first months after transplant with a reduction or alteration of treatment after the initial period of risk.

Prevention of Acute T Cell–Mediated Rejection: Induction Therapy

The use of a brief course of potent immunosuppression at the time of transplant, referred to as *induction therapy,* has become a common strategy for the prevention of acute rejection in all transplant recipients including both those at higher and lower immunologic risk. According to the Scientific Registry of Transplant Recipients (SRTR), 83% of kidney transplant recipients received induction therapy in the United States in 2011. For higher-risk patients such as those with prior sensitization (the presence of HLA antibodies quantified by percent reactivity against a panel of common HLA types, referred to as percent panel reactive antibody [PRA]), prior transplant, or African American ethnicity, induction therapy is usually combined

with standard doses of immunosuppression to prevent rejection. For those with lower risk (living donor kidney recipients, primary kidney transplants), induction therapy is often used in an effort to minimize exposure to maintenance immunosuppression. The use of race as a risk factor for rejection has recently been questioned with a study demonstrating similar acute rejection rates in African Europeans compared with European Caucasians in France.[14] However, most studies still report a higher risk of rejection for African Americans than American Caucasians; thus induction therapy is commonly used in this population.[15]

Induction agents can be classified as T cell depleting or nondepleting. Nondepleting agents include the monoclonal humanized interleukin (IL)–2 receptor antibody (IL-2Ra) agent daclizumab (no longer available for use because of manufacturer withdrawal) and the chimeric agent basiliximab. The IL-2 receptor was identified as a potential immunosuppressive target because it is present on T cells and because inhibition of IL-2/IL-2R signaling inhibits T cell proliferation (see Chapter 101). Use of IL-2Ra has resulted in a reduction in acute rejection rates with minimal side effects when combined with cyclosporine-based immunosuppression in the absence of mycophenolate.[16] It is important to note that these agents have not been studied in a prospective randomized fashion in combination with a tacrolimus-mycophenolate–based maintenance regimen; therefore questions still remain regarding the relative benefits of the addition of IL-2Ra with more potent, commonly used maintenance agents.[17]

Depleting agents include antithymocyte globulin, OKT3, and anti-CD52. Unlike the IL-2Ra agents, none of these agents have been compared with placebo for the prevention of rejection, and thus their use as induction agents is considered off-label in the United States. Antithymocyte globulin is a polyclonal preparation of antibodies directed at T cells prepared by immunizing animals with human lymphoid cells derived from the thymus. An antithymocyte preparation created from equine sources was shown to be inferior to other depleting agents in the treatment of rejection, and its use has diminished.[18] Currently, the most common antilymphocyte preparation in use is rabbit antithymocyte globulin (rATG). Anti-CD3 (OKT3), a mouse monoclonal antibody directed to the CD3 subunit of the T cell receptor, also results in depletion of T cells but also is associated with a significant innate immune response to foreign antibody that results in a cytokine release syndrome that presents with fevers, hemodynamic changes, pulmonary edema, and, less commonly, seizure and is no longer manufactured. Recently the use of anti-CD52 (alemtuzumab) has increased in kidney transplantation. This agent binds to CD52, an antigen of unclear physiologic significance that is present on both B and T cells, and results in depletion of both lymphoid cell lines. Its ability to induce prolonged, significant lymphopenia for up to 6 to 12 months after administration led to its use in refractory chronic lymphocytic leukemia. Unlike other depleting agents, it is a humanized antibody and therefore has fewer infusion-related side effects than either rATG or OKT3. Initial trials suggest equivalence to other depleting agents in the prevention of rejection, but the long-term impact of prolonged lymphopenia on the risk for infection or post-transplant lymphoproliferative disorder has yet to be determined, and comparative trials of induction agents are lacking (see later).

Although effective in the inhibition of the T cell response, all depleting agents raise concerns regarding long-term safety. Registry analyses suggest that there is an increased risk of future development of lymphoma with depleting agents compared with nondepleting agents or no induction therapy,[19-20] an association that appears to be dose dependent. For this reason, repeated or prolonged courses of depleting antibody therapy must be considered with this risk balanced by the potential for graft recovery or prolongation.

Three multicenter randomized trials have compared the efficacy of induction agents in the prevention of acute rejection. A multicenter trial in patients at high risk for acute rejection (defined as recipients with an elevated risk of delayed graft function, elevated PRA, repeat transplants, or HLA mismatches) compared the IL-2Ra basiliximab with rATG with maintenance immunosuppression of cyclosporine, mycophenolate mofetil (MMF), and prednisone.[21] At 12 months, the rate of acute rejection in the basiliximab cohort was 26% versus 16% in the rATG arm. A second trial in patients at high risk for acute rejection (defined by elevated PRA screening result, repeat transplants, or loss of a previous kidney transplant to acute rejection) compared the IL-2Ra daclizumab with rATG, with remarkably similar findings of increased rejection incidence for patients randomized to daclizumab (27%) compared with rATG (15%) at 1 year.[22] Thus, for patients at increased risk for rejection, rATG provided greater prevention of acute rejection, supporting its use in higher-risk populations. Finally, a clinical trial compared anti-CD52 either with rATG in high-risk patients (repeat transplant, elevated PRA, or African American race) or with an IL-2Ra in low-risk patients, followed by early corticosteroid withdrawal and maintenance tacrolimus and mycophenolate immunosuppression.[23] The 12-month acute rejection rates in the high-risk arms were 10% for anti-CD52 and 13% for rATG, and in the low-risk arms were 20% for IL-2Ra and 3% for anti-CD52, suggesting a therapeutic benefit of anti-CD52 over IL-2Ra in the low immunologic risk population. Between 12 and 36 months, however, acute rejection rates in anti-CD52 treated patients were higher in both low- and high-risk arms, suggesting a delayed (>12 month) immunologic risk of immune reconstitution with anti-CD52 therapy. This may be problematic for transplant care providers who generally adhere to less rigorous late (>12 month) clinical monitoring protocols for otherwise stable transplant recipients. In general, the issue of the need for induction therapy in low-risk patients is not fully resolved and requires further prospective head-to-head trials, whereas patients at higher immunologic risk appear to benefit from lymphocyte depleting treatment. Common dosage regimens of induction agents are listed in Table 104-1.

Prevention of Acute Antibody-Mediated Rejection: Desensitization

The patient who has donor-specific antibodies or is blood type incompatible with the donor before transplant has a near-universal risk of developing acute antibody-mediated rejection after transplant without pretransplant therapeutic intervention. "Desensitization" protocols may permit transplantation of these donor-recipient combinations. Desensitization protocols typically involve removal of preformed antibody with plasma exchange and/or suppression of antibody production and action with intravenous immunoglobulin (IVIG) or B cell inhibition with rituximab. Several different desensitization strategies were adopted by transplant centers over the previous decade and are generally influenced by factors such as type of transplant (living vs. deceased donor) and the degree of HLA-antibody reactivity that one is attempting to overcome. In the case of living donation the crossmatch barriers are known in advance, allowing for protocols of plasma exchange followed by low-dose (100-200 mg/kg) IVIG to be used and transplant to be pursued when the desired crossmatch results are obtained. Protocols consisting of monthly high-dose IVIG (1 to 2 g/kg) infusions with or without rituximab[24] have been used in situations where pretransplant plasma exchange is not feasible, such as in sensitized patients without living donor options awaiting deceased donor kidneys.

Agents Used for Induction and Treatment of T Cell–Mediated Rejection			
Agent	**Target**	**Dose (Induction)**	**Dose (Rejection)**
Methylprednisolone	B cells, T cells, macrophages	500 mg IV intraoperatively, followed by taper over 1 to 5 days	3-5 mg/kg (250-500 mg) IV × 3-5 days
Basiliximab	IL-2 receptors on cells	20 mg IV × 2 on days 0, 4	N/A
Daclizumab	IL-2 receptors on cells	1-2 mg/kg IV every 2 weeks for five doses after transplantation	N/A
OKT3	CD3 on T cells	5 mg IV × 7-14 days	5 mg IV × 7-14 days
rATG	T cell surface antigens	1-1.5 mg/kg IV × 4-14 days	1-1.5 mg/kg IV × 7-14 days
Anti-CD52	CD52 on T and B cells	30-60 mg × 1 or 2 on days 0 and 2	Same as induction

Table 104-1 Agents used for induction and treatment of T cell–mediated rejection. *IL,* Interleukin; *IV,* intravenously; *NA,* not applicable; *rATG,* rabbit antithymocyte globulin.

Agents Used for Desensitization and Treatment of Antibody-Mediated Rejection			
Treatment	**Mechanism**	**Protocol (Desensitization)**	**Dose (Antibody-Mediated Rejection)**
Plasma exchange	Antibody removal	Two to four sessions or until XM acceptable, combined with IVIG	Two to five treatments, daily or every other day, combined with IVIG
IVIG	Multiple, antibody inhibition?	100-200 mg/kg after plasma exchange until acceptable XM *or* 1-2 g/kg monthly until transplant	100-200 mg/kg after plasma exchange
Rituximab	Anti-CD20 B cell inhibition	375 mg/m^2 (day 15) combined with IVIG 1-2 g/kg (days 1 and 30)	375 mg/m^2 with plasma exchange and IVIG
Bortezomib	Plasma cell inhibition	Not established	1.3 mg/m^2 × four doses over 1-2 weeks, usually combined with plasma exchange and IVIG
Eculizumab	Terminal complement C5 inhibition	Not established	For prevention in +XM transplant: 600-1200 mg weekly × 4 then biweekly until successful antibody reduction
Splenectomy	B cell removal	No longer used	N/A, for severe refractory cases only

Table 104-2 Agents used for Desensitization and Treatment of Antibody-Mediated Rejection. *IVIG,* Intravenous immunoglobulin; *N/A,* not applicable; *+XM,* positive crossmatch.

Desensitization strategies have allowed for transplantation to occur for sensitized patients who otherwise may not be afforded the opportunity. In return, however, these procedures are generally met with high rates of acute rejection, ranging from 20% to 70% (depending on a variety of factors including specific protocol, induction immunosuppression, and immunologic risk), are often humoral in nature, and frequently progress to chronic antibody-mediated injury.[25-26] Despite these pitfalls, short-term graft survival after desensitization has been acceptable,[25] and data suggest a survival benefit out to 8 years for desensitized patients undergoing transplant compared with matched controls undergoing dialysis while on the waiting list.[27] Thus HLA desensitization for highly sensitized transplant candidates may be a reasonable option, and referral to a transplant center with experience in this field is warranted. Common desensitization agents and protocols are listed in Table 104-2.

Maintenance Therapy for the Prevention of Acute Rejection

Current maintenance immunosuppression most commonly includes a CNI, an antiproliferative agent, and corticosteroids. This combination of agents forms the standard against which novel strategies are compared, such as corticosteroid withdrawal and avoidance and CNI withdrawal and avoidance. Cyclosporine has been replaced by tacrolimus as the preferred CNI in the United States and, together with the antiproliferative agent MMF, forms the most common immunosuppressive regimen in current practice in the United States and most Western countries (Table 104-3); cyclosporine and azathioprine remain commonly used agents worldwide.

Immunosuppression Regimens in the United States, 2011	
Induction Regimens at Time of Transplant	
IL-2Ra	20.9%
T cell depleting	58.6%
Maintenance Regimens at Time of Hospital Discharge	
TAC/MMF-MPS/Pred	59.3%
CSA/MMF-MPA/Pred	1.9%
Corticosteroid free (any) TAC/MMF-MPA CSA/MMF-MPS	29.3% 26.3% 0.5%

Table 104-3 Immunosuppression regimens in the United States, 2011. *CSA,* Cyclosporine; *IL-2Ra,* interleukin (IL)–2 receptor antibody; *MMF,* mycophenolate mofetil; *MPA,* mycophenolic acid; *MPS,* mycophenolate sodium; *Pred,* prednisone; *TAC,* tacrolimus. *(Based on OPTN/SRTR Annual Report, 2012.)*

Calcineurin Inhibitors in the Prevention of Acute Rejection

Since the early 1980s when the introduction of cyclosporine resulted in a reduction in the incidence of acute rejection and improvements

in projected graft survival,[28] calcineurin inhibition has been a cornerstone of maintenance immunosuppression. Tacrolimus, first introduced in the 1990s and compared head-to-head with cyclosporine in a number of trials, appears to provide greater protection from acute rejection but with a different side effect profile. A meta-analysis of trials that compared tacrolimus- and cyclosporine-based immunosuppression demonstrated a reduction in risk of acute rejection of 31% but an increase in risk of development of diabetes of 86%. Tacrolimus was also associated with a better death-censored graft survival (hazard ratio [HR] 0.56), particularly at target trough doses below 10 ng/ml, a finding that was not shown in individual studies.[29]

Antiproliferative Agents in the Prevention of Acute Rejection

The first antiproliferative agent used in kidney transplantation, azathioprine, was introduced in the early 1960s and was used initially in conjunction with corticosteroids and later with cyclosporine. Although its development was critical in the advancement of allotransplantation, acute rejection was quite common, with acute rejection rates of 35% to 40% in a number of clinical trials in which cyclosporine, azathioprine, and prednisone were used. Newer antiproliferative agents emerged in the 1990s (MMF) and later the mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus, which significantly reduced the incidence of acute rejection.

Mycophenolate mofetil, a purine antagonist that interferes with DNA synthesis in rapidly dividing cells such as activated lymphocytes, gained popularity after a number of multicenter prospective clinical trials demonstrated an approximately 50% reduction in the incidence of acute rejection compared with azathioprine.[30-31] A large registry analysis suggests that there is a beneficial effect of MMF on graft survival, independent of acute rejection.[32] One drawback of MMF has been gastrointestinal (GI) intolerance, which often results in reduction of therapy with attendant risks of acute rejection[33] and graft loss.[34] An MMF analogue, enteric-coated mycophenolate sodium (EC-MPS), has been developed and appears to be "noninferior" in efficacy to MMF,[35] with fewer GI side effects reported in one open-label study.[36]

Similar to MMF, the mTOR inhibitors sirolimus and everolimus were initially tested in clinical trials as a substitute for azathioprine and demonstrated reductions in acute rejection rates similar to MMF.[37] mTOR inhibitors inhibit the progression from the G_1 to the S phase of the cell cycle and appear to have additional antiproliferative effects on nonimmune cells that may contribute to an increase in side effects (impaired wound healing, lymphocele formation, proteinuria, and slower recovery from delayed graft function) but also may reduce the incidence of viral infection and malignancy.[38-39]

Acute Rejection Rates in Calcineurin Inhibitor– and Corticosteroid-Sparing Immunosuppression Regimens

Given the advances in immunosuppression over the last decade, attempts to eliminate undesirable side effects of immunosuppression have assumed a greater importance in the management of patients. Avoidance of CNIs offers the hope of prolonged graft survival, given the inherent nephrotoxicity of this medication class, whereas avoidance of corticosteroids offers the hope of reducing a number of cosmetic, metabolic, and cardiovascular side effects attributable to prednisone.

Early corticosteroid cessation (within 7 days after transplant) has become increasingly popular in the United States. In 2011 more than 33% of all patients were discharged after transplant without maintenance prednisone therapy. In general, patients at lower immunologic risk (low PRA, first transplants) are selected,[40-41] and immunosuppression includes induction therapy, a CNI, and an antiproliferative agent. Acute rejection rates in single-center studies range from 10% to 15%. In the largest prospective, double-blind, multicenter study of corticosteroid cessation versus standard corticosteroid maintenance to date,[42] a standard corticosteroid taper or a rapid elimination of corticosteroids at 7 days after transplant was compared on the background of induction therapy plus tacrolimus-MMF–based immunosuppression. Patient survival, graft survival, and creatinine clearance were comparable at 5 years. Cardiovascular risk factors and weight gain were not significantly different, but corticosteroid withdrawal was associated with less bone disease, less insulin-requiring new-onset diabetes, and lower triglyceride levels. One cause for concern with corticosteroid withdrawal was that rejection rates were higher in the corticosteroid withdrawal arm (18% vs. 11%, $P = .04$), and a *post hoc* analysis suggested a higher rate of chronic allograft nephropathy in the corticosteroid withdrawal arm. It is unlikely that another study will be performed with this rigor with follow-up for longer than 5 years; therefore clinicians must weigh a higher incidence of rejection versus the potential benefits when counseling patients regarding corticosteroid withdrawal. The study was performed in patients at low immunologic risk without the presence of delayed graft function; therefore consideration for corticosteroid withdrawal is best supported for the patient with a lower expected risk for rejection (low immunologic risk, expected immediate graft function) or high expected risk for corticosteroid-related complications, such as patients with bone disease or diabetes.

Calcineurin inhibitor avoidance has been studied with both dual therapy (MMF and prednisone) and triple therapy with two antiproliferative agents (sirolimus, MMF, and prednisone) in combination with induction therapy. In general, MMF-prednisone maintenance immunosuppression does not appear to be effective in the prevention of rejection (70% incidence in one pilot study[43]), and although single-center studies report acute rejection rates of 6% to 13% with sirolimus-MMF-prednisone therapy,[44-45] a large multicenter trial using this combination and target trough concentrations of sirolimus of 4 to 8 ng/ml also revealed an excessively high acute rejection rate (38%).[46] CNI avoidance was more successful in the Belatacept Evaluation of Nephroprotection and Efficacy as First-Line Immunosuppression Trial (BENEFIT), which compared the costimulation blocker belatacept at two doses with cyclosporine with IL-2Ra induction and mycophenolic acid (MPA)–prednisone maintenance.[47] Despite higher 1-year acute rejection rates in the belatacept arms (22% and 17% for higher and lower intensity, respectively, vs. 7% for cyclosporine), graft survival was comparable and measured glomerular filtration rate (GFR) significantly higher for those receiving belatacept (65 and 63 mL/min for high- and low-intensity belatacept vs. 50 mL/min for cyclosporine). These trends have continued at 3 years of follow-up.[48] Concerning, however, are higher rates of post-transplant lymphoproliferative disorder associated with patients receiving belatacept, primarily in those who received higher-intensity dosages and were Epstein-Barr virus (EBV) seronegative at transplant.

In contrast to their use in complete CNI avoidance strategies, mTOR inhibitors have achieved relative success when used in CNI withdrawal[49-50] and conversion protocols. In one study, patients receiving a CNI, MMF, and prednisone were randomized to continue this regimen or undergo CNI conversion to sirolimus at 1 to 6 months after transplant; rates of acute rejection were comparable and renal function was statistically similar at 2 years.[51] Another study, using a similar approach of CNI conversion to everolimus at 4 to 5 months after transplant, demonstrated equivalent rates of acute

Maintenance Immunosuppression and Reported Rejection Rates in Randomized Multicenter Trials

Regimen	Induction	CNI Dose or Trough Level Goal	Antiproliferative Dosing	Acute Rejection at 6 months
Low Immunologic Risk				
CSA/AZA/Pred		4.0 mg/kg/d	1.5-2 mg/kg/d	36%[26]
CSA/AZA/Pred	IL-2Ra	Not stated	Not stated	22%[14]
CSA/MMF/Pred		150-300 ng/ml × 3 mo, 100-200 ng/ml	1 g bid	24%[40]
CSA/MMF/Pred	IL-2Ra	125-400 ng/ml × 3 mo, 100-300 ng/ml	1 g bid	12%[54]
TAC/AZA/Pred	OKT3 or Atgam	5-14 ng/ml	1.5 mg/kg/d	32%[55]
TAC/MMF/Pred	OKT3 or Atgam	5-14 ng/ml	1 g bid	7%[55]
TAC/MMF/Pred	IL-2Ra	7-16 ng/ml × 3 mo, 5-15 ng/ml	1 g bid	4%[54]
CSA/SRL/Pred		200-350 ng/ml × 1 mo, 200-300 ng/ml × 1 mo, 150-250 ng/ml	2 mg daily	17%[32]
TAC/SRL/Pred		8-16 ng/ml × 3 mo, 5-15 ng/ml	4-12 ng/ml	13%[56]
High Immunologic Risk				
CSA/SRL/Pred	IL-2Ra or rATG	200-300 ng/ml 0-14 d 150-200 ng/ml	10-15 ng/ml	14%[57]
TAC/SRL/Pred	IL-2Ra or rATG	10-15 ng/ml 0-14 d 5-10 ng/ml	10-15 ng/ml	17%[57]
Drug Minimization or Avoidance				
CSA (low)/MMF/Pred	IL-2Ra	50-100 ng/ml	1 g bid	23%[40]
TAC (low)/MMF/Pred	IL-2Ra	3-7 ng/ml	1 g bid	12%[40]
TAC/MMF	IL-2Ra or rATG	10-20 ng/ml × 3 mo, 5-15 ng/ml	1.5 g bid × 14 d 1 g bid	9%[36]
SRL/MMF/Pred	IL-2Ra	N/A	SRL 4-8 ng/ml MMF 1 g bid	38%[40]
Bela/MMF/Pred	IL-2Ra	N/A	1 g bid	22% (MI) 17% (LI)[45]*
CNI → SRL/MMF/Pred	IL-2Ra or rATG or OKT3	N/A	SRL 5-10 ng/ml MMF 1-1.5 g bid	7.4%[49]*
CSA → EVL/MMF/Pred	IL-2Ra	N/A	EVL 6-10 ng/ml MMF 1 g bid	15%[50]*

Table 104-4 Maintenance immunosuppression and reported rejection rates in randomized multicenter trials. Antiproliferative dosage is shown as SRL trough level goals and for MMF as dose. Mycophenolate trough levels are of limited value. For general comparison only. In comparing acute rejection rates from various clinical trials, the study population and treatment algorithms may be different among trials. *AZA,* Azathioprine; *Bela,* belatacept; *CNI,* calcineurin inhibitor; *CSA,* cyclosporine; *EVL,* everolimus; *IL-2Ra,* interleukin (IL)–2 receptor antibody; *MMF,* mycophenolate mofetil; *N/A,* not applicable; *Pred,* prednisone; *rATG,* rabbit antithymocyte globulin; *SRL,* sirolimus; *TAC,* tacrolimus. *Refers to acute rejection rate at 12 months.

rejection (15% in both groups) and significantly improved estimated glomerular filtration rate (eGFR) at 12 months in the conversion group (72 mL/min vs. 62 mL/min in the CNI continuation arm).[52] Widespread acceptance of CNI to mTOR inhibitor conversion strategies has been hindered because of issues with mTOR inhibitor–related side effects and tolerability as well as reluctance to alter immunosuppression in the otherwise stable transplant recipient.

Acute rejection rates by treatment regimen reported in recent multicenter clinical trials are shown in Table 104-4. These rates are often higher than rates reported to registries (see Fig. 104-1) because of the more rigorous follow-up and mandatory reporting within the context of clinical trials.

TREATMENT

Acute T Cell–Mediated Rejection

Treatment of T cell–mediated acute rejection is often directed by the findings on biopsy and the clinical response to pulse corticosteroids. For the patient with graft dysfunction and biopsy-proven rejection, treatment with intravenous methylprednisolone 3 to 5 mg/kg (250 to 500 mg/d) for 3 to 5 days is often effective if the histologic injury is tubulointerstitial (Banff class IA or IB). Remarkably few studies of the clinical response to corticosteroids in the treatment of acute rejection have been performed under modern immunosuppression, but prior data suggest that 60% to 70% of patients will respond with improved urine output and decreasing serum creatinine within 5 days. If there is inadequate response after corticosteroid pulse therapy or if there is vascular involvement (Banff class IIA, IIB), corticosteroids often must be supplemented with T cell–depleting antibody therapies in a similar dosage strategy but with a longer treatment course when compared with their use for induction (see Table 104-1). Most studies have used these agents in 7- to 14-day treatment courses, with no clinical trials having investigated the efficacy of shorter courses versus longer courses. For patients who are on a maintenance regimen that is not tacrolimus based, tacrolimus conversion may also be considered in the setting of rejection with an inadequate response to corticosteroids,[53] whereas for patients on a corticosteroid-free regimen, reinstitution of maintenance prednisone may be warranted.[54]

For patients who do not respond adequately to corticosteroids, T cell–depleting agents are required. In a meta-analysis of randomized trials comparing monoclonal (OKT3) versus polyclonal (antilymphocyte globulin, antithymocyte globulin) antibody therapy, no differences were noted in reversal of rejection, prevention of subsequent rejection, or prevention of graft loss, but OKT3 (no longer

manufactured) was three times more likely to induce reactions of fever, chills, and malaise.[55] A typical course of rATG for T cell–mediated rejection is 1.5 mg/kg for 4 to 14 days dictated by clinical response and absolute lymphocyte counts, again with no controlled study having compared one treatment regimen versus another.

Acute Antibody-Mediated Rejection

Treatment of acute humoral rejection is indicated when the triad of graft injury, C4d staining in peritubular capillaries on biopsy, and circulating donor-specific antibody is present, but should also be considered in high-risk circumstances (prior desensitization or known donor-specific antibody) even if all three criteria are not met. High-quality randomized trials investigating treatment options for acute humoral rejection are lacking,[56] and strategies are generally dictated by center experience. Traditionally, treatment has entailed removal of the pathogenic immunoglobulin(s) with plasma exchange and inhibition or suppression of antibody production with IVIG. In general, at least five plasma exchange treatments should be administered with 1 to 2 g/kg total dose IVIG. Because IVIG is removed by plasma exchange, a common strategy is to administer IVIG 100 to 200 mg/kg after each exchange. For refractory acute humoral rejection, rituximab may be considered despite targeting B cells at an earlier phase of maturation than the antibody-producing plasma cell line.[57] In contrast, the proteosome inhibitor bortezomib directly inhibits antibody-producing plasma cells and has been reported in single-center case series as a potential treatment for refractory antibody mediated rejection, usually in combination with other modalities such as plasma exchange and IVIG.[58] Eculizumab is a humanized monoclonal antibody that blocks terminal complement activation and has been shown to significantly reduce the risk of acute humoral rejection as well as subsequent transplant glomerulopathy in patients who have undergone positive crossmatch kidney transplant.[59] Finally, there are case reports of splenectomy for refractory acute humoral rejection.[60] These therapies are typically coupled with targeted T cell therapy such as high-dose corticosteroids and/or depleting antibody therapy, because histologic evidence of mixed T cell rejection is often present and helper T cell function may contribute to an enhanced B cell response. Agents used for treatment of acute humoral rejection are summarized in Table 104-2.

Chronic Rejection (T Cell and/or Antibody Mediated)

T cell– or antibody-mediated injury in a graft without features of acute tissue injury remains a therapeutic dilemma in kidney transplantation. No specific intervention has been proven to be effective in reversing the chronic tissue injury; however, consideration should be given to optimizing or enhancing the maintenance immunosuppression by transitioning to tacrolimus-MMF therapy or increasing the dose of these agents if CNI nephrotoxicity is not identified.[61] Any intervention should be weighed against the potential for risk of enhanced immunosuppression and the lack of any long-term data describing the impact of enhancing immunosuppression. This topic is discussed in greater detail in Chapter 107.

PROGNOSIS

Episodes of acute rejection may predispose to chronic graft dysfunction, with increased histologic findings of chronic rejection and/or interstitial fibrosis and tubular atrophy and clinical findings of reduced graft survival. The clinical response to antirejection therapy appears to be critical in this regard, because the change in renal function from 6 and 12 months after transplant is more predictive of long-term graft survival than the occurrence of prior episodes of acute rejection.[62] Two analyses (one examining the U.S. experience[63] and another examining the Australia–New Zealand experience[64]) have shed light on risk factors for graft loss after episodes of acute rejection. In general, acute T cell–mediated rejection that responds to therapy with return to near-baseline renal function does not portend worse graft survival. However, vascular rejection, late rejection (after 3 months), and rejection that does not respond to within 75% of baseline serum creatinine are associated with worse graft outcomes. Although acute rejection rates have fallen significantly over the past decade, graft survival rates have not improved in similar fashion; one explanation for this finding is that the rejection now identified tends to be less responsive to therapy, with fewer patients achieving near-baseline serum creatinine levels. The long-term prognosis after episodes of acute antibody-mediated rejection has not been fully defined in prospective analyses; however, from single-center and retrospective studies it appears that episodes of acute humoral rejection likely affect long-term graft survival. Similarly, the emergence of *de novo* HLA antibodies at any time after transplant has been shown to be associated with a 5% worse graft survival per year compared with patients who do not form anti-HLA antibodies.[65] For this reason, patients who have experienced episodes of acute rejection must be rigorously monitored with optimization of baseline maintenance immunosuppression. Remaining questions include the value of escalated immunosuppression such as longer-term scheduled antibody therapy, or additional IVIG treatment for those without adequate clinical response or with persistently elevated titers of HLA antibodies.

SUMMARY

Acute rejection has decreased in incidence over time but remains an important cause of graft dysfunction and progressive graft loss, particularly when antibody-mediated forms of injury are identified. Although many immunosuppressive regimens have been used to minimize both the incidence of rejection and the side effect profile of chronic immunosuppressive agents, the most effective maintenance immunosuppressive regimen for the prevention of rejection is a three-drug regimen consisting of tacrolimus, mycophenolate, and prednisone. Higher-risk patients benefit from induction therapy with lymphocyte depleting agents for the prevention of rejection. Alternative immunosuppressive strategies may be considered for side effects or toxicities related to immunosuppressive agents, which in clinical practice has led to a myriad of treatment combinations (see Table 104-4). Until there is an accurate means of determining an individual patient's degree of immune function, suppression, or graft-specific immunity, the clinician must determine the best treatment regimen based on potency (minimizing rejection) and tolerability.

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CHAPTER 105

Medical Management of the Kidney Transplant Recipient: Infections, Malignant Neoplasms, and Gastrointestinal Disorders

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Although patient and graft survival rates in recipients of solid organ transplantation have improved significantly, malignant neoplasms and infectious complications continue to adversely affect post-transplantation morbidity and mortality. Antimicrobial prophylaxis has reduced the incidence of previously common infections such as cytomegalovirus (CMV) or *Pneumocystis,* but new or resistant microbial pathogens have emerged as a consequence of prophylactic antimicrobials and nosocomial exposures. In addition, donor-derived infections or malignancy can arise as a result of delayed donor seroconversion after a recent acute infection, unidentified pathogens in an organ donor, occult neoplastic disease at the time of organ procurement, or malignant transformation of donor cells. This chapter discusses infections and post-transplantation–related malignant neoplasms in recipients of kidney transplant. Post-transplantation infectious- and drug-related gastrointestinal complications are also discussed.

INFECTIOUS DISEASES

Infection follows cardiovascular disease as the second most common cause of death with a functioning graft in kidney transplant recipients. Predisposing risk factors include immunosuppression, indwelling Foley or vascular catheters, surgical drains, drug-induced leukopenia, and metabolic derangement. Epidemiologic exposures (travel to regions with endemic pathogens), shifts in nosocomial flora associated with repeated antimicrobial exposures (antimicrobial resistance), and improvement in molecular diagnostic assays have also contributed to the emergence of novel infections and changes in the epidemiology of infections.[1]

Immunizations Before and After Transplantation

All kidney transplant candidates should receive immunization for hepatitis B, pneumococcus, and other standard immunizations appropriate for age. Up-to-date recommendations for routine adult immunizations are available through the Centers for Disease Control and Prevention website (www.cdc.gov/vaccines/schedules/downloads/adult/adult-schedule.pdf). Vaccinations should be administered at least 4 to 6 weeks before transplantation to achieve optimal immune response and to minimize the possibility of live vaccine–derived infection in the post-transplantation period. Household members, close contacts, and health care workers should also be fully immunized.

A minimum of 4 weeks should elapse between live virus vaccine administration and transplantation. Live virus or live organism vaccines should be avoided after transplantation. These include measles-mumps-rubella (MMR), live oral polio and smallpox (vaccinia) (which are also contraindicated for household contacts), varicella, yellow fever, adenovirus, live oral typhoid (Ty21a), bacillus Calmette-Guérin (BCG), and intranasal influenza vaccine. In addition, exposure to persons who have chickenpox or herpes zoster should be avoided until the lesions have crusted over and no new lesions are appearing. Immunizations using inactivated or killed microorganisms, components, and recombinant moieties are safe for transplant recipients. These include hepatitis A and hepatitis B, pneumococcal, *Haemophilus influenzae* type b, inactivated polio, diphtheria-pertussis-tetanus (DPT), and *Neisseria meningitidis* vaccines.

Infection with influenza A (H1N1) virus has emerged as an important cause of morbidity and mortality in the general and dialysis population. Infected patients on chronic dialysis treatment were found to have a 10-fold higher mortality rate compared with the general population. Recipients of solid organ transplants have similarly been reported to be at risk for more severe disease. Hence, unless contraindicated, influenza A (H1N1) vaccine should be considered in all prospective kidney transplant candidates.

Most centers restart vaccinations 3 to 6 months after transplantation. Vaccination before the first 3 to 6 months after transplantation may result in suboptimal response and protection because of heavy immunosuppression. Currently existing data show no conclusive evidence for a link between vaccination and allograft dysfunction.[2] For recommendations for prophylaxis or vaccination for transplant recipients who travel to countries where endemic infections such as malaria are present, please refer to reference 3. Recommended immunizations before and after transplantation are listed in Table 105-1.

Infectious Causes

Both the type and occurrence of infections in the immunocompromised transplant recipient follow a "timetable pattern" (Table 105-2).[1]

Donor-Derived Infections

Donor-derived infections have remained the focus of increased attention since the 2007 report of transmission of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) from an initially antibody-negative donor to four transplant recipients. Other reported donor-transmitted blood-borne and kidney infections include viral (hepatitis B virus [HBV], CMV, and BK virus [BKV], among others), parasitic (malaria, *Babesia,* and *Balamuthia*), bacterial (from undiagnosed bacteremia or renal infections), and fungal (*Candida* species) infections. In recent years, allograft-transmitted infections including lymphocytic choriomeningitis virus, West Nile virus, amebic meningitis, and rabies have been added to the list of unusual viral infections. In addition, transmission of common organisms

including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and azole-resistant *Candida* species occurs with increased frequency despite routine surgical prophylaxis because of the emergence of antimicrobial resistance in both hospital and community settings. Currently, most organ procurement organizations in the United States perform nucleic acid testing (NAT) in an effort to more precisely identify HIV and hepatitis infections during the window period. High vigilance for donor-derived infections must be maintained.

Recommended Immunizations Before and After Transplantation*

Vaccine	Before Transplantation	After Transplantation
Measles-mumps-rubella	X	—
Diphtheria-tetanus-pertussis	X	Diphtheria and tetanus[a]
Varicella	X	Contraindicated
Poliovirus	X	Inactivated polio vaccine[b]
Haemophilus influenzae type b	X	X
Influenza	X	X[c]
Pneumococcus	X	X[d]
Hepatitis B	X	X[e]
Hepatitis A	X	X[f]
Human papillomavirus (HPV)	X[g]	—
Neisseria meningitidis	X[h]	X[h]
Zostavax	X[i]	—

Table 105-1 Recommended immunizations before and after transplantation. All patients who are at least 1 month post-transplant should receive seasonal influenza vaccine.[7] [a]Booster every 10 years. [b]For travelers to endemic areas (i.e., some parts of Asia, Africa). [c]Annually. [d]Every 3-5 years. [e]Monitor titers. [f]For travelers to endemic areas. [g]Nonpregnant female transplant candidates ages 9-26. [h]Recommended for military members; travelers to high-risk areas; properdin-deficient or terminal complement component–deficient patients; patients with functional or anatomic asplenia; college freshmen living on campus (American Society of Transplantation Infectious Diseases Guidelines[3]). [i]Consult with transplant infectious disease specialist.

Month 1 After Transplantation

In the first month after transplantation, donor- and recipient-derived infections with common nosocomial bacterial microorganisms and *Candida* species predominate. Infections caused by multidrug-resistant bacteria are center specific. Infections caused by multidrug-resistant bacteria including gram-positive bacteria (MRSA, VRE), extended-spectrum β-lactamases (ESBLs), gram-negative bacilli, and multidrug-resistant nonfermentative gram-negative bacilli have emerged as important causes of morbidity and mortality in organ transplantation worldwide. Strict adherence to isolation measures and proper hand washing should not be overlooked.

Most bacterial infections during this period involve wounds, catheters, and drainage sites. Aspiration pneumonia and urinary tract infections (UTIs) are common. The U.S. Renal Data System database revealed a cumulative UTI incidence of 17% during the first 6 months after transplantation and 60% at 3 years for women and 47% for men. Infections specific to kidney transplant recipients include perinephric fluid collections caused by lymphoceles, wound hematomas, or urine leaks; indwelling urinary stents; and UTIs secondary to urinary tract abnormalities, such as ureteral stricture, vesicoureteral reflux, or neurogenic bladder. Most UTIs are caused by gram-negative bacteria (*Escherichia coli,* Enterobacteriaceae, and *Pseudomonas*) and gram-positive bacteria *(Enterococcus).* Preventive measures for UTIs include early urethral catheter removal and antibiotic prophylaxis. Trimethoprim-sulfamethoxazole or ciprofloxacin prophylaxis during the first 3 to 6 months after transplantation may reduce the risk of UTIs threefold[4] and essentially eliminates urosepsis unless anatomic or functional derangement of the urinary tract is present. Strict aseptic surgical techniques and perioperative use of first-generation cephalosporins reduce the incidence of wound infections. Although uncommon, donor or recipient pretransplant colonization with multidrug-resistant strains may represent an important risk factor for infection with multidrug resistant bacteria in the post-transplant period. Except for herpes simplex virus (HSV), viral infections are uncommon during this period.

Months 1 to 6

During months 1 to 6, opportunistic infections secondary to immunosuppression are most common. Viral infections such as CMV, HSV, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), HBV, and HCV may occur from exogenous infection or reactivation of latent disease as a result of the immunosuppressed state. Reactivation

Timetable of Infections

Month 1 After Transplant	Months 1-6	After 6 Months
Bacterial infections (sources and sites) Urinary tract Respiratory Catheters, drainage sites Wound Intra-abdominal infections* Bacteremia Center-dependent multidrug-resistant species, *Clostridium difficile* Recipient pre-Tx colonization with multidrug-resistant species or untreated infection **Viral:** HSV, other viral infections uncommon **Fungal:** *Candida,* azole-resistant *Candida* species (recipient pre-Tx colonization or donor derived) **Organisms transmitted with donor organ** (see text)	**Opportunistic or unconventional infections** **Viral:** CMV, HHV-6, HHV-7, HBV, HCV, EBV, VZV, influenza, RSV, adenovirus, BK infection **Fungal:** *Aspergillus* species, *Cryptococcus, Mucor* **Bacterial:** *Nocardia, Listeria, Mycobacterium* species, *Legionella,* tuberculosis **Parasitic:** *Pneumocystis jiroveci, Toxoplasma* and *Strongyloides* species, leishmaniasis, *Trypanosoma cruzi*	**Late opportunistic infections:** *Cryptococcus,* CMV retinitis or colitis, VZV, parvovirus B-19, BK virus, *Listeria,* tuberculosis **Persistent infections:** HBV, HCV **Associated with malignancy:** EBV, papillomavirus, HSV, HHV-8 **Community acquired** **Unusual sites** (e.g., paravertebral abscess)

Table 105-2 Timetable of infections. Geographically focused infections, such as malaria, leishmaniasis, trypanosomiasis, and strongyloidiasis, will need to be considered in certain patients. *Sources of infections specific to recipients of renal transplant include perinephric fluid collections (e.g., lymphoceles, wound hematomas, urine leaks), indwelling urinary stents, or anatomic or functional genitourinary tract abnormalities (e.g., ureteral stricture, vesicoureteric reflux, neurogenic bladder). *CMV,* Cytomegalovirus; *EBV,* Epstein-Barr virus; *HBV,* hepatitis B; *HCV,* hepatitis C; *HHV,* human herpes virus; *HSV,* herpes simplex virus; *pre-Tx:* Pre-transplant; *RSV,* respiratory syncytial virus; *VZV,* varicella-zoster virus. *(Modified from reference 59.)*

Suggested Prophylactic Therapy for Recipients of Kidney Transplants

Regimen	Comments
Trimethoprim-sulfamethoxazole (TMP-SMX)* (80/400 mg) one tablet daily × 6-12 mo	Its routine use reduces or eliminates the incidence of *Pneumocystis jiroveci, Listeria monocytogenes, Nocardia asteroides,* and *Toxoplasma gondii.* In renal transplant recipients, TMP-SMX × 6 mo reduces the incidence of UTIs threefold.
Dapsone† > Atovaquone > monthly aerosolized pentamidine‡	Replaces TMP-SMX for patients with sulfa allergies. Consider adding fluoroquinolone or another agent for antibacterial activity.
Nystatin 100,000 units/ml, 4 ml after meals and before bedtime *or* Fluconazole§ 200 mg one tablet daily × 2 months	For fungal prophylaxis. Close monitoring of cyclosporine or tacrolimus or mTOR inhibitor levels is required when starting and stopping antifungal agents.
Acyclovir, valganciclovir, ganciclovir	For CMV prophylaxis, see Box 105-1.

Table 105-3 Suggested prophylactic therapy for recipients of kidney transplants. *CMV,* Cytomegalovirus; *mTOR,* mammalian target of rapamycin; *UTI,* urinary tract infection. *The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggest UTI prophylactic therapy for at least 6 months after transplantation. For patients receiving sirolimus immunosuppression, we recommend 1 year of therapy for *Pneumocystis* pneumonia prophylaxis. †Check glucose-6-phosphate dehydrogenase deficiency before initiation of therapy. ‡In order of preference. §Fluconazole recommended for recipients of combined kidney-pancreas or combined kidney-liver transplants. Consider reinstituting prophylactic therapy × 3 months after acute rejection episodes requiring intensification of immunosuppression.

or *de novo* HCV infection remains an important cause of morbidity and mortality after transplantation because of the lack of effective antiviral drugs and the risk of precipitating acute allograft rejection associated with interferon therapy. Repeated courses of antibiotics and corticosteroid therapy increase the risk of fungal infections, whereas viral infections not only may result from immunosuppression but may further impair immunity and increase the risk for additional opportunistic infections. Opportunistic infections may occur with *Pneumocystis jiroveci* (previously called *Pneumocystis carinii*), *Aspergillus* species, *Listeria monocytogenes, Nocardia* species, and *Toxoplasma gondii.* Trimethoprim-sulfamethoxazole prophylaxis (see Table 105-3 for trimethoprim-sulfamethoxazole allergy) eliminates or reduces the incidence of *Pneumocystis*, *L. monocytogenes* meningitis, *Nocardia* species infection, and *T. gondii.* Reactivation of latent infection such as *Mycobacterium tuberculosis, Trypanosoma cruzi, Leishmania* species, *Strongyloides stercoralis, Cryptococcus neoformans, Histoplasma capsulatum,* and *Coccidioides* and *Paracoccidioides* species may be observed. Community-acquired respiratory viruses remain a common hazard in these vulnerable immunocompromised patients during this time period. Clinically, patients may present with pneumonitis, viremia, or tissue-invasive disease such as hepatitis or carditis.[1] Over the past two decades, BK polyomavirus–associated clinical syndromes have emerged as important complications in kidney transplant recipients (discussed further under BK infection).

After 6 Months

After 6 months, the infection risk is largely a function of chronic maintenance immunosuppression, exposure to T cell–depleting agents, graft function, and epidemiologic exposures. In essence, patients can be arbitrarily divided into three categories in terms of infection risks.

The first category consists of the majority of transplant recipients (70% to 80%), who have satisfactory or good allograft function, relatively low doses of immunosuppressants, and no history of chronic viral infection. The risk of infection is similar to that of the general population, with community-acquired respiratory viruses constituting the major infective agents. Opportunistic infections are unusual unless environmental exposure has occurred.

The second group (approximately 10% of patients) consists of those with chronic viral infection that may include HBV, HCV, CMV, EBV, BKV, or papillomavirus. In the setting of immunosuppression, such viral infections may lead to the development of progressive liver disease or cirrhosis (HBV, HCV), BK nephropathy, post-transplant lymphoproliferative disease (EBV), or squamous cell carcinoma (papillomavirus). The use of alemtuzumab (a humanized monoclonal antibody directed against CD52 found on T and B cells) has been reported to be associated with increased risk of late invasive viral and fungal infections because of its effect on profound and prolonged pan–T cell depletion. New infections occurring in this time period often reflect new exposures (e.g., *L. monocytogenes* [dietary indiscretions], Lyme disease, and malaria [travelers to endemic areas]).[1]

The third group (approximately 10% of patients) consists of those who experience multiple episodes of rejection requiring repeated exposure to heavy immunosuppression. These patients are the most likely to develop chronic viral infections and superinfection with opportunistic infections. Causative opportunistic pathogens include *Pneumocystis, Listeria, Nocardia, Cryptococcus,* and geographically restricted mycoses (coccidioidomycosis, histoplasmosis, blastomycosis, and paracoccidioidomycosis). We advocate lifelong antifungal prophylaxis in high-risk transplant recipients such as those with a history of past infection or those who live in endemic areas. Environmental exposure (primarily avoidance of pigeons and areas of active building construction) should be minimized.

MANAGEMENT AND PROPHYLACTIC THERAPY FOR SELECTED INFECTIONS

The following section discusses selected important infections and suggested approaches to their management. Suggested prophylactic therapy in kidney transplant recipients is shown in Table 105-3.

Cytomegalovirus Infection

Cytomegalovirus infection may cause primary infection in a seronegative recipient (donor seropositive, recipient seronegative), reactivation of endogenous latent virus (donor seropositive or seronegative, recipient seropositive) or superinfection with a new virus in a seropositive recipient (donor seropositive, recipient seropositive). Primary CMV infection is usually more severe than reactivated infection or superinfection.

Clinical Manifestations

Cytomegalovirus infection may be asymptomatic, presenting as a mononucleosis-like syndrome or influenza-like illness with fever and leukopenia or thrombocytopenia, or a severe systemic disease. Hepatitis, esophagitis, gastroenteritis with colonic ulceration, pneumonia, carditis, and even otitis may occur. In enterically drained pancreas transplantation, CMV has been reported to cause a bleeding ulcer from the duodenal segment. Although chorioretinitis (associated with retinal hemorrhage) is a common manifestation of CMV disease in acquired immunodeficiency syndrome (AIDS)

patients, it seldom occurs in solid organ transplant recipients. Nonetheless, any organ system may be affected by CMV. Clinical manifestations usually occur 1 to 4 months after transplantation except for chorioretinitis, which occurs later in the transplant course. Results of quantitative CMV assays of serum in patients with invasive colitis and gastritis or neurologic disease including chorioretinitis are often negative. Diagnosis in such patients may require invasive testing and biopsies.

Immunomodulating Effects of Cytomegalovirus Infection

Cytomegalovirus infection is associated with immune modulation and dysregulation of helper and suppressor T cells. CMV infection may be a risk factor for acute and chronic allograft rejection, secondary infection with opportunistic agents (such as *Pneumocystis, Candida,* and *Aspergillus*), and reactivation of human herpesvirus 6 (HHV-6) and HHV-7 and may favor development of post-transplant lymphoproliferative disease. CMV infection is also associated with acceleration of HCV infection and the development of new-onset diabetes after transplantation.[5]

Risk Factors for Cytomegalovirus Infection

Donor and recipient seropositive status and the use of blood products from CMV-seropositive donors are well-established risk factors for CMV infection. Other factors associated with an increased risk of CMV infection include the use of antilymphocyte antibodies, prolonged or repeated courses of antilymphocyte preparations, comorbid illnesses, concomitant HHV-6 and HHV-7 viral infections, neutropenia, lack of CMV-specific $CD4^+$ and $CD8^+$ T cells, and acute rejection episodes. Mycophenolate mofetil (MMF) has been reported to increase the risk of CMV viremia and disease in some studies, especially in patients receiving more than 3 g/day. Although the cause-effect relationship of allograft rejection and CMV infection remains conjectural, several studies suggest that one may increase the risk of the other, possibly because of the release of inflammatory cytokines. Prevention of CMV infection, for example, results in a lower incidence of graft rejection.[6]

Prevention

Prophylactic therapy begins in the immediate postoperative period. Preemptive therapy involves treatment of those who are found to seroconvert by quantitative laboratory assays of the blood, such as CMV DNA polymerase chain reaction (PCR) or pp65 antigenemia during surveillance studies. The former assay is highly specific and sensitive for the detection of CMV viremia. The latter is a semiquantitative fluorescent assay in which circulating neutrophils are stained for nonspecific uptake of CMV early antigen (pp65). Screening for CMV is best performed using NAT methods, although CMV antigenemia assays are still being used by some centers. Currently, CMV prophylactic therapy is recommended over initiation of preemptive treatment after detection of CMV viremia or antigenemia.[7]

Various prophylactic and preemptive protocols have been developed. Oral acyclovir provides effective CMV prophylaxis only in recipients of seronegative donor organs. Oral or intravenous ganciclovir or oral valganciclovir provides superior prophylactic or preemptive therapy against primary CMV infection or CMV reactivation. The 2-year results of the Improved Protection Against Cytomegalovirus in Transplant (IMPACT) study demonstrated that in high-risk CMV D+/R– recipients, once-daily oral valganciclovir prophylaxis for 200 days provided a significant reduction in the incidence of CMV disease compared with the 100-day once-daily prophylaxis. Extended prophylaxis to 200 days did not increase the rate of ganciclovir-resistant CMV disease.[8] Furthermore, a cost-effectiveness model also demonstrated that extended prophylaxis using valganciclovir was cost-effective in reducing the incidence of events associated with CMV disease over a 5- and 10-year period.[9]

Seronegative individuals who receive organs from latently infected seropositive donors are at greatest risk for primary infection and severe CMV disease. Delayed-onset (or late-onset) CMV disease developing soon after completion of antiviral prophylaxis occurs in 15% to 38% of high-risk CMV D+/R– solid organ transplant recipients who received 3-month CMV prophylaxis[10] and is associated with poor patient and graft survival. In high-risk kidney transplant patients, the IMPACT study showed that CMV disease developed in 36.8% versus 16.1% in the 100- versus 200-day valganciclovir prophylaxis groups, respectively, at 12 months after transplantation. Other suggested risk factors for delayed-onset CMV disease include allograft rejection, overimmunosuppression, and lack of CMV-specific immunity.[11] The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines suggest oral ganciclovir or valganciclovir in CMV D+/R– or D+/R+ for at least 3 months after transplantation and for 6 weeks after treatment with T cell–depleting antibodies. Suggested CMV prophylaxis protocol is shown in Box 105-1.

Treatment

The 2010 International Consensus guidelines recommend valganciclovir (900 mg orally every 12 hours, adjusted according to glomerular filtration rate [GFR]), or intravenous ganciclovir (5 mg/kg every 12 hours, adjusted according to GFR) for nonsevere CMV disease. In patients with severe or life-threatening disease and in those with

Suggested Cytomegalovirus (CMV) Prophylaxis Protocol

For CMV (–) recipients of a CMV (–) organ
- Acyclovir 400 mg daily (for herpes prophylaxis) × 3 months
- CMV DNA q2wk × 3 months

For CMV (–) recipients of a CMV (+) organ
- During antibody treatment: DHPG* 5 mg/kg IV qd
- After antibody treatment: valganciclovir 900 mg† PO qd × 6 months
- If no antibody treatment: valganciclovir 900 mg PO qd × 6 months
- CMV DNA q2wk × 3 months

For CMV (+) recipients of a CMV (–) organ
- During antibody treatment: DHPG 5 mg/kg IV qd
- After antibody treatment: valganciclovir 900 mg PO qd × 6 months
- If no antibody treatment: valganciclovir 900 mg daily × 3 months
- CMV DNA q2wk × 3 months

For CMV (+) recipients of a CMV (+) organ
- During antibody treatment: DHPG 5 mg/kg IV qd, then
- After antibody treatment: valganciclovir 900 mg PO qd × 6 months
- If no antibody treatment: valganciclovir 900 mg daily × 3 months
- CMV DNA q2wk × 3 months

Box 105-1 Suggested cytomegalovirus prophylaxis protocol. If CMV status is unknown, give intravenous DHPG until CMV status determined. *DHPG,* 9-(1,3-Dihydroxy-2-propoxymethyl) guanine. *Dose adjustment for renal function necessary. †Although low-dose valganciclovir 450 mg daily has been used successfully by some centers, there are insufficient data to support the routine use of low-dose valganciclovir. Such an approach may increase the risk of breakthrough disease and development of resistance in CMV (–) recipient of a CMV (+) organ.[12a]

impaired absorption or who are intolerant of oral medication, intravenous ganciclovir should be used. Antiviral drug dose reduction because of side effects should be done judiciously to avoid loss of efficacy. Reduction or withholding of mycophenolic acid products, azathioprine (AZA), or trimethoprim-sulfamethoxazole should be considered before valganciclovir or ganciclovir dose reduction. Severe leukopenia (absolute neutrophil count <500 to 1000/mm^3) can be treated with granulocyte colony-stimulating factor (G-CSF). Treatment should be continued until clearance of viremia as assessed by PCR or antigenemia, but not shorter than 2 weeks. Reduction of immunosuppression should be considered in severe disease, in slow responders or nonresponders, and in those with high viral loads or leukopenia. The use of CMV immunoglobulin in the treatment of CMV disease may be considered as adjunctive therapy in individuals with hypogammaglobulinemia, in nonresponders to standard therapy, or in those with severe forms of CMV disease such as pneumonitis.[12]

Laboratory monitoring for CMV should be performed weekly during treatment. Results of at least two CMV PCR assays performed 1 week apart should be negative before discontinuation of treatment. Secondary prophylaxis with 900 mg valganciclovir once daily for 1 to 3 months should be considered. Studies evaluating the clinical predictors of relapse after treatment of primary gastrointestinal CMV disease in solid organ transplant recipients showed that only extensive involvement of the gastrointestinal tract was significantly associated with CMV relapse, whereas seroconversion, viral load, treatment duration, maintenance therapy, and endoscopic evidence of resolution of gastrointestinal disease did not translate into a lower risk of CMV relapse.[11]

An emergence of ganciclovir-resistant CMV has been reported to be a result of a mutation in a viral kinase (UL97) that prevents the phosphorylation of ganciclovir to its active form. Cidofovir and foscarnet should be reserved for those with clinically suspected ganciclovir-resistant strains because of their associated nephrotoxicity and potential synergistic nephrotoxicity with calcineurin inhibitors (CNIs). Nonetheless, mutation in the *UL54* gene, which encodes for CMV DNA polymerase (a target for all currently available systemic anti-CMV drugs) could lead to cidofovir or foscarnet resistance or cross-resistance among ganciclovir, foscarnet, and cidofovir.[10]

Candida Infections

Candida infections are common in transplant recipients; *Candida albicans* and *Candida tropicalis* account for 90% of the infections. Risk factors include diabetes, high-dose corticosteroids, broad-spectrum antibacterial therapy, indwelling urinary tract device, and rarely, donor-derived candidiasis (estimated frequency 1:1000 in one study).[13] The latter is thought to be caused by contamination of the preservation fluid before or at the time of organ procurement, or contamination from a ruptured abdominal viscus. When *Candida* is visualized on stains or grown in preservation fluid or when organs are recovered from donors with bowel perforation, cultures from the blood, urine, and other clinically relevant sites should be obtained in the recipient and antifungal therapy initiated.[14] Fluconazole is considered the drug of choice for the prevention or treatment of donor-derived candidiasis.[14]

Superficial candidal infections involving the mouth or intertriginous areas can be treated with nystatin and topical clotrimazole, whereas candidal UTIs require systemic antifungal therapy (see Chapter 55). Whenever possible, foreign objects such as bladder catheter, surgical drains (such as percutaneous nephrostomy tube), and urinary stents should be removed. Management of asymptomatic candiduria in immunocompromised patients is discussed in Chapter 55. Systemic antifungal therapy is indicated in the presence of any blood culture positive for *Candida* species.

BK Virus Infection

BK virus is a ubiquitous human virus with a peak incidence of primary infection in children 2 to 5 years of age and a seroprevalence rate of greater than 60% to 90% among the adult population worldwide. After primary infection, BKV preferentially establishes latency within the genitourinary tract and frequently reactivates in the setting of immunosuppression. In kidney transplant recipients, BKV is associated with a range of clinical syndromes including asymptomatic viruria with or without viremia, ureteral stenosis and obstruction, interstitial nephritis, and BK allograft nephropathy (BKN). Most series have reported that 30% to 40% of renal transplant recipients develop BK viruria, 10% to 20% develop BK viremia, and 2% to 5% develop BKN. The highest prevalence of BK viruria and viremia occurs at 2 to 3 months, and 3 to 6 months, respectively. The risk for BK viremia increases when urine viral load is greater than 10^4 copies/ml, and BKN is unusual in the absence of BK viremia. However, PCR assays are not standardized, and the sensitivity and specificity of the assays may vary among centers.

BK is an important cause of allograft dysfunction and graft loss, and commonly presents with an asymptomatic rise in serum creatinine during the first post-transplantation year. However, BKN may occur as early as the first week and as late as 6 years after transplantation. Diagnosis is made by allograft biopsy that demonstrates BK viral inclusions in renal tubular cell nuclei and occasionally in glomerular parietal epithelium (Fig. 105-1). Interstitial mononuclear inflammation, often with many plasma cells, degenerative changes in tubules, and focal tubulitis, may mimic acute rejection (see Fig. 105-1). BKN often is associated with very focal and sharply demarcated areas of tubulointerstitial inflammation, corresponding to foci of viral infection. Additional diagnostic studies include immunohistochemistry, *in situ* hybridization, or electron microscopy. Approximately 50% of biopsies showing BKN have tubular basement membrane deposition of BK viral antigen containing immune complexes. BK infection and acute rejection may occur simultaneously, and distinguishing between BKN and acute rejection or the presence of both can be a diagnostic challenge. In the late stage of BKN, only a few characteristic intranuclear inclusions are seen and the histopathologic changes may be indistinguishable from those of chronic rejection or nonspecific interstitial fibrosis and scarring, although inflammation may be more marked in BKN. The histologic classification system for BKN based on the degree of active inflammation, acute tubular injury, and tubulointerstitial scarring may have prognostic significance. One single-center retrospective study showed that among individual histologic parameters, only a higher degree of interstitial inflammation was an independent predictor of BKN progression at 3-month follow-up.[15]

Treatment strategies for BK viremia with or without BK nephropathy vary among centers. However, immunologic containment of BKV replication is accepted as the mainstay of therapy. Suggested strategies for reduction in immunosuppression include reduction or discontinuation of antimetabolites (MMF or AZA), judicious reduction in CNI or corticosteroid therapy, or immunosuppressant class switching.

Registry analyses suggest that tacrolimus is associated with a higher risk of BK reactivation than cyclosporine A (CSA).[16] The DIRECT (*D*iabetes *I*ncidence After *R*enal Transplantation: Neoral *C*[2] Monitoring Versus *T*acrolimus) (in which *de novo* transplant recipients were randomized to receive either CSA or tacrolimus)

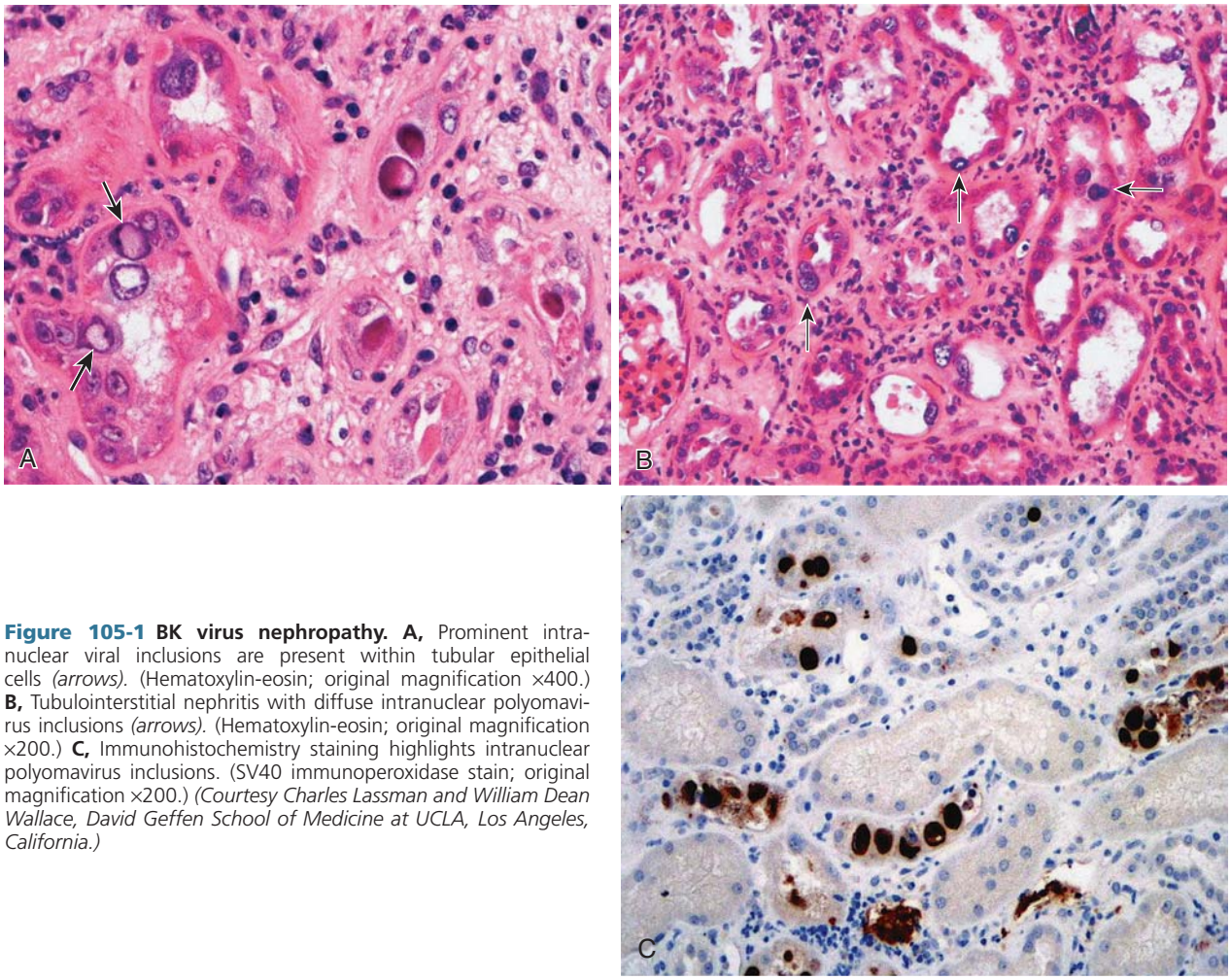

Figure 105-1 BK virus nephropathy. A, Prominent intranuclear viral inclusions are present within tubular epithelial cells *(arrows).* (Hematoxylin-eosin; original magnification ×400.) **B,** Tubulointerstitial nephritis with diffuse intranuclear polyomavirus inclusions *(arrows).* (Hematoxylin-eosin; original magnification ×200.) **C,** Immunohistochemistry staining highlights intranuclear polyomavirus inclusions. (SV40 immunoperoxidase stain; original magnification ×200.) *(Courtesy Charles Lassman and William Dean Wallace, David Geffen School of Medicine at UCLA, Los Angeles, California.)*

demonstrated a lower incidence of BK viremia in CSA-treated patients compared with their tacrolimus-treated counterparts at 1 year (5% vs. 12%, $P < .12$).[17] *In vitro* studies suggest that CSA may exert an antiviral effect on BKV via suppression of viral replication that is not observed with tacrolimus.[18] Nonetheless, not all studies demonstrated a lower incidence of BK viremia with CSA- compared with tacrolimus-treated patients.[19] The UNOS/OPTN (United Network for Organ Sharing/Organ Procurement and Transplantation Network) registry database demonstrated a lower 2-year cumulative incidence of BK treatment in primary kidney transplant recipients receiving mammalian target of rapamycin (mTOR) inhibitor therapy at hospital discharge when compared with patients on other regimens without an mTOR inhibitor (1.74% vs. 3.67%, respectively, $P < .001$).[16] mTOR inhibition may promote differentiation of antiviral memory CD8 T lymphocytes.[20] Nonetheless, BKV infection has been reported to occur under all combinations of immunosuppressive therapy.

In BKV-associated disease refractory to reduction in immunosuppressive therapy alone, antiviral agents such as cidofovir, leflunomide, intravenous immunoglobulin (IVIG), and fluoroquinolones have been used in small series of patients with variable success. However, systemic review of 40 studies showed no graft survival benefit of adding cidofovir or leflunomide to immunosuppressive reduction for the management of BKN.[21] Although experimental studies suggest that human IVIG preparations contain BKV-neutralizing antibodies, one single-center study failed to demonstrate an association between antibody response and viral clearance.[22] It is speculated that humoral response offers incomplete protection, because interferon-γ secretion from BKV-specific T cells may be necessary for resolution of BK viremia. Fluoroquinolones inhibit BK DNA topoisomerase and SV40 large tumor antigen (T antigen) helicase, and potentially may help prevent BK viremia after renal transplantation.[23] However, the routine recommendation of fluoroquinolone prophylactic therapy in the post-transplant period awaits results of randomized, placebo-controlled trials.

Despite treatment, 30% to more than 60% of patients with established BKN show progressive decline in renal function with graft loss. Early diagnosis and intervention may improve prognosis. Therefore, intensive monitoring of urine and serum for BK by PCR and judicious reduction of immunosuppressive therapy are warranted. Monitoring for plasma BK alone appears to be cost-effective because BKN is unusual in the absence of BK viremia.[24] A proactive, preemptive approach often leads to resolution of viruria and/or viremia and halts the progression of BK viremia to BK nephropathy. The KDOQI guidelines recommend reduction in immunosuppression when BKV plasma NAT is persistently greater than 10^4 copies/ml. However, in our opinion the presence of rising plasma BKV DNA copies on serial measurements warrants immunosuppression reduction irrespective of BKV copy levels because early intervention prevents progression to BKN. Patients with biopsy-proven BKN and concurrent acute rejection should be treated with antirejection treatment, with subsequent reduction in immunosuppression.[24]

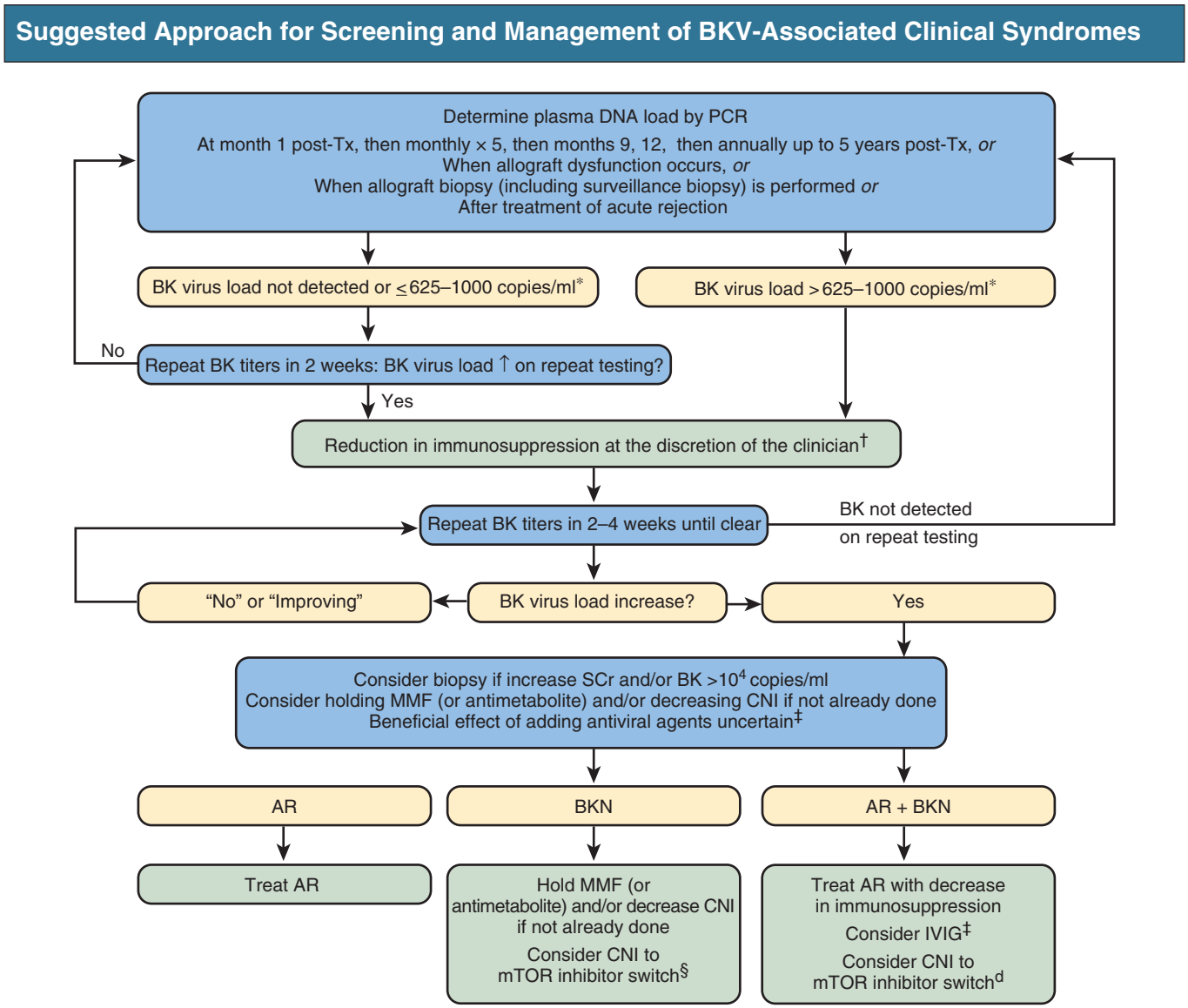

Figure 105-2 Suggested approach for screening and management of BK virus (BKV)–associated clinical syndromes. *No standardized PCR assays for BKV are currently available. Cutoff levels for viral detection should be based on PCR assays used at individual institutions. †Common practice: (1) decrease or hold MMF (or antimetabolite); (2) decrease MMF + CND by 25% to 50%; (3) decrease CNI. Less common practice: (1) decrease prednisone ± decrease CNI; (2) tacrolimus to CSA switch; (3) CNI to mTOR inhibitor switch ± decrease MMF (ongoing clinical trials).‡See text.§Evidence-based recommendations are lacking. May avoid long-term nephrotoxic effect of CNI therapy. Not recommended in patients with baseline significant proteinuria (arbitrarily defined as ≥500 mg/24 h). *AR,* Acute rejection; *BKN,* BK nephropathy; *CNI,* calcineurin inhibitor; *CSA,* cyclosporine A; *IVIG,* intravenous immunoglobulin; *MMF,* mycophenolate mofetil; *mTOR,* mammalian target of rapamycin; *PCR,* polymerase chain reaction; *post-Tx,* post-transplant; *SCr,* serum creatinine.

Anecdotal reports suggested that IVIG may be effective in treating corticosteroid-resistant rejection, and its use may be beneficial in patients with concomitant rejection and BKN or in those with histopathologic changes that are indistinguishable from those of rejection. Suggested guidelines for post-transplant screening and monitoring for polyomavirus replication are shown in Figure 105-2.[24] Patients with graft loss resulting from BKN can safely undergo retransplantation, but preferably after BK viral clearance. Active surveillance for BKV reactivation after transplantation is recommended.

Other Infections

Tuberculosis (TB) remains an important cause of morbidity and mortality in solid organ transplantation. Its incidence among renal transplant recipients is 20 to 70 times higher than that of the general population, whereas its prevalence reflects the prevalence of specific geographic areas (e.g., 13% in the Indian subcontinent including India and Pakistan; 2.0% in the Far East including China, Thailand, and Taiwan; and 0.07% to 1.7% in Western Europe and North America).[25] Although TB commonly results from inhalation of airborne bacilli, it more commonly emerges from the reactivation of dormant lesions in the setting of immunosuppressive therapy. Hence, all potential kidney transplant candidates should undergo a purified protein derivative (PPD) skin test (tuberculin skin test) before transplantation. In recent years, the use of interferon-γ release assays to diagnose latent TB is the preferred alternative to the PPD skin test (www.cdc.gov/mmwr/pdf/rr/rr5905.pdf). The interferon-γ release assay is useful in BCG-vaccinated patients to distinguish between BCG reaction versus TB reaction on PPD skin test. A positive skin

test or interferon-γ release assay result or a prior history of TB mandates further evaluation to rule out active disease. Isoniazid (INH) prophylaxis for a total of 9 months is recommended for those who have a positive skin test or interferon-γ release assay result. In patients with a known history of adequately treated TB infection, we advocate the use of INH prophylaxis for the first 9 months after transplantation and during intensification of immunosuppression. Others, however, have suggested that INH prophylaxis is not indicated for patients whose TB had been properly treated. Clinical, radiologic, or culture evidence of active TB infection is a contraindication to transplantation. INH prophylactic therapy should be considered in the following situations:

- Transplant candidates with a history of prior positive tuberculin skin test or interferon-γ release assay result
- Those with TB disease without adequate treatment
- Patients with evidence of old granulomatous disease on chest radiograph without treatment
- Those with known prolonged exposure to a person with active TB
- Kidney transplant recipients in endemic areas[25]
- Donor with positive tuberculin skin test or interferon-γ release assay result

A rare but important cause of infection in transplant patients, particularly those from endemic areas such as Southeast Asia, is *Strongyloides.* In the presence of immunosuppression, a "hyperinfection" syndrome may be observed with parasitic pneumonia and gastrointestinal involvement.

GASTROINTESTINAL DISEASE

Post-transplantation gastrointestinal complications are common. Only selected complications are discussed; a comprehensive review is provided in reference 26.

Drug-Related Gastrointestinal Complications

Mycophenolate mofetil causes gastrointestinal side effects including nausea, vomiting, dyspepsia, anorexia, flatulence, and diarrhea. Dose reduction, transient discontinuation of the drug, or dividing the dose for administration three or four times a day often ameliorates or resolves the symptoms. Switching to the enteric-coated formulation of MMF (enteric-coated mycophenolate sodium [EC-MPS]) may result in less gastrointestinal side effects. A randomized, multicenter, open-label study demonstrated that switching from MMF to EC-MPS may enable an increase in the maximum tolerated dose of mycophenolic acid and reduce gastrointestinal complications, hence enhancing patients' gastrointestinal health-related quality of life.[27] Conversion of MMF to EC-MPS should be considered in patients with gastrointestinal intolerance associated with MMF use.

Proton pump inhibitor (PPI) use can reduce the dissolution of MMF by increasing gastric pH.[28] In contrast to MMF, EC-MPS is not absorbed in the stomach and its bioavailability is not affected by PPIs. The latter formulation delays the release of mycophenolic acid. The clinical impact of such interactions (e.g., lower mycophenolic acid exposure and increased rejection risk in patients receiving MMF compared with EC-MPS–treated patients) remains to be studied.

Sirolimus may cause oral mucocutaneous lesions that can be confused with HSV or CMV infection but are culture negative. Drug-related oral ulcers usually resolve after discontinuation of the offending agent. Sirolimus, everolimus, tacrolimus, and cyclosporine may all cause diarrhea in some patients.

Infections

Post-transplantation infections of the gastrointestinal tract may have a viral, fungal, or bacterial cause. Viral infections are most commonly caused by CMV and HSV; *C. albicans* and *C. tropicalis* are common opportunistic fungal infections. Leukoplakia and post-transplant lymphoproliferative disorders (PTLDs) may develop in patients with EBV infection (PTLD is discussed in a later section). Commonly encountered bacterial pathogens include *Clostridium difficile* and *Helicobacter pylori.*

Cytomegalovirus Infection

Cytomegalovirus can affect any segment of the gastrointestinal tract. Patients may present with dysphagia, odynophagia, nausea, vomiting, gastroparesis, abdominal pain, diarrhea, or gastrointestinal bleeding. Leukopenia and elevated transaminases are common. Persistent or unexplained symptoms of nausea, vomiting, or diarrhea, particularly in the early post-transplantation period or during intensification of immunosuppression, warrant further investigation with upper and lower endoscopies and biopsies.

Herpes Simplex Virus Infection

Herpes simplex virus infection results primarily from reactivation of endogenous latent virus, causing clinical infection within the first 1 to 2 months after transplantation. Patients commonly present with oral mucocutaneous lesions or gingivostomatitis with or without odynophagia and dysphagia. HSV esophagitis has been noted to occur in patients receiving high-dose corticosteroids and antilymphocyte preparations for acute rejection. Limited oral mucocutaneous lesions are treated with oral acyclovir; extensive infections require intravenous acyclovir or ganciclovir. Rare cases of HSV hepatitis have been reported. The routine use of acyclovir prophylaxis in the early post-transplantation period is recommended (see Table 105-3).

Fungal Infections

Candida stomatitis and esophagitis are common during the first 6 months after transplantation and are increased in patients with leukopenia, severe immunosuppression, diabetes, or concomitant infections. Bleeding or perforation with formation of tracheoesophageal fistulas has been reported. The use of prophylactic oral nystatin "swish and swallow" during the first month after transplantation is recommended. In high-risk candidates, including liver or pancreas transplant recipients and those receiving antilymphocyte antibody therapy, fluconazole prophylactic therapy (3 to 6 months) is warranted.

Helicobacter Infection

Helicobacter pylori infection is associated with a wide range of gastrointestinal complications including chronic gastritis, duodenal and gastric ulcers, mucosa-associated lymphatic tissue (MALT) lymphoma, and gastric carcinoma, both in the general population and in recipients of solid organ transplants. Treatment includes a triple-drug regimen consisting of two antibiotics and an acid-suppressive agent such as an H_2-blocker or a PPI. The first-line *H. Pylori* regimen is shown in Table 105-4. In recipients of orthotopic heart transplant, triple-drug therapy resulted in a lower eradication rate compared with the general population, suggesting that immunosuppression may hinder the clearance of *H. pylori.* Unexplained dyspeptic or reflux symptoms should be investigated further with endoscopy and biopsy to exclude malignancy. *H. pylori* is now recognized as a risk factor for MALT lymphoma, which may occur in kidney, liver, and heart transplant recipients. In kidney transplant recipients infected with *H. pylori,* MALT lymphoma may be less aggressive than other

First-Line Treatment Regimens for *Helicobacter pylori* as Recommended by the American College of Gastroenterology	
Penicillin Allergies	**Regimen**
No	Standard-dose PPI twice daily (or omeprazole once daily) + clarithromycin 500 mg twice daily + amoxicillin 1000 mg twice daily for 10-14 days
Yes	Standard-dose PPI twice daily + clarithromycin* 500 mg twice daily + metronidazole 500 mg twice daily for 10-14 days
Yes	Bismuth subsalicylate 525 mg orally four times daily + metronidazole 250 mg orally four times daily + tetracycline 500 mg orally four times daily + ranitidine 150 mg orally twice daily (or standard-dose PPI once to twice daily) for 10-14 days

Table 105-4 First-line treatment regimens for *H. pylori* as recommended by the American College of Gastroenterology. *PPI,* Proton pump inhibitor. *Close monitoring of cyclosporine or tacrolimus or mTOR inhibitor levels is required when starting and stopping clarithromycin.

lymphomas, and the disorder may be cured by eradication of *H. pylori.*

Colon Disorders

Diverticulitis and colonic perforations may be life-threatening and difficult to diagnose after transplantation because symptoms may be masked by immunosuppressive therapy, particularly in the early postoperative period. Diverticulitis complicated by perforation, abscess formation, phlegmon, or fistula has been reported in 1% of kidney transplant recipients, and its incidence may be increased in patients with polycystic kidney disease (PKD).

Early post-transplantation colonic perforations are largely caused by high-dose corticosteroids, diverticulitis, CMV colitis, and intestinal ischemia; perforations occurring late or years after transplantation are commonly caused by diverticulosis or malignant disease. Abdominal symptoms may be absent because of the effects of immunosuppression and may be suggested only by the presence of tachypnea and tachycardia. Mortality after colonic perforations is high. Management includes prompt exteriorization of the perforated colon, broad-spectrum antimicrobial therapy, and minimization of immunosuppressive therapy. Although uncommon, the presence of abdominal pain and gastrointestinal bleeding with unexplained fevers or weight loss should raise the suspicion for gastrointestinal TB. The characteristic endoscopic findings include circular ulcers, small diverticula, and sessile polyps. The presence of caseating granulomas, acid-fast bacilli, or both confirms the diagnosis.

TRANSPLANT-ASSOCIATED MALIGNANT NEOPLASMS

Recipients of organ transplants are at increased risk for development of neoplasms compared with the general population. The intensity and duration of immunosuppression as well as the ability of these agents to promote replication of various oncogenic viruses are important risk factors. The associations between human papillomavirus (HPV) and cervical and vulvar carcinoma, EBV and PTLD, HBV and HCV and hepatocellular carcinoma, and HHV-8 and Kaposi sarcoma are well established. Table 105-5 provides a summary of the incidence of cancers related to infections in transplant recipients.[29]

Meta-Analysis Standardized Incidence Ratios for Cancers Related to Infections in Transplant Recipients	
Cancers	**Meta-analysis SIRs**
EBV-related cancers	
Hodgkin lymphoma	3.9 (2.4-6.3)
Non-Hodgkin lymphoma	8.1 (6.4-10.2)
HHV-8–related cancer	
Kaposi sarcoma	208.0 (114-369)
HBV- and HCV-related cancer	
Liver	2.1 (1.2-3.9)
HPV-related cancers	
Cervix (uterine)	2.1 (1.4-3.3)
Vulva and vagina	22.8 (15.8-32.7)
Penis	15.8 (5.8-34.4)
Anus	4.9 (1.4-17.3)
Oral cavity and pharynx	3.2 (2.4-4.4)
Possibly HPV-related cancers	
Non–melanocytic-related skin	28.6 (9.4-87.2)

Table 105-5 Meta-analysis standard incidence ratios (SIRs) for cancers related to infections in transplant recipients. *EBV,* Epstein-Barr virus; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HHV,* human herpesvirus; *HPV,* human papillomavirus. *(Adapted from reference 29.)*

Skin cancers are the most common *de novo* post-transplant tumors in the adult transplant population and occur with increasing frequency with time (skin cancers are discussed in a later section). Among nonskin malignant neoplasms, PTLDs are the most common type of post-transplantation malignancy, followed by lung, prostate, and kidney malignancies.[30] The mean time to diagnosis of different neoplasms varies with the type of organ involved. Kaposi sarcoma, PTLD, testicular cancer, cancer of the small intestine, and thyroid cancer occur early after transplantation (defined as less than 800 days after transplantation). An Italian multicenter cohort study demonstrated that kidney transplant recipients are at increased risk of developing Kaposi sarcoma and nonmelanoma skin cancer, followed by non-Hodgkin lymphoma, cancer of the cervix uteri, and thyroid cancer, compared with an age- and sex-matched reference general population.[31] Common cancers in the general population, including cancers of the breast, colon, prostate, lung, bladder, stomach, and pancreas, were found to occur more frequently in kidney transplant recipients in some but not all studies.[30-32] The KDOQI guidelines suggest an individualized screening plan for each kidney transplant recipient, taking into account the patient's past medical and family history, tobacco use, and competing risk for death, and the performance of the screening methodology. In patients with compensated cirrhosis, annual hepatic ultrasound and measurement of alpha fetoprotein level is recommended. Screening for cervical, breast, prostate, and colon cancer should follow local guidelines for the general population. Standard cancer surveillance appropriate for age is shown in Table 105-6. In patients with a history of preexisting malignant neoplasms, close monitoring for recurrences in the post-transplantation period is mandatory. The highest recurrence rates have been observed with multiple myeloma (67%), nonmelanoma skin cancers (53%), bladder carcinomas (29%), sarcomas (29%), symptomatic renal cell carcinomas (27%), and breast carcinomas (23%).[33] In an analysis of the Israel Penn International Transplant Tumor Registry involving 90 patients with a history of pretransplant prostate adenocarcinoma (77 renal, 10 heart, and 3 liver transplant recipients), prostate cancer recurrences were shown to be related to the stage of disease at initial diagnosis. Tumor recurrence rates were 14%, 16%, and 33% for stage I, II, and III disease, respectively

Preventive Care Recommendations for Cancer Surveillance in Kidney Transplant Recipients

Screening For	Starting at Age	Preventive Care	Screening Frequency
Colorectal cancer	Average risk: 50 years	Colonoscopy or FOBT + flexible sigmoidoscopy*	Colonoscopy: every 10 years FOBT*: every year Flexible sigmoidoscopy†: every 5 years
		Colonoscopy or or or	Every 5 years if a parent or sibling had colorectal cancer at younger than 60 years At 10 years younger than the youngest family member with cancer Every 10 years if the relative was older than 60 years Consider referral to medical genetics if two or more first-degree relatives had colorectal cancer
Skin cancer	Monthly self-examination of skin, total-body skin examination every 6-12 months by qualified physicians and dermatologists‡		
Females			
Breast cancer	50-69† years	Breast examination and screening mammography	Every 1 or 2 years
	40-49 years Before age 30 years (if mother or sister had breast cancer)	Breast examination and screening mammography	Every 1 or 2 years (no evidence for or against screening for this age group)
Cervical cancer	Once sexually active	Pap smear and pelvic examination	Every year
Males			
Prostate cancer	50 years 40§ years	Digital rectal examination PSA testing	Every year Frequency for testing is not established

Table 105-6 Preventive care recommendations for cancer surveillance in kidney transplant recipients. *FOBT,* Fecal occult blood testing; *PSA,* prostate-specific antigen. *As recommended by the American Transplant Society and the European Best Practice Guidelines on renal Transplantation. †The U.S. Preventive Services Task Force (USPSTF) recommends against routine screening in adults ages 76 to 85. ‡The American College of Preventive Medicine recommends regular screening for high-risk individuals but none for low-risk individuals. §Recommended for African Americans, patients with a family history of prostate cancer, patients receiving chronic immunosuppression for organ transplantation. *(Based on the 2008 joint guideline from the American Cancer Society, the U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology[60] and reference 58.)*

(American Joint Committee on Cancer, TNM staging system). Hence, a longer waiting time may be necessary for more advanced disease.[34] Nonetheless, the usefulness of clinical staging in predicting recurrence of localized prostate cancer in the general population has recently been questioned by experts in the field. Guidance on tumor-free waiting periods in potential recipients before transplantation is given in Chapter 102 (Box 102-2).

Post-transplant Lymphoproliferative Disorder

Post-transplant lymphoproliferative disorder encompasses a wide spectrum of lymphoid proliferations ranging from reactive polyclonal lesions to frank malignant monoclonal lymphomas. The 2008 modified World Health Organization (WHO) classification of PTLD can be divided into four subtypes including (1) early lesions, (2) polymorphic PTLD, (3) monomorphic PTLD, and (4) classic Hodgkin lymphoma–type PTLD (Box 105-2). The majority of PTLDs are non-Hodgkin lymphoma of B cell origin, 80% to 90% of which are linked to EBV infection. In recent years an increased incidence of EBV-negative PTLD has been reported. PTLD commonly occurs in the first year after transplant, although the cumulative incidence increases with time after transplantation. In a retrospective analysis of registry data for 402 recipients of kidney transplants, PTLD occurred at a median of 18 months after transplantation. The UNOS/OPTN database similarly demonstrated that PTLD occurred at a median of 18.5 months after transplantation.

Very late PTLD occurring more than 10 years after transplantation has been reported to occur in older adult transplant recipients.[35]

World Health Organization (WHO) Classification of Post-transplant Lymphoproliferative Disorder (PTLD)

1. Early Lesions
Plasmacytic hyperplasia
Infectious mononucleosis–like lesion

2. Polymorphic PTLD

3. Monomorphic PTLD

B Cell Neoplasms
- Diffuse large B cell lymphoma
- Burkitt lymphoma
- Plasma cell myeloma
- Plasmacytoma-like lesion
- Other

T Cell Neoplasms
- Peripheral T cell lymphoma, NOS
- Hepatosplenic T cell lymphoma
- Other

4. Classical Hodgkin Lymphoma-type PTLD

Box 105-2 WHO classification of PTLD. *NOS,* Not otherwise specified.

Risk factors for PTLD can be classified into those associated with the type of organ transplant, recipient age, type and intensity of immunosuppression, infectious agents, and human leukocyte antigen (HLA) mismatch.

Risk Factors

Type of Organ Transplant The incidence of PTLD varies according to the type of the transplanted organ. It occurs in 1% to 2% of patients after kidney transplantation, 1% to 4% after liver transplantation, 2% to 3% after pancreas or simultaneous kidney-pancreas transplantation, 2% to 10% after heart, lung, and heart-lung transplantation, and up to 33% after small bowel and multivisceral transplantation. The high incidence of PTLD in bowel and multiorgan transplants has been attributed to the use of more intensive immunosuppression and the amount of donor-derived lymphoid tissue transferred at organ transplantation. This lymphoid tissue has been suggested to act as a reservoir for viruses such as EBV.[36]

Age Post-transplant lymphoproliferative disorder is the most common malignancy in children, whereas in adults it is the second most common malignancy after skin cancer. The higher incidence of PTLD in children compared with adults has been attributed to the pretransplant EBV-naive status of children and the well-described association between primary EBV infection and PTLD.

Type of Immunosuppression

Calcineurin Inhibitors Cyclosporine and tacrolimus may enhance the development of EBV-associated PTLD by directly promoting survival of EBV-infected B cells, presumably via the inhibition of EBV-transformed cells from apoptosis.[37] Tacrolimus has been reported to increase the risk of PTLD by twofold to fivefold compared with cyclosporine.[38]

mTOR Inhibitors Sirolimus has been shown to have a strong antiproliferative effect on PTLD-derived B cell lines.[39] Experimental studies suggest that mTOR inhibitors may be beneficial in reducing the incidence of PTLD in high-risk patients or as an alternative method of immunosuppression in patients with established PTLD.[40,41] However, a higher incidence of PTLD associated with the use of sirolimus-containing regimens compared with "no sirolimus" has also been described. The UNOS/OPTN database demonstrated that in EBV (–) recipients, mTOR inhibitor–tacrolimus combination therapy was associated with a 1.4-fold increased PTLD risk, compared with MMF-tacrolimus combination therapy).[42] Analysis of 719 patients with PTLD similarly demonstrated that *de novo* sirolimus was associated with a 1.2-fold increased risk of PTLD in EBV (–) kidney transplant recipients.[43] It is conceivable that studies evaluating the association of sirolimus and PTLD risk have yielded conflicting results because of differences in methodologies and in overall intensity of induction and maintenance immunosuppression among studies. Limited studies also suggest that high-dose mTOR inhibitor maintenance therapy may carry an increased PTLD risk.[44]

Antimetabolites The use of antimetabolites such as AZA and MMF has not been consistently associated with an increased risk of PTLD. A lower or no increased risk has been observed.[45]

Induction Agents Whereas induction therapy with muromonab-CD3 (OKT3) or antithymocyte globulin has been reported to increase PTLD risk, the use of interleukin (IL)–2 receptor inhibitors (daclizumab and basiliximab) or anti-CD52 antibody (alemtuzumab) induction has not been suggested to increase PTLD risk.[46] Analysis of the UNOS/OPTN database demonstrated that thymoglobulin was associated with significantly increased PTLD risk, whereas alemtuzumab, basiliximab, and daclizumab trended toward a protective effect ($P = .06$). In this study maintenance therapy with an mTOR inhibitor was unexpectedly found to be strongly associated with PTLD, in contrast to earlier reports suggesting its beneficial effect on PTLD because of its antiproliferative and antiangiogenic effects.[46] Although both alemtuzumab and thymoglobulin are T cell–depletional agents, the former has been shown to have a more pronounced B cell–depleting effect. It is speculated that depletional induction is not an independent risk factor for PTLD, but, rather, that maintenance drug selection and the balance between B and T cell depletion may be more relevant determinants of PTLD risk. Nonetheless, aggressive PTLD attributed to alemtuzumab induction has been reported.[47] Overall, the intensity of immunosuppression undoubtedly plays a role in the development of PTLD.

Belatacept Belatacept is a novel non–antigen-specific biologic agent that blocks T cell costimulatory signals, hence preventing T cell activation. Phase III clinical trials suggest that its use in transplant recipients with pretransplant EBV seronegativity is associated with an increased risk of PTLD.[48] Hence, belatacept use is contraindicated in transplant recipients with pretransplant EBV-seronegative or unknown EBV status.

Viral Infection

Epstein-Barr Virus During primary infection, EBV is incorporated into B lymphocytes and establishes lifelong latency. Immunocompetent hosts mount an antibody response and, more important, an EBV-specific cytotoxic T cell immune response. EBV-naive transplant recipients lack both virus-specific antibodies to neutralize the virions released by infected donor-derived B cells and EBV-specific T cells to control the outgrowth of subsequently infected recipient B cells.[36] Hence, an EBV (–) recipient with an EBV (+) donor is at greatest risk for developing PTLD.

Cytomegalovirus Antecedent history of CMV and post-transplant primary CMV infection have been suggested to be risk factors for PTLD. Studies in pediatric liver transplantation demonstrated that children who developed primary CMV infection had a fourfold to sixfold higher risk of developing PTLD.[49] It is speculated that the inflammatory cytokines released in the presence of a primary infection with CMV make the milieu more supportive of EBV proliferation.

Hepatitis C Virus Whereas HCV infection has been linked to increased risk of lymphoma among immunocompetent individuals, the association between HCV and PTLD after solid organ transplantation has not consistently been shown. A large transplant registry study failed to demonstrate the link between HCV and PTLD. However, the risk of PTLD was increased among 2.8% of patients with HCV who were reported not to have received immunosuppressive therapy. It is speculated that chronic antigenic stimulation of the intact immune system is necessary for the development of HCV-related lymphoproliferation.[50]

Miscellaneous Other suggested risk factors for PTLD include fewer HLA matches, pretransplant malignancy, and infections with HHV-8 and simian virus 40.

Clinical Manifestations

Post-transplant lymphoproliferative disorder may present with constitutional symptoms such as fevers, night sweats, malaise, and weight loss or with localized symptoms of the respiratory tract (infection or mass, including tonsillar or even gingival involvement), gastrointestinal tract (diarrhea, pain, perforation, bleeding, mass), or central nervous system (CNS) (headache, seizure, or confusion). Other clinical manifestations may include lymphadenopathy or symptoms related to allograft dysfunction or compression of surrounding structures. Extranodal involvement occurs in more than two third of patients.[51] In contrast to lymphomas in the general population, where CNS involvement is rare, the CNS is frequently involved in PTLD, occurring in up to 25% to 30% of patients, and can be the only site of disease. Early diagnosis requires a high index

of suspicion in the appropriate clinical setting and radiologic findings. Although computed tomography (CT) and magnetic resonance imaging (MRI) are the most commonly used imaging modalities in PTLD, 2-[fluorine-18]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan is superior to conventional imaging methods for detecting extranodal localization. Tissue sampling is necessary for a definitive diagnosis and subcategorization of PTLD. Although measurement of EBV DNA has been suggested to be invaluable in the diagnosis and monitoring of PTLD,[52] clinical trials demonstrating the usefulness of monitoring EBV DNA in the diagnosis of PTLD in solid organ transplant recipients are lacking.

Treatment

Reduction or discontinuation of immunosuppressive therapy, particularly cyclosporine, tacrolimus, or MMF, is the first-line treatment; prednisone can be continued to prevent allograft rejection. Although sirolimus has antiproliferative effects, there is not yet sufficient evidence to recommend or refute its use as a therapy for PTLD. Suggested factors predictive of a poor response to reduction in immunosuppression alone include elevated lactate dehydrogenase (LDH), organ dysfunction at diagnosis, multiple organ involvement of PTLD, bulky disease, advanced stage, and older age.[44]

Rituximab, a chimeric monoclonal antibody with murine variable regions targeting the CD20 antigen and human IgG1-κ constant regions, has antitumor activity against CD20-expressing B cell lymphomas. In patients who fail to respond to manipulation of immunosuppression alone, rituximab has been used with variable success. Suggested favorable predictive factors for response include EBV-positive PTLD, a shorter interval from transplantation to diagnosis of PTLD, a smaller number of involved sites, and a normal LDH level. Chemotherapy is often used in patients refractory to reduction in immunosuppression and rituximab, in those with aggressive disease at presentation, or in those with lesions not amenable to surgery. The treatment regimens are similar to those used to treat non-Hodgkin lymphoma. These have included CHOP (cyclophosphamide, adriamycin, vincristine, and prednisone), VAPEC-B (adriamycin, etoposide, cyclophosphamide, methotrexate, bleomycin, and vincristine), and ProMACE-CytaBOM. CHOP-based chemotherapy with or without rituximab is the most widely used regimen.[51] Adverse effects of chemotherapy include high mortality rates from sepsis and treatment-related toxicities. Surgical resection with or without adjunctive local radiation has been suggested for localized disease. Local radiation has been advocated as the treatment of choice for PTLD involving the CNS.

Acyclovir and ganciclovir are of unproven benefit because their activity is dependent on intracellular phosphorylation by virally encoded thymidine kinase. EBV-driven lymphomas do not express thymidine kinase. An emerging treatment strategy involves the addition of arginine butyrate, an amino acid derivative that induces EBV thymidine kinase transcription. Experimental studies have shown that arginine butyrate renders latently infective EBV-immortalized B cells more susceptible to ganciclovir.[44] Clinical trials evaluating the safety and efficacy of arginine butyrate in combination with ganciclovir in EBV-associated PTLD or other EBV-associated malignancies are currently under way.

Poor prognostic factors include multiple- versus single-site involvement, tumor monoclonality, advanced age, CD-20–negative large cell lymphomas, recipient EBV-negative serostatus, and the use of antilymphocyte globulin or antithymocyte globulin, or OKT3. Other poor prognostic factors include WHO performance status score of 3 or 4 (a score of 3 is defined as confined to bed or a chair for more than 50% of waking hours, and a score of 4 as completely disabled), late onset of disease (defined as onset more than 1 year after transplant), elevated LDH, severe organ dysfunction, and CNS disease.[50,51] In recipients of kidney transplant with PTLD restricted to the allograft alone, transplant nephrectomy may improve survival.

Skin Cancers

Skin cancers are the most common *de novo* post-transplant tumors in the adult transplant population and may occur 20 to 30 years earlier in immunosuppressed patients compared with the general population. Whereas basal cell carcinoma is the most common type of skin cancer in the general population, squamous cell carcinoma is approximately twice as common as basal cell carcinoma. However, multiple cancerous lesions of different types may be observed (i.e., concomitant appearance of squamous cell and basal cell carcinoma). The incidence of skin cancers is 20 times higher in sun-exposed areas and 7 times higher in non–sun-exposed areas. Sirolimus may delay the onset or reduce the incidence of post-transplant skin and nonskin malignant neoplasms (discussed under management of post-transplantation malignancies).

Risk factors for skin cancers in immunosuppressed post-transplant recipients include light skin color, total sun burden and recreational sun exposure (ultraviolet light exposure), genetic factors, history or present use of AZA,[53] and duration of follow-up after transplantation. In addition, immunosuppression in combination with enhanced sunlight exposure may induce malignant changes in papilloma-induced warts.

Management of Immunosuppressive Therapy in Post-transplantation Malignant Neoplasms

There is no consensus on the management of immunosuppressive therapy in patients with post-transplantation malignant neoplasms. In principle, immunosuppression dose reduction improves immune surveillance against malignant cells. Nonetheless, this approach is not without its attendant risk of graft rejection and graft loss. However, there are no systematic studies to demonstrate whether immunosuppression reduction or withdrawal might alter the natural history of established post-transplantation malignant neoplasms. In our opinion, a switch from CNI to sirolimus or CNI minimization in conjunction with sirolimus may be a viable therapeutic option (the antitumoral effect of sirolimus is discussed later). In patients with metastatic cancer, manipulation of immunosuppression is probably futile, and the risk of rejection and graft loss necessitating a return to dialysis is likely to outweigh the benefit.

Studies suggest that immunosuppressive agents have different effects on cancer risk after transplantation. The carcinogenic effects of OKT3, antithymocyte globulin, cyclosporine, tacrolimus, and AZA have been well documented. In contrast to AZA, MMF has been shown to have an antiproliferative effect and has been suggested to be protective of post-transplantation malignant neoplasms.[54] Analysis of more than 17,000 adult patients with pre-existing diabetes indicated a significantly higher incidence of malignancy in AZA-treated than in MMF-treated patients (3.7% vs. 2.2%,). However, whether MMF is protective of post-transplant malignancies remains unclear. Further studies are needed. In clinical practice, MMF is generally discontinued in the presence of malignancies because of the theoretical risk of net protumor effect of overimmunosuppression.

Both preclinical and clinical studies have demonstrated that sirolimus and everolimus have antiproliferative and antitumoral effects. The 5-year malignancy data of the Rapamune Maintenance Regimen

trial demonstrated a lower incidence of both skin and nonskin cancers at 5 years after transplantation in recipients receiving sirolimus with CSA withdrawal at month 3 compared with those receiving sirolimus-CSA combination therapy.[55] Recent meta-analysis of five randomized controlled trials consisting of more than 1400 kidney transplant recipients similarly demonstrated that sirolimus-based immunosuppression significantly decreased the risk of both squamous cell carcinoma and basal cell carcinoma.[56] In a multicenter trial of secondary prevention involving kidney transplant recipients with at least one previous cutaneous squamous cell carcinoma, conversion from CNI to sirolimus was associated with a lower risk of subsequent skin cancers. The study also demonstrated that the earlier the conversion after an initial diagnosis of cutaneous squamous cell carcinoma, the greater efficacy.[57] It has been suggested that the protective effect of sirolimus against skin cancer is a result of its inhibition of several ultraviolet-induced mechanisms involved in skin carcinogenesis. Sirolimus therapy has also been reported to result in successful clinical and histologic remission of Kaposi sarcoma in kidney transplant recipients.[58] Although sirolimus appears to provide satisfactory outcomes in certain cancers after transplantation, its use in the management of malignancies after solid organ transplantation remains to be defined and should be tailored to each individual patient. Nonetheless, sirolimus has increasingly been used in the secondary prevention of skin cancer. It is our current practice to start patients with newly diagnosed skin cancer (or those with a history of skin cancer) on sirolimus or everolimus in conjunction with reduction or discontinuation of other immunosuppressants.

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CHAPTER 106

Medical Management of the Kidney Transplant Recipient: Cardiovascular Disease and Other Issues

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The medical management of transplant-related complications is discussed in this chapter; post-transplant infections, gastrointestinal problems, and malignant neoplasms are discussed in Chapter 105.

CARDIOVASCULAR DISEASE

Cardiovascular (CV) disease is the most frequent cause of death with a functioning graft. In a large multicenter, international study consisting of more than 23,000 kidney transplant recipients, the cumulative incidences of coronary heart disease (CHD) at 1, 3, and 5 years after transplant were 3.1%, 5.2%, and 7.6%, respectively. Of nearly 700 CHD events that occurred in the first post-transplant year, 49% were nonfatal acute myocardial infarction (AMI) and 13% fatal AMI or sudden death.[1] Renal function, estimated glomerular filtrate rate (eGFR), and preexisting CV disease were found to be the most important risk factors for a CV event. Recently, an analysis based on the Assessment of Lescol in Renal Transplantation (ALERT) trial suggested that major CV events could be predicted with a seven-variable model including age, previous CHD, diabetes, low-density lipoprotein (LDL), creatinine, number of transplants, and smoking.[1a] Although kidney transplantation ameliorates some CV risks by restoring renal function, it introduces new CV risks, including impaired glucose tolerance or diabetes mellitus, hypertension, and dyslipidemia, which are derived in part from immunosuppressive medications. Kidney transplant recipients have both conventional and unconventional CV risk factors (Table 106-1).[2]

Conventional Cardiovascular Disease Risk Factors

Post-transplantation Hypertension

Hypertension is a risk factor for both CV disease and kidney graft failure, with a graded risk for graft failure with increasing levels of systolic and diastolic blood pressure.[3] Whether aggressive lowering of blood pressure retards the progression of graft failure beyond that of blood pressure control alone remains to be studied. Hypertension is common after transplantation and is present in 50% to 90% of kidney transplant recipients. Systolic blood pressure is highest immediately after transplantation and declines during the first year. In a Collaborative Transplant Study (CTS) registry, only 8% of transplant recipients had a systolic blood pressure below 120 mm Hg at 1 year; 33% had a blood pressure in the prehypertension range; 39% had stage 1 hypertension; and 20% had stage 2 hypertension despite antihypertensive therapy.[3] Risk factors for post-transplant hypertension include preexisting hypertension, cyclosporine (and to a lesser degree tacrolimus), corticosteroids, poor quality of donor organ, delayed graft function, chronic allograft injury, high body mass index (BMI) or excess weight gain, acute rejection episodes, recurrent or *de novo* glomerulonephritis (GN), and transplant renal artery stenosis. Sodium intake after transplantation may also be contributory in salt-sensitive hypertensive patients. In rare patients, excess renin output from the native kidneys may contribute to post-transplantation hypertension. In kidney transplant recipients with severe hypertension refractory to medical therapy, bilateral native nephrectomy has been reported to ameliorate blood pressure control.[4] Recently, renal artery nerve denervation has been reported to have benefit in nontransplant patients with resistant hypertension (see Chapter 38).[5] Whether native kidney sympathetic denervation procedures improve blood pressure control in kidney transplant recipients with refractory hypertension remains to be studied.

Management of post-transplantation hypertension should include identification and treatment of the underlying cause, lifestyle modifications (see Chapter 35), and treatment of associated CV risk factors. The initial target blood pressure goal is below 130/80 mm Hg, and in patients with proteinuria, below 125/75 mm Hg. Although JNC 8 blood pressure targets for diabetics and patients with chronic kidney disease are set at higher levels than those of JNC 7, whether patients with post-transplant hypertension benefit from higher blood pressure goals remains to be studied. Although there is a lack of controlled clinical trials related to selection of antihypertensive agent, we recommend β-blockers in the perioperative setting because they have been shown to reduce CHD events in high-risk candidates. In the early post-transplantation period, nondihydropyridine calcium channel blockers (CCBs) and diuretics are frequently used, the former for their beneficial effect on intraglomerular hemodynamics and the latter to eliminate salt and water in patients who are volume expanded postoperatively. Although one retrospective cohort study reported an unexpected association between the use of dihydropyridine CCBs and an increased risk for CHD,[6] results of another trial showed no significant association between any CV medication use (β-blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], diuretics, CCBs, antiplatelet agents, and/or statins) and increased major cardiac event risks at 12 months.[7] Studies evaluating the effect of CCBs on renal function have similarly yielded mixed and even contradictory results. In proteinuric chronic kidney disease (CKD) patients, dihydropyridine CCB use was shown to be associated with increased risk of renal disease progression and death except when used in conjunction with angiotensin II blockade therapy. However, results of a meta-analysis of randomized controlled trials demonstrated that CCB improved allograft function and reduced graft loss.[8] The

Cardiovascular Risk Factors in Transplant Recipients			
Traditional		Nontraditional	
Modifiable	**Nonmodifiable**	**Modifiable (± Potentially Modifiable)**	**Nonmodifiable**
Hypertension Dyslipidemia Obesity Smoking	Family history Pre-Tx diabetes Male gender Age White race Cardiac troponin T History of pretransplant and post-transplant cerebrovascular disease	Anemia New-onset diabetes after transplantation Proteinuria Inflammatory cytokines ↑ C-reactive protein CMV infection* Hyperuricemia Delayed graft function† Impaired graft function‡ Left ventricular hypertrophy§ CD4 lymphopenia‖ Post-transplant lymphoproliferative disorder† Low albumin Hyperhomocysteinemia Recipient history of cancer† Duration of pretransplant dialysis†¶	Prior acute rejection Preexisting coronary artery calcification Deceased versus living donor Pre-Tx splenectomy

Table 106-1 Cardiovascular risk factors in transplant recipients. *CMV,* Cytomegalovirus; *CNI,* calcineurin inhibitor; *Pre-Tx,* pretransplant. *Strict adherence to CMV prophylaxis protocol and CMV surveillance in high-risk candidates. †Reference 1. ‡CNI minimization at the discretion of the clinicians. §Optimize blood pressure control. ‖Assess risks and benefits of T cell–depleting antibody treatment (limited data). ¶Discuss living donor kidney transplant option with patient at the time of transplantation evaluation.

Potential Advantages and Disadvantages of Different Classes of Antihypertensive Agents*		
Classes of Drugs	**Advantages**	**Disadvantages**
β-Blockers	Perioperative use: ↓ coronary heart disease events	↑ Risk of bradycardia when used with nondihydropyridine calcium channel blocker Blunting of hypoglycemic awareness
Calcium channel blockers	↓ CNI-induced renal vasconstriction† ↑ CNI level (may permit CNI dose reduction by up to 40%)‡	Monotherapy with dihydropyridine calcium channel blocker should be used with caution§
Diuretics	Beneficial in patients who are volume expanded	Hyperuricemia, gout
ACE inhibitors, ARBs	↓ Proteinuria Potential renal protective and cardioprotective effects Beneficial in patients with post-transplantation erythrocytosis	Potential worsening of anemia
Aldosterone receptor blockers	May improve outcomes in heart failure	Severe hyperkalemia when used in combination with ACE inhibitor or ARB in patients with poor kidney function
α_2-Blockers	Benign prostatic hypertrophy Neurogenic bladder	
Direct vasodilators		Tachycardia
Central α-agonist		Depression

Table 106-2 Potential advantages and disadvantages of different classes of antihypertensive agents. *ACE,* Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *CNI,* calcineurin inhibitor. *In general, there is no absolute contraindication to the use of any antihypertensive agent in renal transplant recipients. †Both dihydropyridine and nondihydropyridine CCBs. ‡Nondihydropyridine CCBs. §See text.

study findings suggest that treating 100 patients with average risk of graft loss over the first year (approximately 10%) with CCBs, compared with no treatment, would prevent three patients from losing their grafts, irrespective of the presence or absence of hypertension. However, CV disease events and mortality were not reported. Based on currently existing literature, there appears to be no contraindication to the use of CCs in the transplant setting, although monotherapy with dihydropyridine CCBs should be used with caution (see also Chapter 80).

Angiotensin-converting enzyme inhibitors and ARBs block calcineurin inhibitor (CNI) toxicity in experimental models and are protective in patients with CKD. However, they can cause acute changes in renal function as well as hyperkalemia and hence are usually not started until allograft function is stable. A meta-analysis of 21 randomized controlled trials demonstrated that ACE inhibitors and ARBs reduced proteinuria in transplant recipients, but they also lowered hematocrit by 3.5% and glomerular filtration rate (GFR) by 6 ml/min; there were insufficient data to determine the effect of ACE inhibitor or ARB use on patient or graft survival.[9] Serum potassium and creatinine concentrations must be closely monitored; if serum creatinine rises more than 30% above baseline, then transplant renal artery stenosis should be considered.

Because of the lack of conclusive evidence that one class of antihypertensive agent is superior to another in the transplant setting, treatment should be individualized. Potential advantages and disadvantages of different classes of antihypertensive agents in kidney transplant recipients are shown in Table 106-2.

Post-transplantation Dyslipidemia

Dyslipidemia is common after transplantation, in part because of the hyperlipemic effect of corticosteroids, cyclosporine, tacrolimus, sirolimus, and everolimus. Sirolimus and everolimus are associated with

the worst lipid profiles, followed by cyclosporine, and to a lesser extent tacrolimus. One single-center study demonstrated that the mean values of total cholesterol, LDL cholesterol, and triglycerides (TGs) and the incidence of CHD were higher among patients receiving mammalian target of rapamycin (mTOR) inhibitors compared with their CNI-treated counterparts (control group). However, the risk of CV events was not significantly higher among patients receiving mTOR inhibitors compared with controls at 4-year follow-up.[10] It is hypothesized that the antiproliferative effects of mTOR inhibitors may offset the adverse effects of hyperlipidemia. The dyslipidemic effect of mTOR inhibitors on the risk for CV disease events after kidney transplantation remains unclear; however, mTOR inhibitor–induced dyslipidemia should be treated aggressively. Other potential etiologic factors for post-transplant dyslipidemia include age, diet, rapid weight gain, hyperinsulinemia, preexisting hypercholesterolemia, allograft dysfunction, proteinuria, genetic predisposition, and the use of β-blockers and diuretics.

Although hyperlipidemia often improves within the first 6 months after transplantation as the doses of immunosuppressive agents are reduced, total and LDL cholesterol goals as defined by the National Cholesterol Education Program (NCEP) guidelines (www.nhlbi.nih.gov/about/ncep/index.htm) are usually not achieved. Hence, management of hyperlipidemia is usually required, and includes lifestyle changes (diet and exercise) and statins. In addition to their lipid-lowering effect, statins may offer protection against CV disease via their antiproliferative and anti-inflammatory properties and ability to reduce circulating endothelin-1, C-reactive protein levels, systolic and diastolic blood pressure, and pulse pressure.

The clinical benefits of statins in the general population have been demonstrated in several large randomized controlled trials. To date, there has been only one single prospective randomized trial in transplant recipients comparing statins (fluvastatin) with placebo—the ALERT study. The ALERT study showed that treatment of kidney transplant recipients with fluvastatin over a 5- to 6-year period significantly and safely reduced LDL cholesterol levels. The incidence of major adverse cardiac events was also shown to be reduced, albeit not statistically significantly. However, further analysis demonstrated a beneficial effect of early initiation of fluvastatin on outcome—the earlier the initiation of therapy, the greater the reduction in cardiac events. Patients who received statin therapy within the first 4 year after transplantation had a risk reduction of 64% compared with 19% for those who received therapy after 10 years. No statin effect on graft loss or doubling of serum creatinine was observed.[11-12] Despite the well-established efficacy and safety of the use of statins in transplant recipients, clinicians should be aware that the use of statins with CNIs, particularly cyclosporine, often results in a several-fold increase in statin blood level and an increased risk for myopathy and rhabdomyolysis.[13] Compared with other statins, simvastatin appears to be particularly prone to drug-drug interactions because of its extensive metabolism by CYP3A4.

Ezetimibe and statin combination therapy can significantly improve cholesterol control because of their complementary mechanisms of action. Ezetimibe blocks intestinal absorption of dietary cholesterol, whereas statin inhibits hepatic cholesterol synthesis. Ezetimibe used alone or as adjunctive therapy with statin appears safe and effective in the treatment of dyslipidemia in kidney transplant patients who are refractory to statin therapy. In a single-center study consisting of 67 patients with post-transplantation hyperlipidemia resistant to statins, treatment with ezetimibe alone or with ezetimibe and statin significantly reduced total cholesterol and LDL cholesterol by 25% and 34%, respectively, during the first month of treatment.[14] In another study of 56 kidney transplant recipients, the addition of ezetimibe to statin therapy slowed the decline in renal function compared with controls.[15] Whether ezetimibe-statin combination therapy is superior to statin-alone therapy in CV disease risk factor reduction remains to be elucidated.

Severe hypertriglyceridemia (TG level >500 mg/dl or 5.65 mmol/l) may occur with the use of sirolimus and everolimus. Management includes dose reduction, addition of a fibric acid derivative or nicotinic acid, and, in refractory cases, switching of sirolimus or everolimus to mycophenolate mofetil (MMF) or tacrolimus. The National Kidney Foundation expert panel recommends gemfibrozil as the fibrate of choice. However, fibrates should be avoided in those with CKD stage 5. Of the major fibric acid medications (bezafibrate, ciprofibrate, fenofibrate, and gemfibrozil), the first three can increase serum creatinine in cyclosporine-treated patients. Although all fibrates in combinations with statins have been associated with creatinine kinase elevations with or without overt rhabdomyolysis and myopathy, gemfibrozil may have a greater risk for the development of myopathy compared with bezafibrate or fenofibrate.[13]

Niacin monotherapy has not been reported to cause myopathy, but its combined use with lovastatin, pravastatin, or simvastatin may be associated with rhabdomyolysis. Bile acid sequestrants must be used with caution because of their potential interference with the absorption of CNIs and mycophenolic acid derivatives. Coadministration of bile acid sequestrants and mycophenolic acid products is not recommended. It should also be noted that studies in the general population suggest that bile acid sequestrants may increase TG levels. A more complete list of drug-drug interaction of statins with other lipid-lowering agents is provided in reference 13.

Statins should be the first-line therapy for the treatment of non–high-density lipoprotein (non-HDL) cholesterol because of their well-established safety and efficacy in preventing CV disease in randomized trials in the general population. Fibrates should be considered in those intolerant to statins despite dose reduction or despite switching to another statin. There are currently no data to suggest that adding fibrates to statin therapy is superior to adding nicotinic acid to statin therapy (or vice versa) in the treatment of post-transplant hypertriglyceridemia. Hence the choice of one agent over the other should be based on adverse effects and potential drug-drug interactions.

For patients with fasting TG levels above 1000 mg/dl (11.3 mmol/l), the Adult Treatment Panel (ATP) III recommends a very-low-fat diet (<15% total calories), medium-chain TGs, and fish oils to replace some long-chain TGs.

Suggested guidelines for pharmacologic treatment of dyslipidemia are summarized in Figure 106-1.

New-Onset Diabetes After Transplantation

New-onset diabetes mellitus after transplantation (NODAT) occurs in 4% to 25% of kidney transplant recipients. Variations in incidence may result from differences in definition, duration of follow-up, and the presence of both modifiable and nonmodifiable risks factors.[16] Major risk factors include African American, Hispanic, and South Asian ethnicity (compared with Caucasians or East Asians), obesity (defined as BMI greater than 30 kg/m^2), age older than 40 to 45 years, family history of diabetes among first-degree relatives, impaired glucose tolerance before transplantation or presence of other components of the metabolic syndrome, recipients of deceased donor kidneys, hepatitis C infection, and immunosuppressive therapy including corticosteroids; tacrolimus and to a lesser extent cyclosporine; and the mTOR inhibitors sirolimus and everolimus (Fig. 106-2).[16] Neither azathioprine (AZA) nor MMF is diabetogenic.

Other potential risk factors for the development of NODAT include the presence of certain human leukocyte antigens (HLAs)

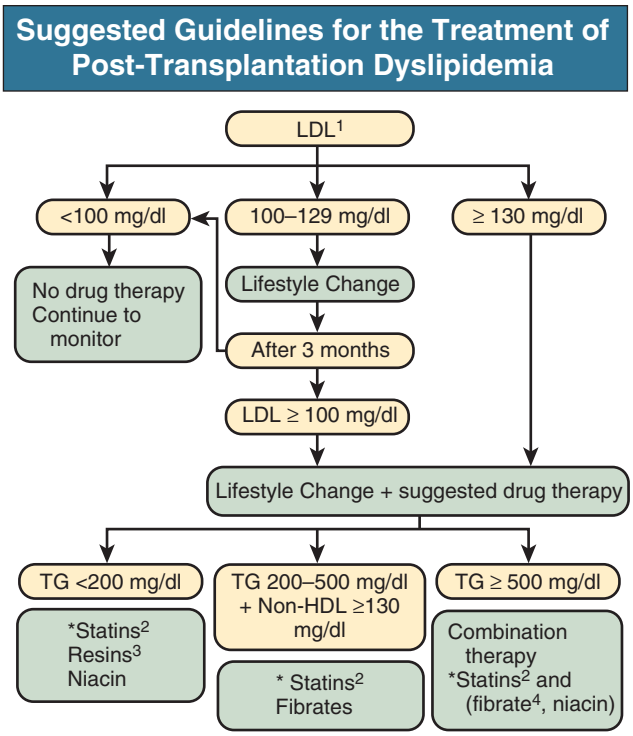

Figure 106-1 Suggested guidelines for the treatment of post-transplantation dyslipidemia. All transplant recipients should be regarded as CHD risk equivalent. Goals: LDL cholesterol below 100 mg/dl (optional <70 mg/dl[1]), TGs below 200 mg/dl, HDL above 40 to 50 mg/dl. *If LDL cholesterol targets not achieved with statin monotherapy, consider statins + cholesterol absorption inhibitor[5] combination. [1]LDL cholesterol below 70 mg/dl has been suggested for very-high-risk patients (NCEP, ATP III guidelines). [2]Statins are the most effective drugs and should be the agents of first choice. Start at low dose in patients on cyclosporine and tacrolimus. Monitor for myositis and transaminitis, particularly in those receiving combination therapy. [3]Coadministration of bile acid sequestrants and mycophenolic acid products is not recommended. [4]Extreme caution should be used with statin and fibrate combination therapy. *ATP III,* Adult Treatment Panel III; *CHD,* coronary heart disease; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein; *NCEP,* National Cholesterol Education Program; *TG:* triglyceride.

(such as A30, B27, and B42), increasing HLA mismatches, acute rejection history, cytomegalovirus (CMV) infection, male recipient, and male donor.[16] Polycystic kidney disease has been suggested to confer an increased risk of developing diabetes after kidney transplantation in some studies but not in others. Studies evaluating the association between genetic variations (single nucleotide polymorphism) and NODAT have been inconclusive. The findings of one single-center study suggest that new-onset hyperglycemia in the immediate postoperative period is predictive of future NODAT risk.[17]

Management of New-Onset Diabetes After Transplantation

In the general population, glycemic management in type 2 diabetes mellitus (T2DM) has become increasingly complex and often controversial because of the uncertain risks and benefits associated with intensive glycemic control and the widening array of pharmacologic agents available.[18] Both T2DM and NODAT are characterized by a relative or absolute impairment in insulin secretion, along with varying degrees of peripheral insulin resistance. In essence, NODAT resembles T2DM and it seems plausible to manage NODAT with a stepwise approach similar to that for patients with T2DM.

Patient-Centered Approach Medical management usually involves a multidisciplinary team approach involving patients (and frequently family members), transplant coordinators, transplant physicians, and diabetic educators. A shared decision-making approach whereby clinicians and patients mutually exchange information and reach a consensus on the therapeutic course of action is helpful.[18]

Target Hemoglobin A_{1c} Levels The 2011 American Diabetes Association's Standards of Medical Care in Diabetes recommend lowering hemoglobin A_{1c} (HbA_{1c}) to below 7.0% in most patients to reduce the incidence of microvascular disease. More stringent control (HbA_{1c} 6.0% to 6.5%) might be considered in a subset of patients with short disease duration, long life expectancy, and no significant CV disease, if this can be achieved without significant hypoglycemia or other treatment-related adverse effects.[18] For NODAT, the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines suggest a target A_{1C} level from 7.0% to 7.5%, not to fall below 6.0%, particularly if hypoglycemic reactions are

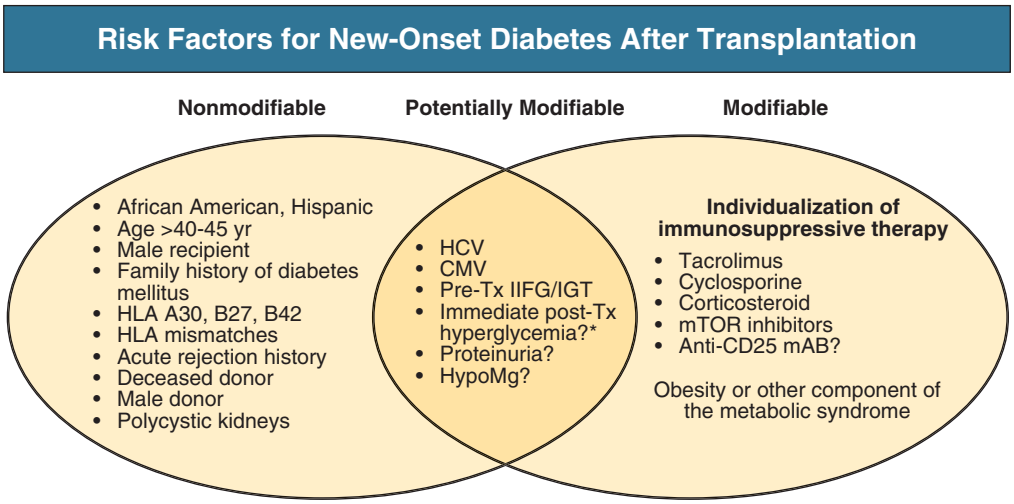

Figure 106-2 Risk factors for new-onset diabetes after transplantation (NODAT). *See text. *Anti-CD25 mAB,* anti-CD25 monoclonal antibody; *CMV,* cytomegalovirus; *HCV,* hepatitis C; *HLA,* human leukocyte antigen; *HypoMg,* hypomagnesemia; *IFG,* impaired fasting glucose; *IGT,* impaired glucose tolerance; *mTOR,* mammalian target of rapamycin; *Post-Tx,* post-transplant; *Pre-Tx,* pretransplant. *(Modified from reference 16.)*

common. In patients with diabetes, the use of low-dose aspirin (75 mg or 100 mg daily in Europe, 81 mg daily in the United States) for the primary prevention of CV disease should be based on patient preferences and values, balancing the risk of ischemic vascular events with the risk of bleeding.

Therapeutic Interventions

Nonpharmacologic Management The effect of lifestyle modification to prevent or delay the progression of post-transplantation impaired glucose to overt NODAT has not been studied. A small cross-sectional and observational study showed that higher levels of physical activity were associated with a lower risk of abnormal glucose tolerance and obesity in kidney transplant recipients. In contrast, individuals with limited physical activity consistently showed higher rates of abnormal glucose tolerance and central obesity.[19] Because higher pretransplant BMI correlates with insulin resistance after transplantation, obesity treatment seems to be a reasonable target for intervention.[20]

We recommend promoting lifestyle modification in kidney transplant recipients, including moderation of dietary sodium (<2400 mg sodium per day) and saturated fat intake (<7% calories from saturated fats, 2% to 3% calories from *trans*-fatty acids), regular aerobic exercise, and weight reduction. Carbohydrate intake should be limited to 50% to 60% of caloric intake. The American Heart Association guidelines in non–transplant recipients also suggest intake of at least 25 g of dietary fiber per day and two servings of fish per week. Defining realistic goals such as a target weight loss of 5% to 10% of total body weight and a patient-centered approach to education may be invaluable in achieving success.

Modification of immunosuppression should be considered in high-risk patients. Corticosteroid dose reduction significantly improves glucose tolerance during the first year after transplantation. However, any dose reduction should be weighed against the risk of acute rejection. A corticosteroid-sparing regimen or corticosteroid avoidance protocol should be individualized. Tacrolimus-to-cyclosporine conversion therapy in patients who fail to achieve target glycemic control or in those with difficult-to-control diabetes has yielded variable results. At the authors' institution, tacrolimus-treated patients who develop NODAT are often switched to cyclosporine. Conversion therapy has resulted in variable improvement in glycemic control and should be considered in such patients. However, mycophenolate exposure is lower with cyclosporine than with tacrolimus immunosuppression; hence mycophenolate dosage adjustment or drug level monitoring may be necessary.

Pharmacologic Treatment Orally administered agents are often required to treat NODAT. Although oral hypoglycemic agents may be effective, insulin therapy may be necessary in up to 40% of patients, particularly in the early post-transplantation period.

Metformin is preferred for overweight patients but is contraindicated in patients with a GFR below 50 ml/min because in such patients it can cause lactic acidosis. Sulfonylureas should be titrated slowly for patients with reduced GFR or in elderly patients because of the increased risk of hypoglycemia. In these patients, it is best to start with a low dose and titrate upward every 1 to 2 weeks. Sulfonylureas may also be associated with modest weight gain and secondary failure rate from exacerbation of islet dysfunction.[18] The nonsulfonylurea meglitinides are insulin secretagogues with a mechanism of action similar to that of the sulfonylureas. They have a more rapid onset and shorter duration of action and seemingly a lower risk of hypoglycemia and lower weight gain. These agents are therefore best suited for patients whose food intake is erratic, elderly patients, and patients with impaired graft function. They are best taken before meals, and the dose may be omitted if a meal is skipped.

The thiazolidinedione (TZD) derivatives are insulin sensitizers that may allow for a reduction in insulin requirement. They do not increase the risk of hypoglycemia and may have a more durable effect than sulfonylureas or metformin.[18] Potential adverse effects of these agents include weight gain, peripheral edema, anemia, pulmonary edema, congestive heart failure, and increased fracture risks. The incidence of peripheral edema is increased when TZDs are used in combination with insulin. Rosiglitazone has been removed from the market because of the concerns of increased myocardial infarction risk. More recently, pioglitazone has been reported to be associated with a possible risk of bladder cancer.[18]

Glucagon-like peptide 1 (GLP-1) analogues and dipeptidyl peptidase–4 (DDP-4) inhibitors are incretin-based agents that amplify the effects of naturally occurring GLP-1. In contrast to insulin and most other glucose-lowering agents that cause weight gain or hypoglycemia, GLP-1 inhibitors and DDP-4 inhibitors have a favorable or neutral effect on weight reduction and no inherent risk of hypoglycemia. Concerns regarding an increased risk of pancreatitis and pancreatic cancer associated with the use of GLP-1 receptor agonists remain unresolved.

Routine recommendations include measurement of HbA_{1c} level every 3 months and regular screening for diabetic complications including microalbuminuria, retinopathy, and polyneuropathy with associated lower extremity ulcerations and infections. Fasting lipid profile should be measured annually. In transplant recipients with multiple CV disease risk factors, more frequent monitoring of lipid profile should be performed at the discretion of the clinicians. Box 106-1 provides guidelines for the management of NODAT. Of note, HbA_{1c} cannot be accurately interpreted within the first 3 months after transplantation because anemia and impaired graft function can directly interfere with the HbA_{1c} assay. Recent blood transfusion or the use of dapsone may also alter HbA_{1c} levels.

Cigarette Smoking

Smoking by donor or recipient may affect outcomes after solid organ transplantation.[21] A history of smoking in kidney donors has been shown to be associated with decreased graft and recipient survival.[21]

As in the general population, cigarette smoking is associated with increased CV disease morbidity and mortality in kidney transplant recipients. Smoking cessation 5 years before transplantation reduces the risk of death by 29%.[22] Every effort should be made to encourage patients to quit smoking. A multifaceted approach including behavioral and pharmacologic strategies appears to be most effective.

Obesity

Obesity at transplantation (defined as BMI ≥30 kg/m^2) has a reported prevalence of 9.5% to 29%, and its prevalence among transplant recipients in the United States doubled between 1987 and 2001. A high BMI at transplant is a significant independent predictor of congestive heart failure and atrial fibrillation.[23] The impact of BMI on cardiac-related death follows a U-shaped risk, with an adjusted risk of cardiac death increased at both low and high BMI compared with a reference group with a BMI of 22 to 24 (with a hazard ratio [HR] of 1.3 for BMI <20; HR 1.2 for BMI 30 to 32; HR 1.4 for BMI >36).[24]

Management of post-transplantation obesity includes lifestyle and dietary modification. Corticosteroid reduction or withdrawal must be balanced against the risk of graft rejection and graft loss. The use of pharmacologic agents for weight reduction in the post-transplantation period is currently not recommended because of unknown potential drug-drug interactions.

Management of New-Onset Diabetes After Transplantation

Dietary Modification

- Dietician referral.
- For diabetic dyslipidemia: A diet low in saturated fats and cholesterol and high in complex carbohydrates and fiber is recommended.
- The AHA* guidelines suggest limiting cholesterol (<200 mg/day for those with diabetes mellitus); less than 7% of calories from saturated fats; 2% to 3% of calories from *trans*-fatty acids; and 2400 mg or less of sodium per day. More than 25 g of dietary fiber per day and two servings of fish per week are also recommended.

Lifestyle Modifications

- Exercise
- Weight reduction or avoidance of excessive weight gain
- Smoking cessation

Adjustment or Modification in Immunosuppressive Medications†

- Rapid corticosteroid taper, corticosteroid-sparing or corticosteroid-avoidance protocols
- Tacrolimus to cyclosporine conversion

Pharmacologic Therapy

- Acute, marked hyperglycemia (may require inpatient management)
- Insulin therapy (consider insulin drip when glucose is 400 mg/dl or higher)
- Chronic hyperglycemia: target HbA_{1c} 7.0% to 7.5%, not to fall below 6.0% (see text)
- Oral glucose-lowering agent monotherapy or combination therapy‡ and/or insulin therapy
- Consider diabetologist referral if HbA_{1c} remains at 9.0% or higher

Monitoring of Patients with NODAT

- HbA_{1c} every 3 months
- Screening for microalbuminuria
- Regular ophthalmologic examination
- Regular foot care
- Annual fasting lipid profile
- Aggressive treatment of dyslipidemia and hypertension

Box 106-1 Management of new-onset diabetes after transplantation (NODAT). *American Heart Association. †Clinicians must be familiar with the patient's immune history before manipulating immunosuppressive therapy. ‡The choice of a particular agent should be based on the characteristics of each individual patient (see text). *(Modified from reference 2.)*

Data are inadequate regarding the safety and efficacy of post-transplantation gastric bypass surgery or adjustable gastric banding in ameliorating comorbid conditions such as hypertension, diabetes mellitus, and dyslipidemia. In an analysis of the United States Renal Data System (USRDS) database, mortality rates in patients undergoing gastric bypass surgery after transplantation were higher compared with those without kidney disease who had undergone the same surgery. Nonetheless, the difference in mortality rates was thought to be within "acceptable range" and attributed to poor wound healing associated with the use of immunosuppressive therapy. In a small series of five patients (mean age 40.8 years; mean BMI 52.2) who underwent laparoscopic bariatric surgery after kidney transplantation, there were no postoperative complications and the percent of excess weight loss at 2 years was over 50% in all patients.[25] With the refinement in surgical techniques and advancement in postoperative care, post-transplantation bariatric surgery for morbid obesity should be explored.

Aspirin and Antiplatelet Therapies

Aspirin is widely used to reduce CV events in nontransplant patients. Among patients with a functioning graft at 1 year, the use of antiplatelet medications in the first year after transplantation was also associated with a 27% lower risk of major cardiac events at 5 years.[7]

Unconventional Cardiovascular Disease Risk Factors

Proteinuria

Proteinuria occurs in 9% to 40% of kidney transplant recipients with a functioning graft. Proteinuria from native kidneys typically decreases rapidly after transplantation, whereas worsening proteinuria frequently suggests allograft pathology. As in the nontransplant setting, post-transplantation proteinuria increases the risk of CV events, graft loss, and mortality. Controlled trials evaluating the beneficial effect of treating proteinuria in reducing CV risk in kidney transplant recipients are lacking. The Canadian randomized double-blind controlled trial evaluating the effect of ramipril versus placebo in kidney transplant recipients with proteinuria and an eGFR of 20 to 55 ml/min/1.73 m^2 is anticipated to complete enrollment by the end of 2014. While the routine recommendations regarding ACE inhibitor or ARB use for the treatment of proteinuria after kidney transplant await results of controlled trials, ACE inhibitors or ARBs should be considered in transplant recipients with proteinuria because of their well-established antiproteinuric and cardioprotective effects. The 2009 KDIGO clinical practice guidelines recommend ACE inhibitors or ARBs as first-line therapy for patients with hypertension and documented proteinuria of 1 g/day or more.

Cardiac Troponin T

Cardiac troponin T (cTnT) has been recently proposed to provide prognostic information in the cardiac evaluation of patients with end-stage renal disease (ESRD). Increased levels of cTnT correlate with all-cause and cardiac death risk in asymptomatic patients with ESRD, and higher pretransplant cTnT was associated with increased risk of post-transplant death and cardiac events independent of CV risk factors. Although cTnT levels decline rapidly after transplant, patients in whom cTnT do not fall to normal have a high risk of death or cardiac events.[26] Therefore, persistently elevated cTnT levels in the pretransplant and post-transplant period can be used to define a target population for CV risk modification or intervention programs.

COMMON LABORATORY ABNORMALITIES

Anemia

In the immediate post-transplantation period, aggressive perioperative volume expansion may result in dilutional anemia. Refractory or severe anemia mandates aggressive evaluation to exclude the possibility of surgical postoperative bleeding, particularly in those with a rapid fall in hemoglobin and hematocrit levels.

Mild anemia is common in the early post-transplantation period when erythropoietin (EPO) therapy is typically discontinued, but usually improves within several weeks to months. Suggested etiologic factors for post-transplantation anemia include iron deficiency, impaired graft function, acute rejection episodes, recent infection, and medications (such as AZA, MMF, sirolimus, everolimus, and

ACE inhibitors and ARBs). Anemia has also been reported to be more common in African American and female transplant recipients.

Assessment of baseline iron stores at the time of transplantation may be invaluable because iron deficiency is not uncommon in the dialysis population. Profound iron deficiency should be treated with intravenous iron as tolerated. EPO therapy and darbepoetin alfa are effective in the treatment of anemic kidney transplant recipients. Although the 2009 Kidney Disease Outcomes Quality Initiative (KDOQI) anemia guidelines recommend a target hemoglobin level of 11 to 13 g/dl for patients with CKD, high hemoglobin and high epoetin doses in large CKD anemia trials demonstrated a possible harmful effect. Furthermore, observational studies in kidney transplant recipients suggested that mortality may be increased with hemoglobin levels above 12.5 g/dl. Although evidence-based recommendations await the result of large randomized trials comparing the safety and efficacy of EPO-stimulating agents versus placebo, management of post-transplantation anemia to keep hemoglobin level in the range of 10 to 12 g/dl seems plausible.

Refractory anemia or anemia that fails to rise gradually to a normal or near-normal level after the first few post-transplantation weeks can be a result of occult gastrointestinal bleeding, tertiary hyperparathyroidism, underlying inflammatory conditions, or parvovirus B19 infection. Sirolimus or everolimus, AZA, MMF, and other commonly used drugs including ACE inhibitors and ARBs may cause or exacerbate anemia and should not be overlooked. EPO-resistant anemia has been described in patients receiving sirolimus immunosuppression. In stable kidney transplant recipients, conversion from sirolimus to enteric-coated MMF may help resolve anemia. Although uncommon, drug-induced hemolysis from agents including dapsone or other causes of hemolysis should also be considered.

Leukopenia and Thrombocytopenia

Leukopenia and thrombocytopenia are most commonly related to adverse drug effects from agents including AZA, antilymphocyte antibody treatment, MMF, sirolimus, everolimus, and trimethoprim-sulfamethoxazole, among others. Withholding of the offending agent or dose reduction generally corrects these hematologic abnormalities. Severe leukopenia may be safely treated with granulocyte-stimulating factor. Thrombotic microangiopathy (TMA) or CMV infection should be excluded. Parvovirus B19 infection may present with refractory anemia, pancytopenia, and TMA. An increase in the incidence of leukopenia was found in transplant recipients receiving alemtuzumab induction. Other hematologic adverse effects of alemtuzumab include anemia, lymphopenia, and thrombocytopenia. Alemtuzumab-induced aplastic anemia has also been reported in the postmarketing phase. Bortezomib, a novel first-in-class proteasome inhibitor recently introduced into clinical transplantation for the treatment of antibody-mediated rejection and desensitization protocols, has been shown to cause leukopenia and thrombocytopenia. The risk of thrombocytopenia is increased in patients with baseline low-platelet counts

Erythrocytosis

Post-transplant erythrocytosis (PTE) occurs in 8% to 25% of transplant recipients within the first 2 years. The incidence of PTE appears to have decreased in recent years, ascribed to more frequent use of ACE inhibitors and ARBs. Risk factors for PTE include the presence of native kidneys, male gender, excellent graft function and the absence of rejection episodes, high baseline hemoglobin before transplant, and hypertension. Smoking and diabetes have been shown to be risk factors for PTE in some but not all studies. Other suggested risk factors include polycystic kidney disease and GN as the cause of ESRD. Transplant renal artery stenosis has not been consistently shown to be a risk factor for PTE. Both hormonal systems and growth factors have been implicated in the pathogenesis of PTE. These may include defective feedback regulation of EPO metabolism, direct stimulation of erythroid precursors by angiotensin II, abnormalities in levels of circulating insulin-like growth factor 1 (IGF-1) and its binding proteins, and an increase in serum-soluble stem cell factors, which stimulates the growth of erythroid progenitor cells. Serum-soluble stem cell factors have been shown to correlate with both hematocrit values and with the observed and expected EPO values in kidney transplant recipients with PTE.[27]

Treatment is generally recommended for a hemoglobin level exceeding 17 to 18 g/dl or a hematocrit level over 51% to 52% because of the associated risk of thromboembolic complications, hypertension, and headaches. Treatment with ACE inhibitors or ARBs is often sufficient, although phlebotomy may occasionally be necessary. A negative association between the use of sirolimus and PTE has been reported. Nonetheless, modification of immunosuppressive medications to treat PTE has generally not been done in clinical practice.

Hyperkalemia

Mild hyperkalemia is commonly encountered in kidney transplant recipients particularly in the early post-transplantation period with higher doses of CNI. It is often associated with mild hyperchloremic acidosis, a clinical presentation reminiscent of type 4 renal tubular acidosis. Suggested mechanism(s) of CNI-induced hyperkalemia include hyporeninism hypoaldosteronism, aldosterone resistance, and inhibition of cortical collecting duct potassium secretory channels. Cyclosporine has been shown to decrease Na^+,K^+-ATPase activity in K^+ secretory cells in the cortical and outer medullary collecting tubules, thereby decreasing intracellular K^+ accumulation required for urinary secretion. In patients receiving cyclosporine or tacrolimus immunosuppression, a potassium level in the range of 5.2 mmol/l to 5.5 mmol/l is typically seen. Higher potassium levels, especially in the presence of concomitant use of drugs that may exacerbate hyperkalemia such ACE inhibitors, ARBs, and β-blockers, may require their discontinuation. Caution is needed when potassium-containing phosphorus supplements are prescribed. Although trimethoprim can cause hyperkalemia via an amiloride-like effect, the routine use of low-dose trimethoprim-sulfamethoxazole prophylactic therapy is rarely the cause of severe or refractory hyperkalemia in kidney allograft recipients. Finally, because efficient renal potassium secretion requires good urine flow, urinary obstruction must also be considered in the presence of hyperkalemia. Treatment of hyperkalemia is discussed in Chapter 9. Sodium polystyrene sulfonate (Kayexalate) or calcium resonium enemas should be avoided in the early post-transplantation period to avoid colonic dilation and perforation.

Hypokalemia

Sirolimus may be associated with hypokalemia. Hypokalemia has been reported in 34% and potassium supplementation was required in 27% of patients treated with sirolimus.[28] Sirolimus-induced increased tubular secretion of potassium has been suggested as a possible mechanism.[29] Furosemide is frequently used in the early

post-transplantation period, and hence diuretic-induced hypokalemia should also not be overlooked.

Hypophosphatemia

Hypophosphatemia is frequently encountered in the first months after transplantation. Concomitant hypercalcemia suggests post-transplantation hyperparathyroidism. In the absence of hypercalcemia, renal phosphate wasting syndrome or malnutrition should be considered. Early after transplantation, hypophosphatemia has been attributed to a massive initial diuresis, particularly after a living-donor kidney transplant, defective renal phosphate reabsorption caused by ischemic injury, glucosuria (caused by hyperglycemia-induced osmotic diuresis), magnesium depletion, and corticosteroid use—the latter by inhibiting proximal tubular reabsorption of phosphate. There has been increasing evidence suggesting that fibroblast growth factor 23 (FGF-23) plays a major contributory role in the development of early post-transplantation hypophosphatemia independent of parathyroid hormone (PTH) level. FGF-23 is a phosphaturic hormone and its levels are increased in the early stages of CKD and significantly elevated in dialysis patients. Pretransplant FGF-23 was found to be the main predictor of post-transplant phosphate levels.[30] In contrast to hypophosphatemia occurring in the early post-transplant period, persistent hypophosphatemia beyond 1 year after transplant has been attributed mainly to persistent hyperparathyroidism rather than to increased FGF-23 levels.

Hypercalcemia

Hypercalcemia is common after transplantation and is generally a result of persistent secondary hyperparathyroidism. The concomitant presence of severe hypophosphatemia, particularly in patients with excellent graft function, may exacerbate hypercalcemia through stimulation of renal proximal tubular 1α-hydroxylase. Resolution of soft tissue calcifications, high-dose corticosteroid therapy, and immobilization are potential contributing factors. In about two thirds of patients, hypercalcemia resolves spontaneously within 6 to 12 months. However, spontaneous resolution occurs in less than half of those whose hypercalcemia existed before transplantation. Persistent hyperparathyroidism has generally been attributed to continued autonomous production of PTH from nodular hyperplastic glands, reduced density of calcitriol receptors, and decreased expression of the membrane calcium sensor receptors that render cells more resistant to physiologic concentrations of calcitriol and calcium. Persistently elevated FGF-23 levels after transplant may contribute to persistent hyperparathyroidism through inhibition of 1α-hydroxylase activity leading to low calcitriol levels. The risk of persistent hyperparathyroidism is increased with the duration of dialysis and the severity of pretransplant hyperparathyroidism. Severe hypercalcemia or persistent hypercalcemia (≥12 months) requires further evaluation. Initial assessment should include an intact PTH level. Imaging studies, including neck ultrasound or parathyroid technetium 99m (^{99m}Tc)–sestamibi scan, are required to determine if the clinically observed hyperparathyroidism arises from parathyroid adenoma or parathyroid gland hyperplasia, or hyperplastic nodular formation of the parathyroid glands.

Early studies demonstrated that cinacalcet, a calcimimetic drug, reduces serum calcium in kidney transplant recipients with hypercalcemic hyperparathyroidism. However, with the increasing use of cinacalcet, cinacalcet-induced nephrocalcinosis and graft failure have been reported.[31] Parathyroidectomy is warranted in patients with tertiary hyperparathyroidism or persistent severe hypercalcemia (>11.5 to 12 mg/dl [2.87 to 3.0 mmol/l]) for longer than 6 to 12 months, symptomatic or progressive hypercalcemia, nephrolithiasis, persistent metabolic bone disease, calcium-related renal allograft dysfunction, or progressive vascular calcification and calciphylaxis.[32] In a retrospective cohort study of 83 kidney transplant recipients with tertiary hyperparathyroidism, parathyroidectomy resulted in a lower serum calcium level (9.28 mg/dl) compared with cinacalcet (10.20 mg/dl) ($P < .01$) at 6 weeks. The highest pretreatment calcium level was higher in patients treated with parathyroidectomy compared with cinacalcet (12.2 vs. 11.7 mg/dl, $P < .01$). One fourth of the "observation" group showed persistent hypercalcemic symptoms, compared with 7.7% in the cinacalcet and 0% in the parathyroidectomy group ($P < .01$).[33] Whether calcimimetics confer better normalization of biochemical parameters and obviate the need for parathyroidectomy remains to be determined. Furthermore, clinicians should remain vigilant for the potential development of nephrocalcinosis associated with the use of cinacalcet.

Hypomagnesemia

Cyclosporine, tacrolimus, and sirolimus can cause hypomagnesemia by inducing urinary magnesium wasting. Other factors that may contribute to post-transplantation hypomagnesemia include loop diuretic therapy, recovery from acute tubular necrosis, post–obstructive polyuria status, and renal tubular acidosis. Hypomagnesemia may be more common in diabetics. In the first 3 months after transplantation, a magnesium level below 1.5 mg/dl (0.62 mmol/l) is common. Dietary magnesium intake is usually insufficient, and high-dose oral magnesium supplementation (i.e., 400 to 800 mg magnesium oxide three times a day) may be required. Intravenous magnesium should be considered in patients with severe hypomagnesemia (<1.0 mg/dl or 0.41 mmol/l), particularly patients with a prior history of CHD or cardiac arrhythmias and those taking digoxin. Aggressive treatment of hypomagnesemia reduces cyclosporine-induced neurotoxicity and may enhance blood pressure control.

Abnormal Liver Function Tests

Elevation of hepatic enzymes is common in the early post-transplantation period and is generally caused by drug-related toxicity. Potential culprits include acyclovir, ganciclovir, trimethoprim-sulfamethoxazole, cyclosporine, tacrolimus, sirolimus, everolimus, statin therapy, and proton pump inhibitors. Cyclosporine and less commonly tacrolimus may cause transient, self-limited, dose-dependent elevations of transaminase levels and mild hyperbilirubinemia secondary to defective bile secretion. Elevated liver enzymes caused by drug-related adverse effects generally improve or resolve after drug discontinuation or dose reduction.

Persistent or profound elevation in hepatic liver enzymes should prompt further evaluation to exclude infectious causes including CMV, hepatitis B virus (HBV), and hepatitis C virus (HCV). In high-risk candidates for primary CMV infections (recipient seronegative, donor seropositive), it may occasionally be necessary to initiate CMV therapy pending laboratory results, particularly when there is a high index of clinical suspicion (fever, fatigue, malaise, gastroenteritis, leukopenia or thrombocytopenia). Evidence of post-transplant HBV reactivation (elevated alanine transaminase (ALT), histologic hepatitis, and serum DNA $>10^5$ copies/ml) should be treated with lamivudine or the newer nucleoside analogue entecavir. Some programs routinely initiate antiviral prophylaxis in all hepatitis B surface antigen (HBsAg)–positive candidates at the time of transplantation. Pretransplantation antiviral prophylactic therapy is recommended in

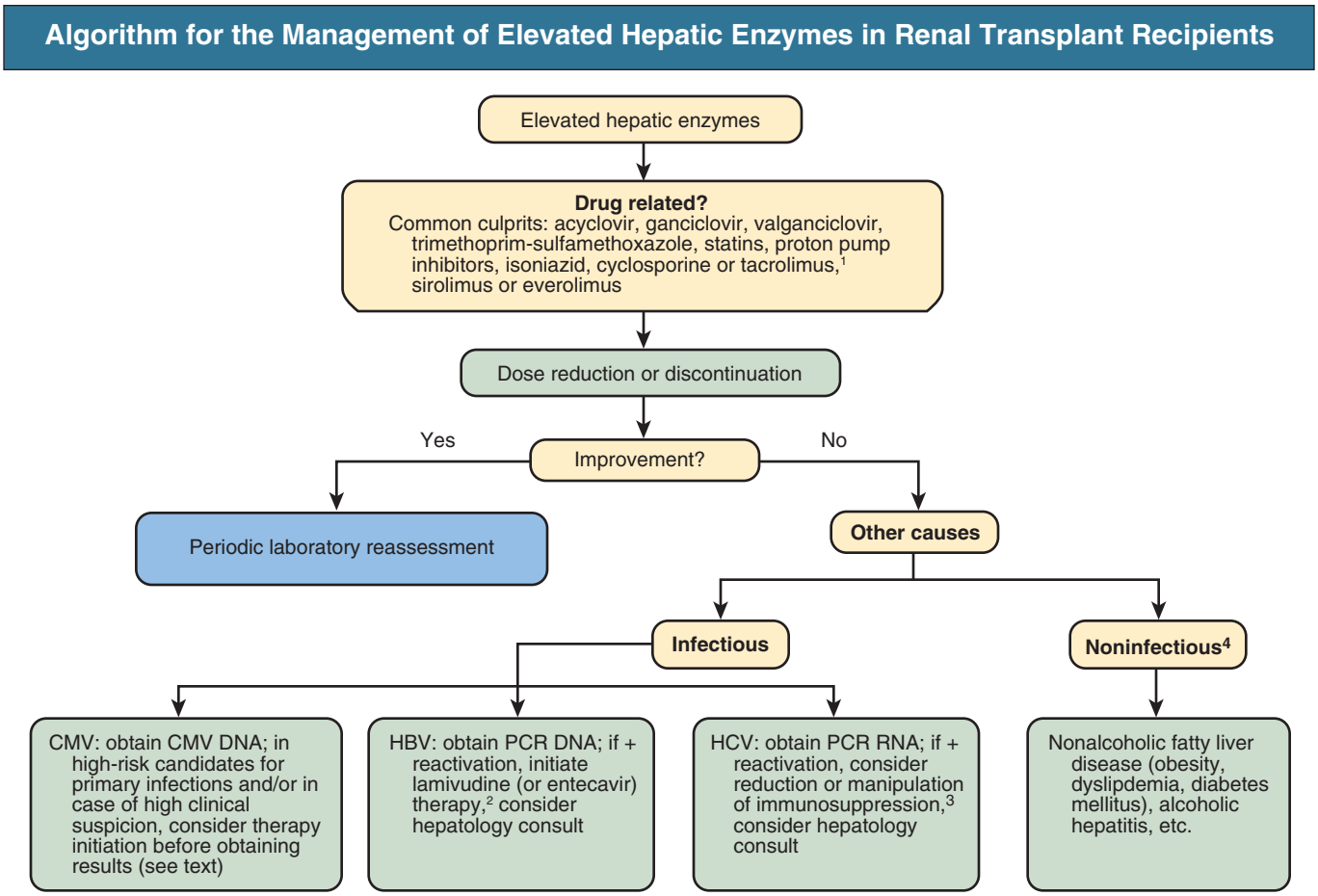

Figure 106-3 Algorithm for the management of elevated hepatic enzymes in kidney transplant recipients. [1]Cyclosporine and less commonly tacrolimus may cause transient, self-limited dose-dependent elevations of aminotransferase levels and mild hyperbilirubinemia secondary to defective bile secretion. [2]Some programs routinely commence antiviral prophylactic therapy in all HBsAg-positive candidates at the time of transplantation. [3]There is currently no effective treatment for chronic hepatitis C in kidney transplant recipients (see text). [4]Appropriate evaluation and management similar to nontransplant settings. *CMV,* Cytomegalovirus; *HBsAg,* hepatitis B surface antigen; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *PCR,* polymerase chain reaction.

kidney transplant candidates who have HBV DNA exceeding 10^5 copies/ml and active liver disease defined as ALT more than two times the upper limit of normal or biopsy-proven hepatic disease. Suppression of HBV replication with nucleotide analogues has been suggested to improve the survival of HBV-infected kidney transplant recipients.[34] There is currently no effective treatment for chronic hepatitis C in kidney transplant recipients. Although treatment with interferon-α may result in clearance of HCV RNA in 25% to 50% of patients, rapid relapse after drug withdrawal is nearly universal. More important, interferon-α treatment has been shown to precipitate acute allograft rejection and graft loss and is currently not routinely recommended for kidney transplant recipients with HCV infection. Its use should be individualized at the discretion of the transplant nephrologist and hepatologist. Studies evaluating interferon-free regimens showed promising results. At present, the management of HCV infection in this patient population should probably rely on manipulation of immunosuppressive therapy. Experiences gained from liver transplantation indicate that corticosteroid therapy and antilymphocyte antibody treatment are associated with enhanced viral replication and more rapid progression to cirrhosis. Based on these observations, it is advisable to avoid antilymphocyte antibody induction therapy and minimize corticosteroid dosage in transplant recipients with chronic HCV infection. A suggested algorithm for the management of kidney transplant recipients with elevated hepatic enzymes is shown in Figure 106-3.

BONE AND MINERAL METABOLISM AFTER TRANSPLANTATION

Post-transplantation Bone Disease

Post-transplantation bone disease is a common and complex complication after kidney transplantation because of the adverse effects of immunosuppression, mainly with corticosteroids, hypophosphatemia, and disturbances in the FGF-23–PTH–vitamin D axis. Corticosteroids act on the skeletal system by directly inhibiting osteoblastogenesis and inducing apoptosis of osteoblasts and osteocytes, and by increasing bone resorption through osteoclast activation. Other adverse effects of corticosteroids on bone mechanical integrity include inhibition of intestinal calcium absorption, enhancement of renal calcium excretion, and direct suppression of gonadal hormone secretion. Low plasma calcidiol 25(OH) vitamin D level may also contribute to bone disease and is very common in kidney transplant recipients, with a reported prevalence of calcidiol deficiency of 30% and insufficiency of 81%. Suggested causative factors include nutritional deficiency, malabsorption, decreased sun exposure, and increased metabolism of calcidiol to calcitriol after a successful kidney transplant.

Other factors that have been suggested to contribute to post-transplantation bone loss include "normal" age-dependent osteoporosis, persistent metabolic acidosis, phosphate depletion, diabetes

mellitus, hypogonadism, and smoking. Experimental animal models suggest that CNIs may contribute to post-transplantation bone loss by stimulating bone resorption. However, *in vivo* studies show that CNIs may increase bone resorption, leading to bone formation.[35] Sirolimus may interfere with the proliferation and differentiation of osteoblasts, but more important, it inhibits osteoclast formation. One small European study showed that sirolimus decreased serum level of bone resorption markers in patients treated with sirolimus compared with those receiving a CNI-based regimen.[36] Everolimus may also inhibit bone resorption and prevent bone loss based on experimental studies.[37] The effects of mTOR inhibitors on post-transplantation bone disease remain unclear.

Osteoporosis

Post-transplantation decline in bone marrow density (BMD) is most pronounced in the first 6 months and correlates with higher corticosteroid exposure in the early post-transplantation period. This early rapid decrease in BMD is usually followed by a slower rate of bone loss, which reflects cumulative corticosteroid dose. BMD has been reported to decrease at a mean of 5.5% to 19.5% during the first 6 months after transplant, 2.6% to 8.2% from months 6 to 12, and 0.4% to 4.5% thereafter.[38] Controversy exists as to whether bone loss continues to decline, stabilizes, or even reverses after the first year. A decrease in BMD averaging 1.7% per year in later post-transplant years has been reported by some, whereas stabilization during the second year, followed by an improvement of 1% to 2% per year thereafter has been observed by others. Limited bone biopsy studies in kidney transplant recipients demonstrated that low-turnover bone disease including adynamic bone and osteomalacia are common.[38] However, larger studies involving bone biopsies to better assess the combined effects of pretransplantation renal osteodystrophy and post-transplantation bone disease associated with immunosuppression are needed.

Evaluation of patients for bone loss or osteoporosis relies on the measurement of BMD using dual energy x-ray absorptiometry (DXA) scan. In kidney transplant recipients with an eGFR over 30 ml/min/1.73 m^2, the KDIGO guidelines suggest BMD measurement in the first 3 months after transplant if patients receive corticosteroids or have risk factors for osteoporosis as in the general population (low quality of evidence). In patients in the first 12 months after transplant with an eGFR exceeding 30 ml/min/1.73 m^2 and low BMD, the KDIGO guidelines suggest that consideration should be given to treatment with vitamin D, calcitriol or alfacalcidol, or bisphosphonates (low quality of evidence). In transplant recipients with CKD stage 4 or 5, the KDIGO guidelines do not recommend routine BMD screening because it does not predict fracture risk as it does in the general population. It should be noted that in the setting of combined osteoporosis and CKD, DXA may be completely misleading. For instance, adynamic bone disease, mild hyperparathyroidism, and genuine osteoporosis may yield the same BMD, yet therapy is very different. Hence, BMD can be interpreted only in the clinical and laboratory settings, and bone biopsy should be performed if uncertainty arises.

Avascular Necrosis

Post-transplantation osteonecrosis (avascular necrosis [AVN]) occurs with an incidence of 3% to 16% and most commonly affects the femoral head and neck. AVN usually occurs within the first few years after transplantation and may affect other joints including the knees, the shoulders, and less commonly the ankles, elbows, and wrists. Predisposing factors for the development of AVN include greater exposure to intravenous corticosteroid pulse therapy, low bone mass, hyperparathyroidism, increasing dialysis duration, excessive weight gain, hyperlipidemia, microvascular thrombosis, and a history of local trauma. Studies in kidney transplant recipients maintained on a corticosteroid-free immunosuppressive regimen demonstrated low rates of AVN at 3-year follow-up.[39] Cyclosporine has also been suggested to increase the risk of osteonecrosis because of its vasoconstrictive effect.

Early AVN of the femoral head commonly presents with hip or groin pain or referred knee pain. Symptoms may be aggravated by weight bearing but may also be paradoxically worse at night. Magnetic resonance imaging is the most sensitive technique for early detection. Plain radiographs are of limited diagnostic value in the early stage. Use of crutches to avoid weight bearing on the affected side and orthopedic referral are advisable. Drastic corticosteroid dose reduction or discontinuation has little if any effect on altering the course of established AVN and may jeopardize graft function.

Prevention and Management of Post-transplantation Bone Diseases

Management of post-transplantation bone disease has largely been based on studies involving postmenopausal osteoporosis and corticosteroid-induced osteopenia in nontransplant settings. Limited studies in solid organ transplantation have yielded variable and conflicting results, in part because of the complex pathophysiology of bone and mineral metabolism after transplantation, particularly in recipients of kidney transplants. Nonetheless, preventive measures to minimize post-transplantation bone loss should be initiated early after transplantation. Early ambulation and physical exercise should be encouraged. Adequate calcium supplementation (1000 mg/day) in nonhypercalcemic patients is recommended in the first post-transplantation year to prevent rapid bone loss resulting from corticosteroid-induced decreased intestinal calcium absorption. The KDIGO practice guidelines recommend measuring calcidiol levels and correcting vitamin D deficiency and insufficiency with use of treatment strategies recommended for the general population. In patients at increased risk for fracture, consideration should be given to rapid corticosteroid withdrawal or corticosteroid-free immunosuppressive protocols after weighing the risks and benefits of acute rejection. High pretransplantation PTH levels predict persistent hyperparathyroidism after transplantation, which may contribute to bone loss after transplantation. Hence, preexisting hyperparathyroidism associated with CKD should be treated according to the KDOQI guidelines.

In patients with preexisting secondary hyperparathyroidism, hypercalcemia and hypophosphatemia may develop after a successful kidney transplant because of the combined effect of persistent hyperparathyroidism and the newly elevated calcitriol level. The contributory role of FGF-23 in the development of post-transplant hypophosphatemia was previously discussed. Conservative management with phosphate replacement and suppression of hyperparathyroidism with cinacalcet has generally been recommended. Although no guidelines exist, phosphate supplementation should be considered in patients with a phosphate level below 1.5 mg/dl (0.5 mmol/l) to avoid complications associated with severe hypophosphatemia (e.g., rhabdomyolysis, left ventricular dysfunction, respiratory muscle weakness, and hemolysis). However, overaggressive phosphate replacement is not recommended because it can result in hypocalcemia, persistent hyperparathyroidism, hyperphosphatemia, and calcitriol deficiency and increase the risk of nephrocalcinosis and acute phosphate nephropathy.[35] Various forms of vitamin D derivatives with or without calcium supplementation have been used by independent investigators with variable improvement in post-transplantation bone and mineral parameters including serum calcium, phosphorus, PTH, and alkaline phosphatase.[38] Cinacalcet

is currently used off-label by most U.S. centers to treat hypercalcemia associated with persistent hyperparathyroidism.

Bisphosphonates increase BMD in postmenopausal women and patients with corticosteroid-induced osteoporosis, particularly at the lumbar spine and trochanter. Studies in kidney transplant recipients similarly show that bisphosphonates significantly improve BMD at the lumbar spine and femoral neck and may reduce fracture risk.[40] In a meta-analysis of randomized controlled trials, treatment with bisphosphonates or vitamin D reduced the number of patients with fracture (odds ratio [OR] 0.50 [95% confidence interval (CI), 0.29-0.83]) and the number of vertebral fractures (OR 0.24 [95% CI, 0.07-0.78]). An increase in BMD at the lumbar spine (2.98% [95% CI 1.31-4.64]) and femoral neck (3.05% [2.16, 3.93]) was also observed. When bisphosphonate trials were examined separately, there was a reduction in the number of patients with fractures (OR 0.53 [0.30, 0.91]), whereas no significant reduction in vertebral fractures was observed.[40] However, the beneficial effects of bisphosphonate therapy in the post-transplantation period have recently been questioned. In a randomized, controlled, double-blind trial of 129 renal transplant recipients with early stable renal function, the addition of ibandronate therapy to a regimen of calcitriol 0.25 μg/day and calcium 500 mg bid showed no significant difference in lumbar spine BMD at 12-month follow-up. Lumbar spine BMD was increased in both groups. There was a small overall decline in BMD of 0.5% in the femur and 1.9% at the radius in the placebo group.[41] It is speculated that the stability in BMD was mainly a result of the efficacy of calcitriol and calcium.

Calcitonin inhibits osteoclastic action by a direct receptor-mediated signal. Similar to bisphosphonates, calcitonin has been shown to be effective in postmenopausal patients as well as patients with corticosteroid-induced osteoporosis. However, the beneficial effects of calcitonin on bone loss have not consistently been shown in the transplant setting. Furthermore, calcitonin has been shown to have no effect on fracture risk in kidney transplant recipients.

Teriparatide is a recombinant human PTH that has been shown to exert anabolic effects on the skeleton when given intermittently. In one single-center study, teriparatide administered to transplant patients for 6 months showed no change in BMD in the lumbar spine or distal radius compared with placebo. However, femoral neck BMD remained stable in teriparatide-treated group but was significantly decreased in the placebo group.[42] There are currently insufficient data to recommend teriparatide use in kidney transplant recipients.

Hormone deficiencies have also been suggested to contribute to bone loss after transplantation. Estrogen or androgen deficiency may persist after transplantation. Limited studies have shown that estrogen replacement therapy improves BMD in postmenopausal liver, lung, and bone marrow transplant recipients. To date, there have been no data to support or refute the use of hormonal therapy to prevent post-transplantation–related bone loss in postmenopausal women; hence treatment should be individualized. The association of hormonal therapy and CV risk should not be overlooked. Testosterone deficiency has also been implicated in the development of bone loss and fractures after transplantation. However, the role of hormonal replacement therapy in men with hypogonadism is not well defined. Because of its potential side effects, including dyslipidemia, hepatic enzyme abnormalities, erythrocytosis, and prostatic hypertrophy, testosterone should probably be given only to men with true hypogonadism.

In summary, vitamin D analogues and bisphosphonates are the most consistently effective agents for the prevention and treatment of bone and mineral bone disorders in recipients of solid organ transplants. However, with the recent findings of a lack of significant beneficial effect of bisphosphonate therapy compared with calcitriol and calcium therapy alone,[41] and the potential for bisphosphonate to oversuppress bone metabolism, its use in the post-transplantation setting should best be individualized. In our opinion, bisphosphonate therapy may be justifiable in high-risk individuals including those with preexisting osteoporosis or documented overall low bone mass, those who are receiving high-dose corticosteroids or those with history of fractures, and those who are postmenopausal. The 2009 KDIGO guidelines suggest bone biopsy to guide treatment, especially before bisphosphonate therapy, because of the high incidence of adynamic bone disease.

Gout

Hyperuricemia and gout are common among kidney transplant recipients receiving cyclosporine-based immunosuppression, with a reported prevalence of 30% to 84% and 2% to 28%, respectively. Cyclosporine has been suggested to impair renal excretion of uric acid secondary to decreased GFR as well as increased net uric acid reabsorption by the proximal tubule. Potential contributing risk factors for the development of post-transplantation hyperuricemia and gouty arthritis include pretransplantation hyperuricemia, graft impairment, obesity, and diuretic use. In one retrospective cohort study, cyclosporine was found to have an increased relative risk of new-onset gout compared with tacrolimus (adjusted HR 1.25, 95% CI 1.07-1.47).[43] Purine-rich foods such as meat and seafood and purine-rich alcoholic beverages such as beer have been well described to increase gout risk. Of interest, however, purine-rich vegetables were not found to be associated with increased gout risk.[44]

Management of the acute gouty attack includes topical ice and rest of the inflamed joint. Pharmacologic treatments include colchicine, increased corticosteroid dose, or nonsteroidal anti-inflammatory drugs (NSAIDS). The use of NSAIDS, however, should be avoided in patients with impaired allograft function. Other treatment options have included intra-articular corticosteroids and parenteral adrenocorticotropic hormone (ACTH)—the latter being reserved for patients with multiple medical problems such as allograft impairment, gastrointestinal bleeding, or gouty arthritis refractory to conventional therapy.

Management of chronic gout is directed at lowering uric acid levels. Allopurinol, a xanthine oxidase inhibitor, should be started at a low dose (100 mg to 200 mg/day), particularly in the presence of impaired allograft function, because renal insufficiency predisposes to severe allopurinol toxicity as a result of retention of the metabolite oxypurinol. In allopurinol-allergic patients, febuxostat (a non–purine analogue xanthine oxidase inhibitor) can be used. It is administered as 40 mg or 80 mg daily, and the dosage is not modified in renal failure. Both allopurinol and febuxostat should be used cautiously in patients taking AZA because of the inhibition of AZA metabolism by xanthine oxidase inhibitors (e.g., when used in combination therapy with allopurinol or febuxostat, consider AZA dose reduction by 25% and close monitoring of complete blood counts). Alternatively, AZA-to-MMF conversion therapy may be considered. MMF does not interact with allopurinol or febuxostat).

Recombinant pegylated uricase, which converts uric acid to the more soluble product, allantoin, may be rarely used to rapidly reduce uric acid levels in patients refractory to standard therapy. Whether recombinant pegylated uricase has a role in kidney transplant recipients with refractory gout remains to be explored.

Long-term prophylaxis may include reduction or discontinuation of diuretics, chronic low-dose allopurinol or febuxostat therapy, dietary modification, and consideration of alternative immunosuppressive therapy. A cyclosporine-to-tacrolimus switch has been

reported to result in resolution of severe polyarticular gout refractory to conventional therapy. Small doses of colchicine at 0.6 mg daily may also prevent recurrent gouty attacks. However, colchicine should be used with caution, particularly in patients on statin therapy, because of the increased risk of myopathy.

OUTPATIENT CARE

We recommend that patients be seen two to three times a week for the first 2 weeks after transplantation, twice a week for the next 2 weeks, and weekly for the next month. After the first 2 months, the frequency of outpatient visits depends on the complexity of the patient's early postoperative course. Patients with stable graft function and an uneventful postoperative course can return to work or their regular daily activities 2 to 3 months after transplantation. Laboratory assessment during the first month after transplantation should include serum creatinine and electrolyte values, fasting glucose level, liver enzymes, immunosuppressive drug levels, and complete blood count with platelets. Urinalysis (and, if clinically indicated, urine culture and urine protein-creatinine ratio) should also be performed. After the first post-transplant year, annual follow-up at a transplantation center is generally recommended.

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CHAPTER 107

Chronic Allograft Injury

Christian Morath and Martin Zeier

DEFINITIONS AND EPIDEMIOLOGY

The results after kidney transplantation have steadily improved over the last 30 years, with a 1-year overall graft survival rate of about 94% and acute rejection rates within the first year after transplantation of 12%.[1] Loss of an allograft because of acute rejection has become a rare event and predominantly occurs in patients who are presensitized against human leukocyte antigens (HLAs).[2] Today, most allografts are lost because of a phenomenon called *chronic allograft injury.* Every year, about 4% of kidney grafts are lost (Fig. 107-1). Only a decade ago, it was believed that nonimmunologic causes were the main factors leading to chronic allograft injury and graft loss.[3] However, our understanding has changed, and HLA alloantibodies are today believed to be the main culprit, accounting for more than half of graft losses in the long run.[4] With the acknowledgment of alloantibodies as the major factor that contributes to graft failure, the term *chronic allograft nephropathy* has been replaced by more specific terminology in the Banff classification of renal allograft pathology (Box 107-1).[5,6] A frequent pathologic feature of chronic allograft injury is interstitial fibrosis or tubular atrophy (see the later discussion of pathology and Fig. 107-2), but this is a nonspecific finding and does not imply any specific cause for the chronic allograft injury.

Whereas immunologic causes are now believed to be mainly responsible for late allograft injury and graft failure, nonimmunologic causes still represent significant risk factors for (late) graft injury and graft loss. The donor graft itself may present with significant preexisting disease, limiting long-term graft survival.[7] In addition, chronic interstitial fibrosis and tubular atrophy may result from early damage to the allograft such as ischemia-reperfusion injury or early acute rejection. Calcineurin inhibitor (CNI) nephrotoxicity, recurrent glomerular disease, and BK virus (BKV) infection but also chronic interstitial fibrosis and tubular atrophy originating from either hypertension or dyslipidemia further contribute to graft damage and graft loss in the long-run.

Although some allografts are lost as a result of one specific cause, others accumulate the burden from several different causes with gradual loss of functioning nephrons. Main contributors to late graft injury and late graft loss are summarized in Box 107-2.

PATHOGENESIS: NONIMMUNOLOGIC FACTORS

Donor Age, Donor Gender, and Donor-Recipient Size Mismatching

Long-term graft survival is reduced in kidneys from older donors, an effect that is more pronounced in deceased compared with living kidney transplant recipients.[8] Impaired graft survival is attributed to a differential response of the older organ to injury, an impaired capacity to withstand stress, a limited ability to repair structural damage, or amplification of external injury as a result of preexisting structural abnormalities.[9]

Reduced nephron mass resulting in glomerular hyperfiltration and hypertension with accelerated senescence is also a postulated mechanism for a progressive decline in graft function.[10] The effect of kidney size mismatching is thought to be related to insufficient numbers of nephrons within the donor kidney, which in turn leads to compensatory hyperfiltration.[11] Although there are experimental data to support this hypothesis, the extent to which an inadequate number of nephrons contributes to chronic injury in clinical transplantation is unknown.

Female donor gender negatively affects kidney graft survival, with reduced survival when female grafts are transplanted into male recipients (risk ratio 1.22). This is not only a result of reduced nephron mass ("nephron underdosing"), because a comparable effect is found for cardiac allografts. Other mechanisms may include possible differences in the immunogenicity of male and female grafts.[12,13]

Ischemia-Reperfusion Injury and Delayed Graft Function

Graft survival is lower in recipients with longer ischemia times, and longer cold ischemia time represents a risk factor for the development of interstitial fibrosis and tubular atrophy at 6 months after transplantation.[14] Ischemia-reperfusion injury may also trigger immune-mediated injury because ischemia and oxidative injury resulting from reperfusion are associated with upregulation of major histocompatibility complex (MHC) antigens, activation of the adaptive immune response, especially antigen-presenting cells and Toll-like receptors (TLRs), and release of proinflammatory cytokines, which can lead to acute rejection and subsequent interstitial fibrosis and tubular atrophy.[15]

Delayed graft function, commonly defined by the need for dialysis in the first week after transplantation, is a risk factor for interstitial fibrosis and tubular atrophy.[16] There are also independent associations between delayed graft function and late graft failure and between delayed graft function and graft failure that is mediated by acute rejection. Major risk factors for delayed graft function are prolonged cold ischemia time, donor age older than 50 years, and the presence of HLA alloantibodies.[2]

BK Virus Nephropathy

BK virus is an endemic polyomavirus that is usually acquired during childhood and persists in the urinary tract. Although it is asymptomatic in the immunocompetent host, it becomes activated in the immunocompromised patient. Viremia may be found in 10% to 30% of patients within the first 6 months after transplantation, with

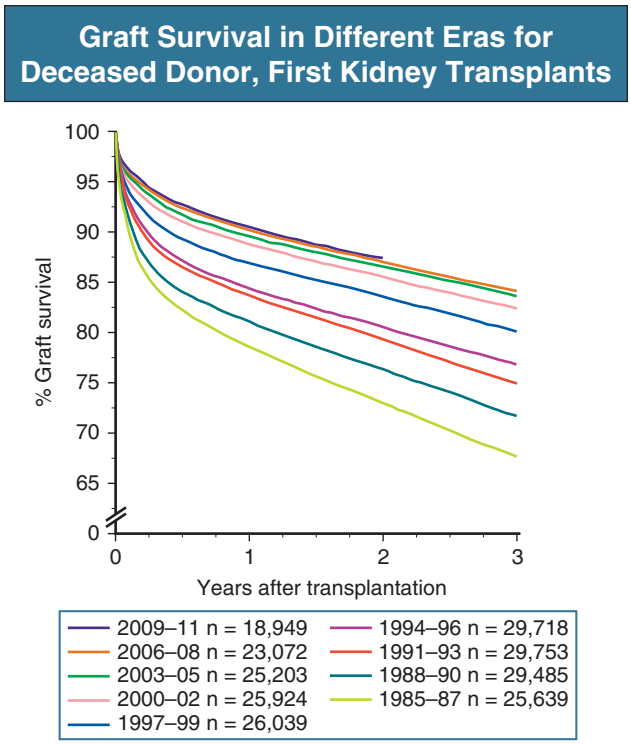

Figure 107-1 Graft survival for recipients of a first deceased donor kidney transplant according to the year of transplantation. Graft survival has steadily improved over the last 25 years because of a reduction in both early and late graft loss. *(With permission from Prof. Gerhard Opelz, CTS Study.)*

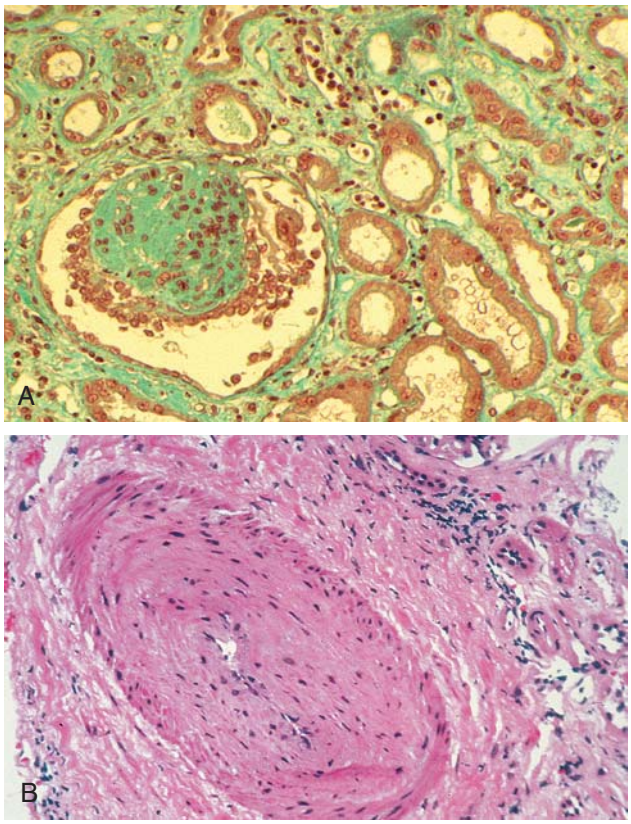

Figure 107-2 Histologic features of chronic allograft injury and interstitial fibrosis–tubular atrophy with no evidence of specific cause. A, Interstitial fibrosis and glomerulosclerosis (trichrome stain). **B,** Fibrointimal proliferation in an intrarenal artery (PAS stain).

Banff Classification of Renal Allograft Pathology

1. Normal

2. Antibody mediated rejection

- Documentation of circulating antidonor antibodies and C4d or allograft pathology
- C4d deposition without morphologic evidence of active rejection (C4d+), presence of circulating antidonor antibodies, no signs of acute or chronic T cell–mediated or antibody-mediated rejection

Acute antibody-mediated rejection

- C4d+, presence of circulating antidonor antibodies, morphologic evidence of acute tissue injury, such as:
  - I. ATN-like minimal inflammation
  - II. Capillary and glomerular inflammation and/or thromboses
  - III. Arterial—v3

Chronic active antibody mediated rejection

- C4d+, presence of circulating antidonor antibodies, morphologic evidence of tissue injury such as:

  Glomerular double contours and/or peritubular capillary basement membrane multilayering and/or interstitial fibrosis–tubular atrophy and/or fibrous intimal thickening

3. Borderline changes

- Suspicious for acute T cell–mediated rejection
- No intimal arteritis but foci or tubulitis (t1, t2, or t3 with i0 or i1)

4. T cell–mediated rejection

Acute T cell–mediated rejection

Type

- IA Interstitial infiltration and moderate tubulitis (i2 or i3 and t2)
- IB Interstitial infiltration and severe tubulitis (i2 or i3 and t3)
- IIA Mild to moderate intimal arteritis (v1)
- IIB Severe intimal arteritis (v2)
- III Transmural arteritis and/or fibrinoid change and/or smooth muscle necrosis

Chronic active T cell–mediated rejection

- Chronic allograft arteriopathy
- Arterial fibrosis with mononuclear cell infiltration in fibrosis

5. Interstitial fibrosis and tubular atrophy, no specific cause (formerly known as *chronic allograft nephropathy* [CAN])

Grade

- I Mild interstitial fibrosis and tubular atrophy (<25% of cortical area)
- II Moderate interstitial fibrosis and tubular atrophy (26% to 50% of cortical area)
- III Severe interstitial fibrosis and tubular atrophy (>50% of cortical area)

6. Changes thought not due to rejection—either acute or chronic

Box 107-1 Banff classification of renal allograft pathology (2007 update of original 1997 classification). *ATN,* Acute tubular necrosis.; *i,* interstitial inflammation; *t,* tubulitis; *v,* vasculitis.

Main Factors Contributing to Late Graft Injury and Late Graft Loss

Donor Factors
- Deceased donor kidney (DBD or DCD)
- Older donor age, female donor
- Donor vascular disease
- Ischemia-reperfusion injury and long ischemia time
- Delayed graft function

Recipient Risks (Nonimmune)
- Obesity
- Urinary tract infection
- Transplant ureteral obstruction
- BK virus nephropathy
- Calcineurin inhibitor toxicity
- Recurrent renal disease or *de novo* glomerulonephritis
- Hypertension, dyslipidemia, smoking
- Diabetes (preexisting or post-transplantation)

Recipient Risks (Alloimmune)
- Child or adolescent recipient, ethnicity
- Variable medication trough concentrations from malabsorption or nonadherence
- HLA mismatches, presensitization status (donor-specific HLA alloantibodies)
- Acute rejection that is severe, corticosteroid resistant, vascular, antibody mediated, or late occurring
- Late *de novo* donor-specific antibodies and chronic (antibody-mediated) rejection

Box 107-2 Main factors contributing to late graft injury and late graft loss. *DBD,* Donation after brain death; *DCD,* donation after cardiac death; *HLA,* human leukocyte antigen. *(Modified from reference 57.)*

biopsy-proven BKV-associated nephropathy in 1% to 10% of patients. BKV-associated nephropathy mimics the pattern of interstitial cellular rejection but may be distinguished in immunohistochemistry by a positive staining for the SV40 antigen. BKV-associated nephropathy, if untreated, may lead to severe interstitial fibrosis and tubular atrophy and graft loss in the majority of patients. The mainstay of therapy is the reduction of immunosuppression.[17] The diagnosis and management of BKV nephropathy are discussed further in Chapter 105.

Calcineurin Inhibitor Toxicity

Calcineurin inhibitor nephrotoxicity affects all histologic compartments of the transplanted kidney. Characteristic chronic CNI lesions include medial arteriolar hyalinosis, striped interstitial fibrosis, global glomerulosclerosis, and tubular microcalcification unrelated to other causes, such as tubular necrosis and hyperparathyroidism.[18,19] CNI-induced arteriolopathy is characterized by nodular hyaline deposits in the media of afferent arterioles sufficient to cause narrowing of the vascular lumen.[20,21] It is attributed to eosinophilic transformation and vacuolization of smooth muscle cells with subsequent necrosis. Arteriolar hyalinosis is the most reliable diagnostic marker of CNI nephrotoxicity. Confirmation of the diagnosis is made by exclusion of other causes, such as donor hyalinosis (which can be detected on the implantation biopsy specimen), diabetes, and hypertensive nephrosclerosis. Striped fibrosis is subjectively defined by a dense stripe of cortical fibrosis and atrophic tubules adjacent to normal cortex and is traditionally regarded as pathognomonic of CNI nephrotoxicity, but its appearance can be seen in any cause of fibrosis, especially if it is a result of microvascular injury. It is likely that the associated arteriolopathy and narrowing of the lumen contribute to development of fibrosis and atrophy after watershed infarcts within areas of ischemia. Local hypoxia leads to formation of free oxygen radicals, which promote cellular death by apoptosis. In addition, upregulation of transforming growth factor β (TGF-β) is considered an important etiologic factor in CNI toxicity.[19]

Calcineurin inhibitor toxicity was long believed to be the major factor contributing to late allograft loss. However, there has been a shift in this paradigm, and today CNI nephrotoxicity is believed to be responsible for only a smaller proportion of graft failures. The Long-Term Deterioration of Kidney Allograft Function (DeKAF) study demonstrated that 70% of patients with a primary or secondary histologic diagnosis of CNI nephrotoxicity had evidence of deposition of the complement split-product C4d and had donor-specific antibodies (DSAs) linking chronic graft failure to alloimmunity rather than CNI nephrotoxicity.[22,23]

Recurrent and *De Novo* Glomerular Diseases

Recurrent glomerulonephritis (GN) is diagnosed by exclusion of donor-transmitted disease and *de novo* GN. Its relative importance for graft loss increases as graft survival lengthens.[24] Given that it is a relatively common occurrence and has implications for treatment and retransplantation, recurrent GN should be looked for carefully in patients with a prior diagnosis of GN. Diagnosis and management of recurrent disease are discussed further in Chapter 108.

Cardiovascular Risk Factors

The vasculopathy in chronic allograft injury resembles systemic vascular disease, raising the possibility that conventional risk factors for cardiovascular disease may be implicated. Hypertension occurs in about 70% to 90% of transplant recipients. In a multicenter, retrospective study of 29,751 kidney transplant recipients, elevated systolic blood pressure above 180 mm Hg (compared with <140 mm Hg) at 1 year was associated with a doubled risk of graft failure at 7 years.[25] Hypertension in these patients may be related to pretransplant hypertension, vascular disease, corticosteroid therapy, CNI therapy, or graft dysfunction.

Dyslipidemias, including raised levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides, and cigarette smoking have also been associated with late graft failure. Some studies also suggest that hyperuricemia, which is common in patients with metabolic syndrome, may have a role in chronic allograft injury.

The management of hypertension, dyslipidemia, and other cardiovascular risk factors in the transplant recipient is discussed further in Chapter 106.

PATHOGENESIS: IMMUNOLOGIC FACTORS

Acute Rejection

Acute cellular rejection, vascular or corticosteroid-resistant rejection, subclinical rejection, and late acute rejection all contribute to the burden of chronic allograft injury. Early acute cellular rejection (within 3 months of transplantation) that is adequately diagnosed and treated and in which the serum creatinine returns to baseline values after treatment usually has no impact on long-term graft survival. But late acute rejection and rejection in which serum

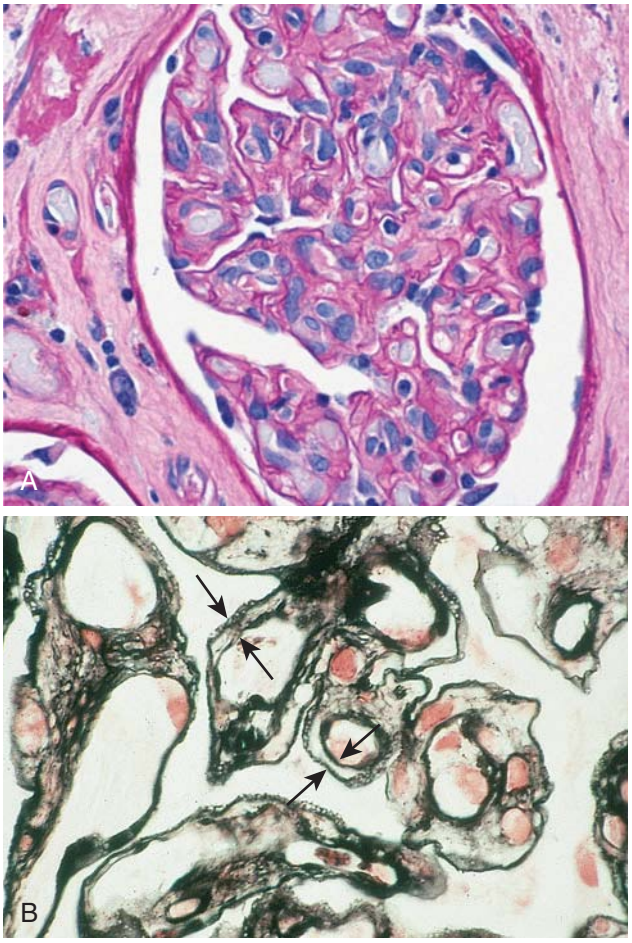

Figure 107-3 Transplant glomerulopathy: light microscopy. A, Note the mesangial expansion and thickening of the glomerular basement membrane (GBM). **B,** Note the GBM reduplication in capillary loops *(between arrows).*

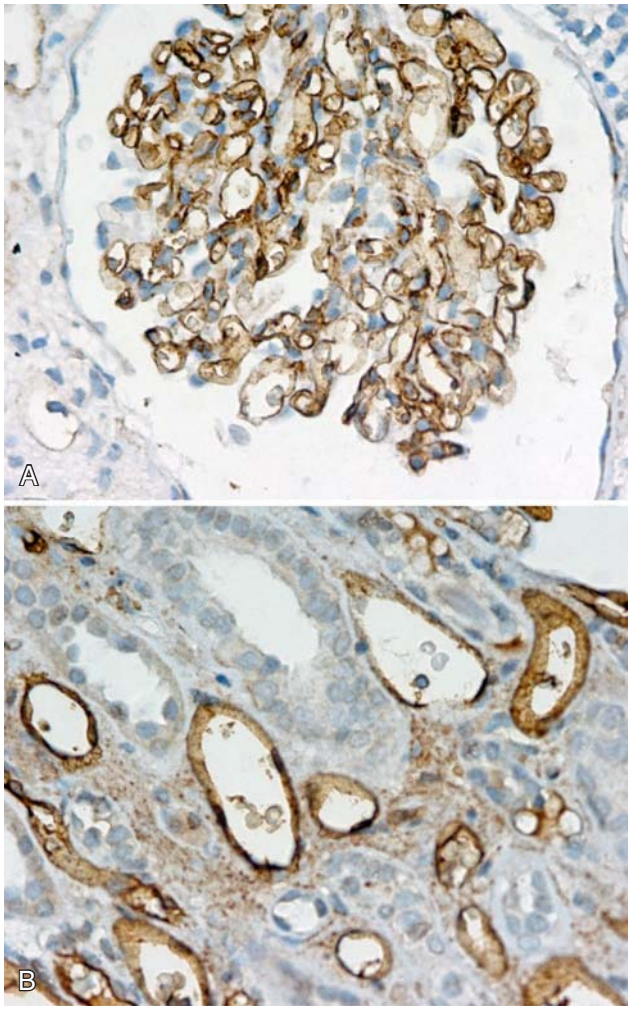

Figure 107-4 C4d immunoperoxidase staining in association with chronic antibody-mediated rejection. Staining of glomerular capillaries **(A)** and circumferential staining of peritubular capillaries **(B)** are typical.

creatinine does not return to baseline usually translates into interstitial fibrosis and tubular atrophy and/or vascular damage, contributing to graft injury. Multiple and severe late acute cellular rejection episodes are predictive of chronic graft dysfunction more than early cellular rejection and acute vascular rejection, which have stronger associations with acute graft loss.[26] There is some evidence from protocol biopsy studies that subclinical cellular rejection may also be an important factor contributing to chronic graft injury, although there is no consensus on this point.[27,28]

In addition to the direct effects of cellular rejection on graft function, acute cellular rejection may be linked to the development of DSA and subsequent antibody-mediated rejection.[29]

Chronic Antibody-Mediated Rejection

Chronic antibody-mediated rejection is one of the leading causes of graft loss, together with death with a functioning graft, recurrent renal disease, and interstitial fibrosis and tubular atrophy of unknown origin.[30]

For the diagnosis of antibody-mediated kidney graft rejection, histologic features of antibody-mediated rejection in the biopsy (Figs. 107-3 to 107-5), together with positivity for the complement split product C4d in peritubular capillaries (see Fig. 107-4) and/or the detection of circulating DSAs, are required. Especially in chronic antibody-mediated rejection, however, C4d in peritubular capillaries may be negative (C4d-negative antibody-mediated rejection).[6] C4d-negative antibody-mediated rejection shares the same histologic and ultrastructural features as C4d-positive rejection. Exact criteria for the definition of C4d-negative antibody-mediated rejection are currently lacking; however, it is believed that more than 50% of all chronic antibody-mediated rejection episodes are C4d negative.

Unrecognized DSAs, if strongly reactive and complement activating, can cause hyperacute rejection or accelerated antibody-mediated rejection in the early phase after kidney transplantation. Acute antibody-mediated rejection in the early phase occurs in about 1% to 6% of patients; however, this number may increase up to 21% to 55% in patients who had detectable DSAs already before transplantation and who received desensitization therapy.[31-33] Weakly positive DSAs have been associated with rather subtle types of graft damage, often leading to delayed graft function.[2] Early damage can later translate into chronic rejection, most probably because the structure of the endothelium is no longer intact and new antigenic epitopes are expressed on the surface of transplanted tissue. During later phases after transplantation, insufficient immunosuppression can facilitate the development of *de novo* DSAs against these new epitopes and result in chronic antibody-mediated rejection and failure of the transplanted organ. *De novo* DSAs but also persistence or re-emergence of DSAs that were detectable before transplantation are associated with poor allograft outcome.

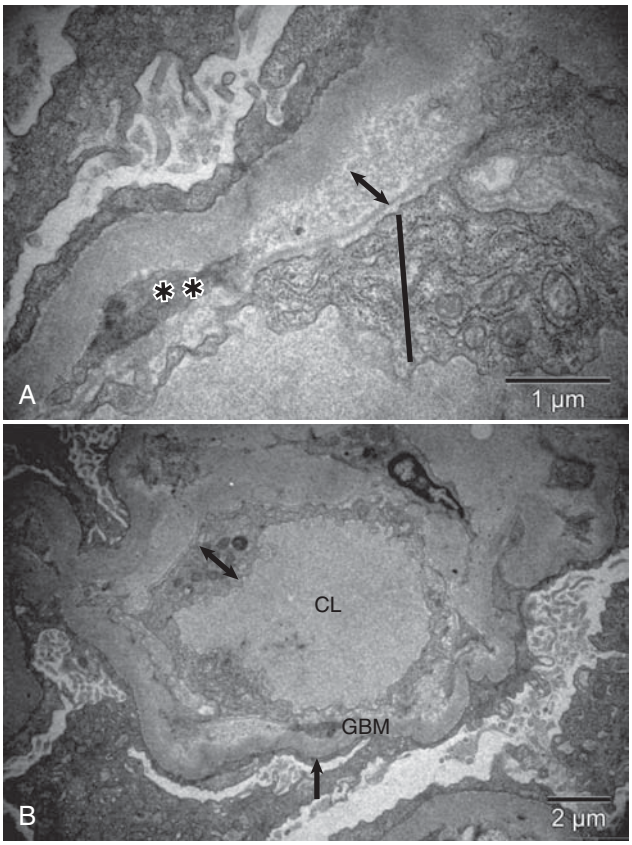

Figure 107-5 Transplant glomerulopathy: electron microscopy. A, Section of a glomerular capillary loop (×24,000) demonstrating mesangial interposition *(asterisks),* subendothelial expansion and new lamina densa *(double arrow),* and endothelial hypertrophy *(line).* **B,** A complete glomerular capillary loop *(CL)* with glomerular basement membrane (GBM) thickening *(single arrow),* endothelial hypertrophy *(double arrow),* expanded subendothelial space, and new lamina densa *(single arrow).* Apparent GBM duplication is a result of mesangial interposition and formation of new lamina densa.

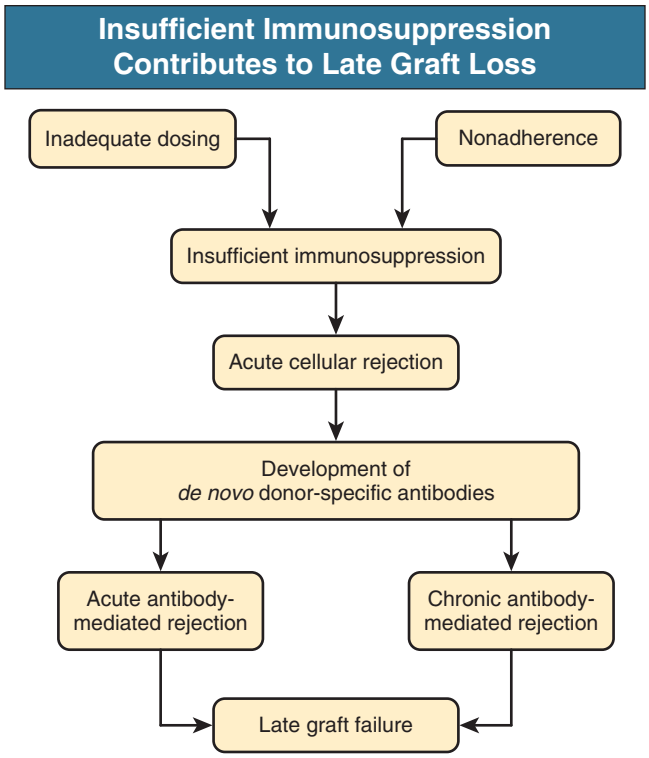

Figure 107-6 Insufficient immunosuppression contributes to late graft loss. *HLA,* Human leukocyte antigen.

Chronic antibody-mediated rejection is found more frequently in patients who are nonadherent to immunosuppressive medication or in whom immunosuppression was reduced for other reasons—for example, because of recurrent infection or malignancy or planned conversion to CNI-free or corticosteroid-free immunosuppressive protocols.[34-36] Additional risk factors for the development of *de novo* DSAs and antibody-mediated rejection are HLA class II DR mismatches between donor and recipient, prior cellular rejection episodes, and younger recipient age. In many patients with late antibody-mediated graft loss, even when HLA class I alloantibodies are detectable, HLA class II *de novo* DSAs are considered to be mainly responsible for rejection. In a recent study on the evolution of HLA alloantibodies after transplantation, *de novo* DSAs appeared at a mean of 4.6 years after transplantation, and the prevalence of *de novo* DSAs after 10 years was 20% in those adherent to the immunosuppressive regimen, as compared with 60% in nonadherent graft recipients.[36] In another study, DSAs were found in 37% of patients who had an indication biopsy 7 days to 31 years after transplant.[4] Especially *de novo* DSAs, which made up 60% of all DSAs, that were directed against HLA class II antigens were associated with strongly impaired graft survival.

Other antibodies that are discussed in the evolution of chronic antibody-mediated rejection are MHC class I–related chain A (MICA) antibodies, angiotensin II type 1 receptor-activating antibodies, and other antiendothelial cell antibodies.[37,38] The exact impact of these antibodies on the outcome of kidney and other organ transplants is yet to be determined.

Insufficient Immunosuppression and Nonadherence to Medication

The recognition that HLA alloantibodies are responsible for a great proportion of late graft losses[38,39] has focused attention on the role of insufficient immunosuppression and nonadherence to immunosuppressive medication as significant factors in chronic graft loss (Fig. 107-6).[34,40]

A retrospective analysis of more than 25,000 kidney transplant recipients showed that reduction or discontinuation of cyclosporine, tacrolimus, or mycophenolate mofetil after the first post-transplant year in patients with good graft function was associated with significantly reduced subsequent kidney graft survival.[34] In a recent study in which 64% of graft losses in a cohort with indication biopsies were attributable to (antibody-mediated) rejection, about half of the patients with rejection-associated loss of the allograft were identified as nonadherent.[40]

Patients at high risk for nonadherence are young adults who are in the transition phase from pediatric to adult nephrology care. Other risk factors are previous nonadherence, psychiatric disorders, substance abuse, and insufficient socioeconomic support, and also adverse effects from immunosuppressive medication. Insufficient immunosuppression may also occur during immunosuppressive minimization (tapering) or CNI avoidance trials. In a recent study, 14 out of 61 patients (23%) who were converted from cyclosporine to everolimus at 3 to 4.5 months after transplantation developed DSAs, compared with only 7 out of 65 patients (11%) who continued on cyclosporine.[35] Eight patients on everolimus but only two patients on cyclosporine developed antibody-mediated rejection. Therefore

these patient cohorts should be screened rigorously for the development of alloantibodies and antibody-mediated allograft injury.

CLINICAL MANIFESTATIONS

Routine laboratory evaluation of graft function does not facilitate the early diagnosis of chronic allograft injury. A rise in serum creatinine is a late marker of graft dysfunction. The reduction in the glomerular filtration rate (GFR) is usually estimated by equations such as the Modification of Diet in Renal Disease (MDRD) formula, the Nankivell formula, or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. However, substantial nephron loss may occur before a rise in serum creatinine becomes evident.

Persistent or worsening proteinuria is also a late sign of chronic allograft injury. Proteinuria may be assessed by dipstick urine analysis, by spot urine protein-creatinine ratio, or by measurement of the 24-hour urine protein excretion. Proteinuria exceeding 1 g/day or in the nephrotic range may predominantly occur with recurrent or *de novo* GN or with severe chronic antibody-mediated changes such as transplant glomerulopathy (see Figs. 107-3 to 107-5). A definite diagnosis of the allograft pathology may be achieved only by a transplant biopsy together with the serologic testing for alloantibodies, and the exclusion of viral disease such as BKV or cytomegalovirus (CMV).

PATHOLOGY

Chronic interstitial fibrosis and tubular atrophy, which may be accompanied by vascular changes and glomerulosclerosis (see Fig. 107-2), represent the final pathway of nephron injury and are not specific for any graft disease. Interstitial fibrosis and tubular atrophy are found in most late graft biopsies, whether from early graft damage (such as tubular injury from ischemia-reperfusion injury, overt or subclinical rejection, or even preexisting disease of the donor) or later graft damage (from CNI toxicity, hypertension and hyperlipidemia, recurrent glomerular disease, or immune-mediated injury) or of unknown origin.

Chronic antibody-mediated rejection is characterized by structural remodeling of the glomerular basement membrane (GBM; so-called *transplant glomerulopathy*) and similar changes in the peritubular capillaries together with interstitial fibrosis and tubular atrophy and fibrous thickening of arteries (see Figs. 107-3 to 107-5). Transplant glomerulopathy is characterized by duplication of glomerular capillary basement membranes and mesangial matrix expansion, in the absence of immune deposits. In addition, there may be (but not necessarily) a deposition of C4d in glomerular capillaries, and also in peritubular capillaries (see Fig. 107-4). Clinicopathologic studies suggest that transplant glomerulopathy is a manifestation of capillary injury occurring in conjunction with interstitial, peritubular capillary, and glomerular inflammation, although it may also occur independently of interstitial fibrosis and tubular atrophy, or transplant arteriopathy.[41] On electron microscopy, there is expansion of the subendothelial space with deposition of flocculent or fibrillary material, interposition of mesangial cell cytoplasm in the lamina densa, and mesangial matrix expansion (see Fig. 107-5). Ultrastructural abnormalities characteristic of endothelial activation occur long before GBM duplication and graft dysfunction are evident, implying that endothelial injury is the initial insult that resulted in GBM remodeling.[42] An association between transplant glomerulopathy and peritubular capillary basement membrane duplication has been well described, suggesting that the process resulting in transplant glomerulopathy involves the entire glomerular and peritubular capillary beds.[43,44]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

When chronic allograft injury has been identified by a gradual rise in serum creatinine with or without proteinuria, ultrasound should be performed to exclude ureteral or vascular problems and to assess the Doppler resistive index. The Doppler resistive index gives an estimate of intrarenal (but also systemic) compliance and is most useful in longitudinal studies in the same patient to assess progressive graft vascular injury.

Screening for BKV in serum or urine is also advised for all kidney transplant recipients at 3-month intervals during the first two years after transplantation. Circulating HLA alloantibodies should also be documented and may further guide diagnostics and therapy. Many centers now perform routine HLA alloantibody screening in stable graft recipients at different time points after transplantation to facilitate early diagnosis of antibody-mediated rejection. Although there is consensus that HLA alloantibodies are responsible for a significant proportion of late graft losses and that HLA antibodies in the context of deteriorating graft function are harmful, the significance of HLA alloantibodies that are detected solely during routine screening remains uncertain.[45,46]

Allograft biopsy is required to document the presence of interstitial fibrosis and/or transplant glomerulopathy and to look for other treatable causes of chronic allograft injury (see Box 107-1). The role of protocol biopsies in the early detection of chronic allograft injury remains controversial.

Because the etiology of chronic allograft dysfunction is multifactorial, any specific diagnosis is made by combination of a biopsy with a review of the patient's past history to identify important etiologic factors, such as preexisting donor disease, prior rejection, and high-titer anti-HLA antibodies, as well as issues not related to alloimmunity, such as CNI nephrotoxicity, *de novo* GN, or recurrent renal disease. Chronic allograft dysfunction is common and can have many causes; however, if it is left untreated, it can ultimately result in progressive renal injury, which in turn will heal by scarring and interstitial fibrosis. An overview of the differential diagnosis of chronic allograft dysfunction is given in Box 107-2.

MANAGEMENT

Prevention of Antibody-Mediated Allograft Injury

Prevention of antibody-mediated allograft injury should be initiated early, indeed before transplantation. Preventive measures include avoidance of sensitization by limitation of blood transfusions and poor HLA matching in previous transplants.[47,48] The introduction of erythropoietin (EPO) about 20 years ago led to a dramatic decrease of recipient sensitization by a significant reduction in blood transfusions.[48] Sensitization should especially be avoided in young patients who may require retransplantation during their lifetime. New measures, such as matching for antibody epitopes in addition to whole HLA alleles, may further help prevent sensitization.

When the patient is already sensitized, antibody-mediated allograft injury can best be prevented by transplantation of the patient with an organ against which the recipient has not developed HLA alloantibodies. This may be achieved by inclusion of patients in special programs such as the Eurotransplant Acceptable Mismatch (AM) Program or by kidney-paired donation.[49,50] However, most

Strategies for the Prevention of Chronic Allograft Injury

- Avoid sensitization in future organ recipients (e.g., avoid blood transfusions, avoid poor HLA matching during first transplantation).
- Obtain complete donor and recipient typing and precise knowledge on HLA alloantibodies at time of transplantation.
- Minimize ischemia-reperfusion injury (e.g., short cold ischemia time).
- Avoid insufficient immunosuppression.
- Perform prophylaxis for CMV (first 3 to 6 months).
- Screen for BKV after transplantation.
- Monitor donor-specific HLA alloantibodies after transplantation (at least in presensitized patients or during drug minimization).
- Perform protocol biopsies to detect subclinical rejection (at least in presensitized patients or during drug minimization).
- Review for nonadherence.

Box 107-3 Strategies for the prevention of chronic allograft injury. *BKV,* BK virus; *CMV,* cytomegalovirus; *HLA,* human leukocyte antigen.

Treatment of Chronic Allograft Injury

Nonimmune

- Treat hypertension (consider ACE inhibitors or ARBs) (see Chapter 106).
- Perform lifestyle modification (stop smoking, control lipids).
- Control diabetes.
- Prevent and treat urinary tract infection (see Chapter 105).
- Target CNI toxicity by reducing or replacing CNI (be aware of risk for insufficient immunosuppression).
- Treat BK virus nephropathy by reducing immunosuppression with or without antiviral therapy (see Chapter 105).

Allloimmune (see Chapter 104)

- Diagnose and treat early acute cellular rejection with corticosteroids or antithymocyte globulin.
- Diagnose and treat acute antibody-mediated rejection by means such as plasma exchange, or immunoadsorption with or without anti-CD20 therapy.
- Diagnose and treat chronic antibody-mediated rejection by means such as intravenous immunoglobulins with or without anti-CD20 therapy.

Box 107-4 Treatment of chronic allograft injury. *ACE,* Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *CNI,* calcineurin inhibitor.

patients with preexisting HLA alloantibodies need desensitization in combination with other measures, to undergo successful transplantation (see Chapter 104).[51]

After transplantation, according to our current knowledge, chronic antibody-mediated rejection is best prevented by the use of conventional triple-drug therapy including CNI, an antiproliferative agent (preferably mycophenolic acid based), and corticosteroids. Induction therapy, with an interleukin-2 receptor antagonist or antithymocyte globulin, should be used to prevent early acute cellular rejection.

Unless a patient is prone to tolerance, insufficient immunosuppression and nonadherence may lead to cellular rejection and then, via development of *de novo* DSAs, to antibody-mediated rejection and graft loss. Precise knowledge of the patient's alloantibody status before and after transplantation is a prerequisite for early diagnosis of allograft injury and early and targeted treatment to prevent antibody-mediated rejection and ensure long-term graft survival. Although it is currently a matter of debate whether alloantibodies should be monitored routinely in all patients who have undergone transplantation, it seems to be justified in immunologically high-risk patients, desensitized patients, and patients with suspected rejection and during therapy for antibody-mediated rejection, with the goal of recognizing allograft injury in its early stages and preventing its progression to chronic rejection. Additional patient groups that may benefit from HLA alloantibody monitoring are those patients undergoing reduction, withdrawal, or change of immunosuppressive drugs, especially in the context of CNI- or corticosteroid-free regimens. Protocol biopsies may further help in guiding post-transplant therapy at least in high-risk recipients, although definitive proof of the usefulness of protocol biopsies is currently lacking.

Strategies for the prevention of chronic allograft injury are summarized in Box 107-3.

Treatment of Chronic Allograft Injury

In all patients with chronic allograft injury, there must be a focus on the effective management of nonimmunologic risk factors for progressive graft failure.

Although reduction of blood pressure to a target below 130/80 is believed to be beneficial, the preferred agent for blood pressure reduction remains controversial; in particular, the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) has not uniformly shown benefit.[52,53] Nor have there been specific studies confirming the benefits of reducing proteinuria in chronic allograft injury, although by extrapolation for other progressive proteinuric diseases (see Chapter 80), there is strong *a priori* evidence for the benefits of reducing proteinuria by renin-angiotensin system (RAS) blockade with dietary salt restriction.

A beneficial effect of treating dyslipidemia with statins in the transplant recipient also remains controversial,[54-56] and the adverse effects of statins such as rhabdomyolysis when used with CNIs must be considered. The management of hypertension, dyslipidemia, and other cardiovascular risk factors in the transplant recipient is discussed in Chapter 106.

After a specific diagnosis has been established, targeted treatments can be initiated. These are discussed further in other chapters and summarized in Box 107-4.

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CHAPTER 108

Recurrent Disease in Kidney Transplantation

Steven J. Chadban and Tony Kwan

Kidney transplantation is a treatment, not a cure. Although transplantation may restore kidney function, it does not necessarily remove the cause of the original kidney disease. Glomerulonephritis (GN) and diabetes are the two leading causes of end-stage renal disease (ESRD) worldwide and are the primary underlying diseases of patients undergoing kidney transplantation, and both diseases may recur.

The longer that a transplant remains *in situ,* the more likely it is to be affected by recurrence. As graft survival rates have increased over the past 30 years, mostly because of more effective antirejection therapies that prevent early graft loss, the apparent incidence of recurrence has grown.[1] An analysis of U.S. Renal Allograft Disease Registry data examining GN recurrence demonstrated a prevalence of 2.8% at 2 years, 9.8% at 5 years, and 18.5% at 8 years of follow-up after transplantation, and such patients were twice as likely to experience graft failure compared with those without recurrence.[2]

Recurrence has a powerful impact on transplant survival and one that is increasingly apparent with time after transplantation. In an analysis of data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) including more than 1500 patients with biopsy-proven GN who received a kidney transplant, biopsy-proven recurrence was found to cause graft loss in 0.5% within 1 year after transplantation, 3.7% within 5 years, and 8.4% within 10 years after transplantation[3] (Fig. 108-1). This study and several others have found recurrent disease to be the third most common cause of graft failure beyond the first year after transplantation, behind death with a functioning graft and chronic allograft nephropathy (CAN), but substantially ahead of acute rejection[3] (see Fig. 108-1).

De novo GN and new-onset diabetes after transplantation (NODAT) may also affect the transplanted kidney, although both are relatively uncommon. Both conditions may be difficult to distinguish from recurrence or from CAN. Like recurrent disease, the prevalence of both appears to increase with time after transplantation. Given the high incidence of NODAT coupled with general increases in graft survival,[4] it is possible that *de novo* diabetic nephropathy in particular may become a significant clinical problem in the future. However, present data suggest that the major impact of NODAT in the first 10 years after transplantation is an increase in cardiovascular mortality with little impact on death-censored graft failure.[5]

DEFINITIONS

Diagnosis of recurrence requires histologic demonstration of the same disease involving both the native and transplanted kidneys. Diagnosis of recurrence causing graft failure requires a clinical decision that recurrence was the dominant contributor to graft loss (other contributors, such as CAN, may be present). A histologic diagnosis of the primary kidney disease is not obtained for all patients with ESRD, and the majority of transplant recipients do not undergo biopsy to look specifically for recurrent disease (which may require immunohistologic and electron microscopic examination of the biopsy specimen).[1] Coupled with the tendency of clinicians to make a clinical diagnosis of CAN and thereby avoid biopsy in patients with declining graft function and proteinuria, the true incidence of disease recurrence is not known and is likely underestimated in existing literature.

Additional factors confound the available evidence. Many reports of disease recurrence are retrospective, single-center studies. Recall bias and incomplete documentation, changes in practice over time, and peculiarities of local patient populations and local practices may limit relevance to other populations. The most definitive reports have come from analyses of the large registry databases of Europe, the United States, and Australasia. Registries capture data on large numbers of patients but are subject to bias because of factors including unit participation rates; quantity and type of data collected; accuracy, uniformity, and consistency of reporting by units; and reliability of data entry. How recurrence is defined and diagnosed and which outcomes are measured is crucial. For example, IgA nephropathy (IgAN) recurred in 58% of patients in one series in which all recipients underwent biopsy,[6] but in approximately 25% of cases in which biopsy was performed only when clinically indicated.[7] When graft loss from IgAN recurrence is the outcome measure, the risk decreased to approximately 10% at 10 years of follow-up.[3] Thus, definition of recurrence, outcome measures, study design, era, and source of data all need to be considered in assessing the published literature.

RECURRENT GLOMERULONEPHRITIS

Virtually all GN may recur after transplantation; however, the rate and consequences of recurrence vary enormously. For example, anti–glomerular basement membrane (GBM) disease (Goodpasture disease) recurs only rarely, but when it does, it is likely to cause rapid graft loss. In contrast, dense deposit disease (DDD; formerly known as type II membranoproliferative *glomerulonephritis* [MPGN]) recurs in more than 80% of patients; however, the disease tends to be very slowly progressive, and graft survival beyond 10 years is typical. Numerically, recurrence of focal segmental glomerulosclerosis (FSGS), IgAN, and membranous nephropathy (MN) are the most frequently encountered clinical problems (Fig. 108-2).

Several factors may influence the risk of recurrence in addition to the underlying type of GN. Time of follow-up is clearly important and may be related to the duration of exposure of the graft to the nephritogenic factors responsible for GN.[1] In general, grafts that are lost early because of rejection are exposed relatively briefly and rarely develop recurrence. In contrast, those grafts that survive long term are exposed to nephritogenic factors for longer and are more likely to develop recurrent GN. Consistent with this concept, recipients of human leukocyte antigen (HLA)–identical transplants rarely suffer

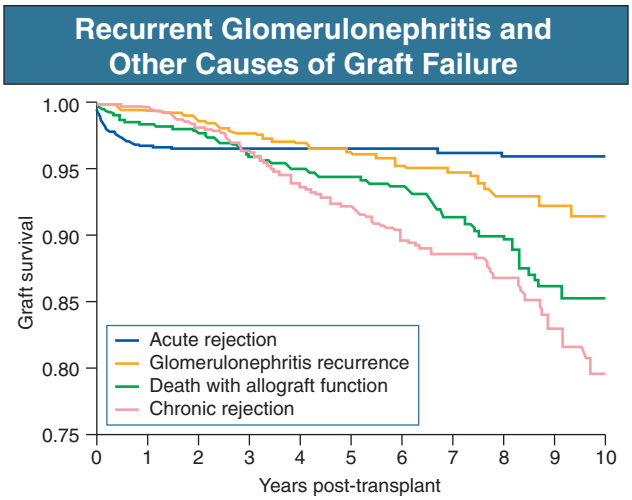

Figure 108-1 Recurrent glomerulonephritis and other causes of graft failure. Kaplan-Meier analysis of the relative contributions of acute rejection, glomerulonephritis recurrence, death, and chronic allograft nephropathy to graft loss during the first 10 years post-transplantation among patients who underwent transplantation because of end-stage renal disease caused by glomerulonephritis. *(Modified from reference 3.)*

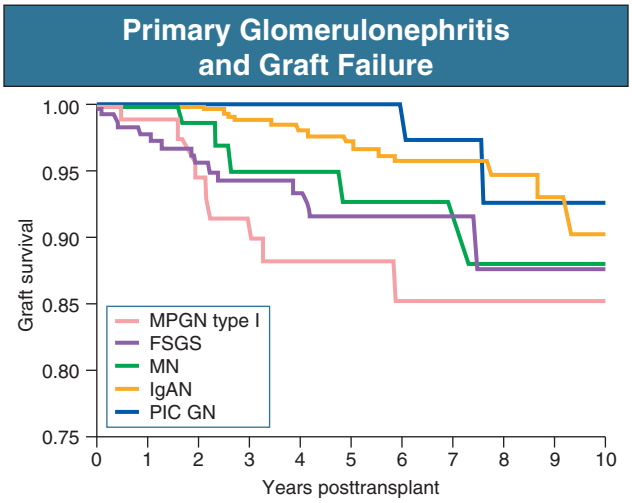

Figure 108-2 Primary glomerulonephritis and graft failure. Kaplan-Meier analysis of freedom from graft loss caused by recurrent glomerulonephritis during the first 10 years after kidney transplantation among patients with a primary diagnosis of glomerulonephritis. *FSGS,* Focal segmental glomerulosclerosis; *IgAN,* IgA nephropathy; *MN,* membranous nephropathy; *MPGN,* membranoproliferative glomerulonephritis; *PIC GN,* pauci-immune crescentic glomerulonephritis. *(Modified from reference 3.)*

rejection and enjoy prolonged graft survival but have a high rate of recurrent GN.[8] In one report of HLA-identical recipients, recurrent GN was present in 36% to 42% of those in whom biopsy was performed and resulted in 24% of graft losses, being the second most frequent cause of graft loss after death in this group.[8] Patients sustaining first graft loss from recurrent GN are also at higher risk of recurrence in a subsequent graft.

The type of immunosuppressive agents may be significant; however, data in this area are sparse. Given that immune mechanisms contribute to the pathogenesis of most types of GN and that immunosuppression is effective in the treatment of several types, it is logical that immunosuppression should decrease the incidence and severity of recurrence after transplantation. Improvements in immunosuppression over the past 40 years have led to reduced rates of acute rejection. Such improvements may also have also had an impact on rates of graft loss from GN recurrence, which have declined by nearly 50% over the past 10 years according to one ANZDATA registry analysis.[9]

United States Renal Data System (USRDS) registry data failed to demonstrate superiority of any individual immunosuppressive agent over others on the incidence of recurrence.[10] Nevertheless, there are reports that suggest the immunosuppressive regimen may be important. For example, one small retrospective study found that induction therapy with rabbit antithymocyte globulin was associated with a lower risk of IgAN recurrence compared with either anti-CD25 antibodies or no induction.[11] Corticosteroid withdrawal may also lead to increased rates of recurrence,[12] especially in patients with underlying IgAN, in whom a twofold increase in the risk of graft failure from recurrence of IgAN has been reported.[9] Similarly, inclusion or addition of cyclophosphamide to immunosuppressive regimens may be helpful in the treatment of recurrent vasculitis affecting the graft.[13] The use of sirolimus may also result in proteinuria and renal dysfunction, especially in patients with an underlying GN, suggesting that sirolimus may accelerate glomerular injury in the graft.[14] Effects of individual agents are likely to be disease specific, and much needs to be learned in this area.

Strategies to reduce the risk of recurrence have been reported. Bilateral native nephrectomy as a means of eliminating persistent antigenic stimulation appears unhelpful; indeed, nephrectomized patients experienced a higher incidence of recurrence compared with those with native kidneys left *in situ* in one large single-center, retrospective study.[15] Induction of disease remission before transplantation and prolonged time on dialysis pretransplantation, both aimed at permitting disease "burnout," do not appear to be effective except in the case of anti-GBM disease, in which a delay in transplantation until the patient has been serologically negative for at least 6 months virtually eliminates the risk of recurrence.[3] Avoidance of living related donation has been debated for years but overall appears not to have any impact on risk of recurrence.[16]

As with GN in native kidneys, proteinuria, hematuria, and deterioration in kidney function are the cardinal manifestations of recurrent GN. The pattern of renal and extrarenal manifestations is frequently similar to that of the native disease, except that, in our opinion, the rate of progression may in general be slower. Extrarenal features of the primary condition may recur, such as thrombocytopenia and hemolysis in hemolytic uremic syndrome (HUS) and extrarenal vasculitis in recurrent antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis. Serology may be helpful in some patients, such as anti-GBM antibody detection in those with Goodpasture disease, but may be inconsistent in others, such as those with recurrent lupus nephritis (LN).

The differential diagnosis of recurrent GN is clinically important because management may vary according to the diagnosis (Table 108-1). CAN and diabetic nephropathy, recurrent or *de novo,* may both present with progressive graft dysfunction, proteinuria, and hypertension and may therefore be clinically indistinguishable from recurrence. *De novo* GN should also be considered. Viral diseases of the kidney, particularly BK nephropathy, are an important alternative to consider because a reduction in immunosuppression and specific antiviral therapy may provide benefit. The need to exclude obstructive uropathy and tumors involving the graft warrants an ultrasound scan. Finally, recurrence may coexist with CAN or calcineurin inhibitor toxicity. Indeed, every condition that can lead to chronic graft dysfunction should be considered in the differential diagnosis of recurrence (see Table 108-1 and Chapter 107).

Differential Diagnosis of Recurrent Glomerulonephritis

Diagnosis	Frequency and Timing	Clinical Features	Lab Features	Biopsy Features	Management
Recurrent glomerulonephritis	Common; variable timing, days to years	Proteinuria, hematuria, renal impairment, hypertension	Similar to primary glomerulonephritis; serology may be negative	Same as primary glomerulonephritis[4,5]	Disease specific
De novo glomerulonephritis	Uncommon; variable timing but typically later than recurrence	Proteinuria, hematuria, renal impairment	Type specific	Type specific[4,5,8]	Antiprogression strategies (see Chapter 73)
Chronic allograft nephropathy	Very common; increasing incidence with time	Hypertension, proteinuria, renal impairment Calcineurin inhibitor exposure		Tubulointerstitial fibrosis, arteriolar hyalinosis, transplant glomerulopathy	Minimize calcineurin inhibitor and antiprogression strategies (see Chapter 73)
Graft pyelonephritis	Uncommon Typically early after transplantation	Fever, pyuria, renal impairment	Positive blood or urine cultures	Neutrophil infiltration	Antibiotics
BK nephropathy	Uncommon; typically 1-5 yr after transplantation	Renal impairment, decoy cells in urine	Serum BK PCR positive	Tubulitis with tubular cell atypia and inclusions, normal glomeruli	Minimize immunosuppression and consider antiviral drugs
Acute rejection	Common; early	Renal impairment, oliguria	Nonspecific	Tubulitis with or without vasculitis[15]	Increase immunosuppression
Renal tumor/PTLD	Uncommon, rare; early or late	Renal impairment, renal mass	Anemia, EBV positive	Atypical cells, mitoses, monoclonality	Minimize immunosuppression, consider chemotherapy

Table 108-1 Differential diagnosis of recurrent glomerulonephritis. *EBV,* Epstein-Barr virus; *PCR,* polymerase chain reaction; *PTLD,* post-transplantation lymphoproliferative disease.

Histologic evidence of recurrence is required in all patients. Biopsy can provide the diagnosis, exclude alternative diagnoses that may require different approaches to treatment, and provide important prognostic information pertinent to the affected graft and also relevant to any future consideration of retransplantation. Full evaluation of the biopsy specimen by light microscopy, immunohistology, and electron microscopy is desirable and in many patients essential to confirm recurrence.[17] Light microscopy and immunohistology are necessary to differentiate recurrent from *de novo* GN, rejection, and calcineurin inhibitor toxicity. The presence of tubulitis should suggest acute rejection. CAN may produce chronic interstitial inflammation and transplant glomerulopathy, which may be indistinguishable from MPGN on light microscopy (Fig. 108-3; see also Chapter 107). The use of immunohistology to define the immunoglobulin and complement component content of immune deposits and electron microscopy to establish the structure of basement membrane and location of deposits may clarify the diagnosis.[17] Histologic appearances are typically no different from the patterns of GN in native kidneys and are illustrated in the relevant chapters of Section IV. The risk of recurrence in common patterns of renal disease is summarized in Table 108-2.

RECURRENCE OF SPECIFIC GLOMERULAR DISEASES

IgA Nephropathy and Henoch-Schönlein Purpura

IgA nephropathy is the most common form of GN leading to ESRD, and affected patients frequently become transplant recipients. Histologic recurrence is frequent and increases with time; one study in which all recipients were subjected to protocol biopsy found recurrence in 58%.[6] Recurrence is difficult to predict. Patient characteristics, pretransplantation course, serum IgA glycosylation, and angiotensin-converting enzyme (ACE) genotype have been found to have no predictive value.[1,6,7] Choice of immunosuppression after transplantation is controversial. One large USRDS registry analysis suggested that individual drug choices did not affect the risk of graft loss attributed to recurrence.[10] In contrast, a recent retrospective analysis of ANZDATA including 1521 allograft recipients who underwent transplantation because of biopsy-proven GN found that continuation of corticosteroids was strongly associated with protection from graft loss caused by recurrence of IgAN, although not from other types of GN.[9] Observational data also suggest that induction with antithymocyte globulin may afford relative protection.[11] Living related donor transplantation has been associated with an increased risk of recurrence and graft loss in some series but not in others,[3] and the avoidance of living related donor transplantation in patients with IgAN is not justified.

The clinical expression of disease is variable and time dependent. Graft loss within the first 3 years after transplantation is uncommon (see Fig. 108-2), although it can occur, particularly when IgAN in the native kidney was rapidly progressive or after previous graft loss resulting from recurrence.[7] The longer-term outlook is not benign, because progressive graft loss over time has been documented by all major studies. In one registry study that included 587 patients with biopsy-proven IgAN, the risk of graft loss from IgAN recurrence was approximately 10% within 10 years after transplantation,[3] although a follow-up study suggests that this risk may be halved in the current era, particularly when corticosteroids are used during the maintenance phase.[9]

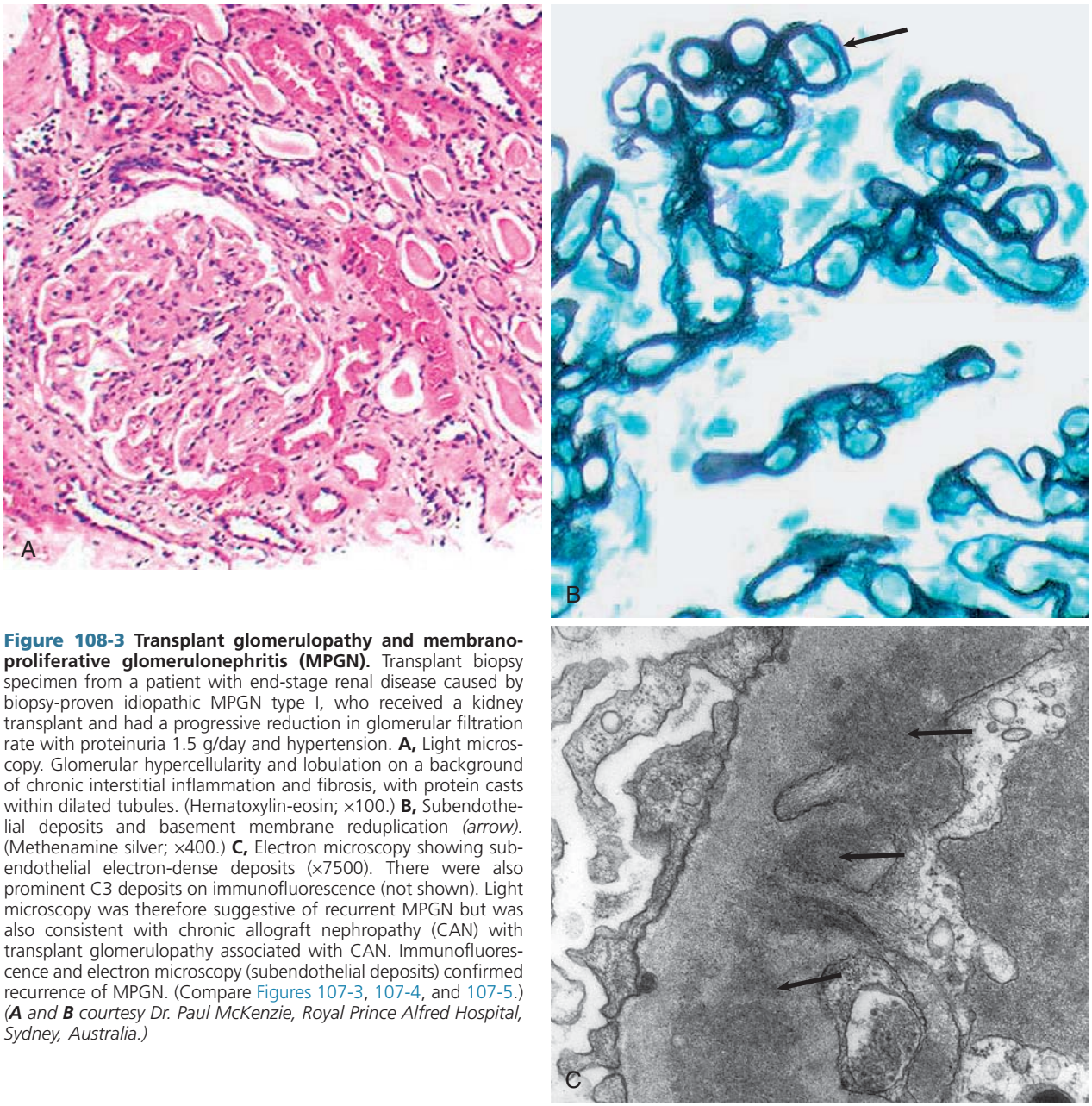

Figure 108-3 Transplant glomerulopathy and membranoproliferative glomerulonephritis (MPGN). Transplant biopsy specimen from a patient with end-stage renal disease caused by biopsy-proven idiopathic MPGN type I, who received a kidney transplant and had a progressive reduction in glomerular filtration rate with proteinuria 1.5 g/day and hypertension. **A,** Light microscopy. Glomerular hypercellularity and lobulation on a background of chronic interstitial inflammation and fibrosis, with protein casts within dilated tubules. (Hematoxylin-eosin; ×100.) **B,** Subendothelial deposits and basement membrane reduplication *(arrow).* (Methenamine silver; ×400.) **C,** Electron microscopy showing subendothelial electron-dense deposits (×7500). There were also prominent C3 deposits on immunofluorescence (not shown). Light microscopy was therefore suggestive of recurrent MPGN but was also consistent with chronic allograft nephropathy (CAN) with transplant glomerulopathy associated with CAN. Immunofluorescence and electron microscopy (subendothelial deposits) confirmed recurrence of MPGN. (Compare Figures 107-3, 107-4, and 107-5.) *(**A** and **B** courtesy Dr. Paul McKenzie, Royal Prince Alfred Hospital, Sydney, Australia.)*

Recurrence of Henoch-Schönlein purpura (HSP) nephritis is less well characterized but appears to be similar to IgAN in all respects. A recent analysis of the United Network for Organ Sharing (UNOS) database including 339 patients with ESRD caused by HSP who received a first kidney allograft reported a frequency of graft loss caused by recurrence of 13.6% and no difference in 10-year graft survival between recipients with IgAN (58.4%) or HSP (59.3%) as their primary renal disease.[18]

Treatment of recurrent IgAN and HSP has not been systematically evaluated. In our opinion, the addition of corticosteroid maintenance in corticosteroid-free patients with recurrence is unproven but reasonable. A change to mycophenolate mofetil (MMF) or the use of fish oil, antiplatelet agents, and tonsillectomy cannot be recommended. The use of nonspecific measures to prolong kidney survival, such as tight blood pressure control, renin-angiotensin system (RAS) blockade, and avoidance of nephrotoxins, is appropriate.

Membranous Nephropathy

The recent identification of the M-type phospholipase A_2 receptor (PLA_2R) as the antigen targeted in idiopathic MN[19] has spurred interest in the use of anti-PLA_2R antibody titers in monitoring disease activity and predicting recurrence. Data on this are conflicting thus far, and further investigation is warranted before adoption of PLA_2R measurement as a clinical tool in transplantation.

Our knowledge of recurrent MN is clouded by two key issues: the small number of patients in reported series and the frequency of *de novo* MN post-transplantation. *De novo* MN has been reported in 2% to 15% of transplant recipients and tends to present more insidiously and later than recurrent MN.[20]

The largest series (pooled from centers in Belgium and France) reported a recurrence rate of 29% in 30 patients at 3 years post-transplantation[21] and graft loss of 38% at 5 years and 52% at 10 years of follow-up. Recurrence is a significant clinical event causing

Recurrent Diseases in Renal Transplants and Effects on Graft Survival		
Disease	**Clinical Recurrence Rate (%)**	**Graft Loss in Recurrent Disease (%)**
Primary focal segmental glomerulosclerosis	20-50 (children), 10-15 (adults)	40-50
Membranoproliferative glomerulonephritis Type 1	20-30	30-40
Dense deposit disease	80	20, often late
Hemolytic uremic syndrome (HUS) Classical D+ HUS Atypical D– HUS Familial HUS	 0-13 30-50 57	 Uncommon 55-100 Approaching 100
IgA nephropathy	30-40, increases with longer duration of follow-up (30%-60% histologic recurrence rate)	16-33
Henoch-Schönlein purpura	Rare (despite 50% histologic recurrence rate)	Rare
Membranous nephropathy	10-29 (histologic recurrence may be more common)	Up to 50
Systemic vasculitis, including Wegener granulomatosis and microscopic polyangiitis	10-20	20-50
Anti-GBM disease (Goodpasture disease)	<5	50
Systemic lupus erythematosus	1-30	Rare
Amyloidosis	25	10-20

Table 108-2 Recurrent diseases in renal transplants and effects on graft survival. *GBM,* Glomerular basement membrane.

proteinuria, nephrotic syndrome, and graft loss in 12% of recipients within 10 years after transplantation.[3] Clinical factors including pretransplantation disease course, duration of dialysis, HLA genotype, graft source, and immunosuppression are not predictive of risk. However, those with a previous graft loss caused by recurrence are at high risk if they undergo retransplantation.[21]

Management of recurrent MN is based on anecdotal reports and extrapolation of data on the management of native kidney MN. There has been some success with rituximab reported in small case series, but the findings await confirmation in a prospective trial. Spontaneous remission appears to be less common than is seen in MN affecting native kidneys. The cumulative exposure to immunosuppressive therapy should be considered because these patients may be at increased risk of lymphoma. Living donor transplantation appears warranted for first grafts but in our opinion should probably be avoided for second grafts if the first was lost early because of recurrence.

Focal Segmental Glomerulosclerosis

Focal segmental glomerulosclerosis recurs in 20% to 30% of first transplants.[22,23] FSGS is a heterogeneous group of conditions, and those with familial or sporadic forms associated with mutation of slit-diaphragm proteins such as podocin, those with FSGS secondary to vascular disease, and those with a very slow rate of progression are at substantially lower risk, whereas patients with an aggressive initial course (heavy proteinuria and renal failure within 3 years of onset), who are younger than 15 years, who have mesangial hypercellularity on biopsy, or who experienced recurrence in a previous graft are at greatest risk.[22,23] The rate of recurrence is higher than 75% in subsequent grafts when the first graft was lost because of recurrence.[24] Living related donor transplantation has been implicated as a risk factor for recurrence; however, a major analysis of U.S. registry data (USRDS) refutes this notion.[16]

Recurrence occurs early, typically within the first month posttransplantation, and manifests initially with heavy proteinuria, followed by hypertension and graft dysfunction. Patients with recurrent disease appear more susceptible to acute rejection and acute kidney injury,[25] as well as graft loss. Recurrence has been associated with early graft loss in up to 50% of patients[23]; however, the adoption of plasma exchange appears to have delayed graft loss in many patients and decreased the incidence of overall graft failure[3] (see Fig. 108-2).

A circulating 50-kd plasma protein that is bound to immunoglobulin, with an affinity for galactose, appears to cause recurrent FSGS.[26] Soluble urokinase plasminogen activator receptor (suPAR) may be one of the proteins.[27] Attempts to use the presence of the circulating "permeability factor" as a guide to the risk of recurrence have not as yet produced a clinically useful test. Plasma exchange or immunoadsorption with either a protein A or anti-IgG column effectively removes the permeability factor because it is bound to immunoglobulin and as a result provides an effective therapy for many patients who develop recurrent FSGS.[28,29] Although not subjected to a randomized, controlled, prospective trial, several series have reported disease remission in the majority of patients who receive treatment within 2 weeks of recurrence.[23,29] The potential for positive publication bias and the absence of randomized clinical trial evidence make prognostic information speculative; however, in the our assessment, response rates appear likely to exceed 50% when therapy is commenced within 2 weeks of clinical recurrence, with lower response rates anticipated when therapy is delayed. Given that graft survival appears to be significantly prolonged in patients who respond to therapy, a course of plasma exchange is warranted in all patients unless contraindications exist (see Chapter 99). Immunosuppression should include a calcineurin inhibitor, and addition of an ACE inhibitor should also be considered, based on case report evidence. A minority of patients with an incomplete response or relapse after cessation of initial therapy will require repeated or long-term plasma exchange[30] or concurrent treatment with secondary agents such as rituximab or cyclophosphamide.[29,31,32] For such patients we recommend a course of rituximab, 500 mg weekly for 4 weeks, in addition to existing immunosuppression and weekly plasma exchange. Pretransplantation plasma exchange has not been shown to be of benefit in the prevention of recurrence in the graft. See Figure 108-4 for an approach to the management of recurrent FSGS.

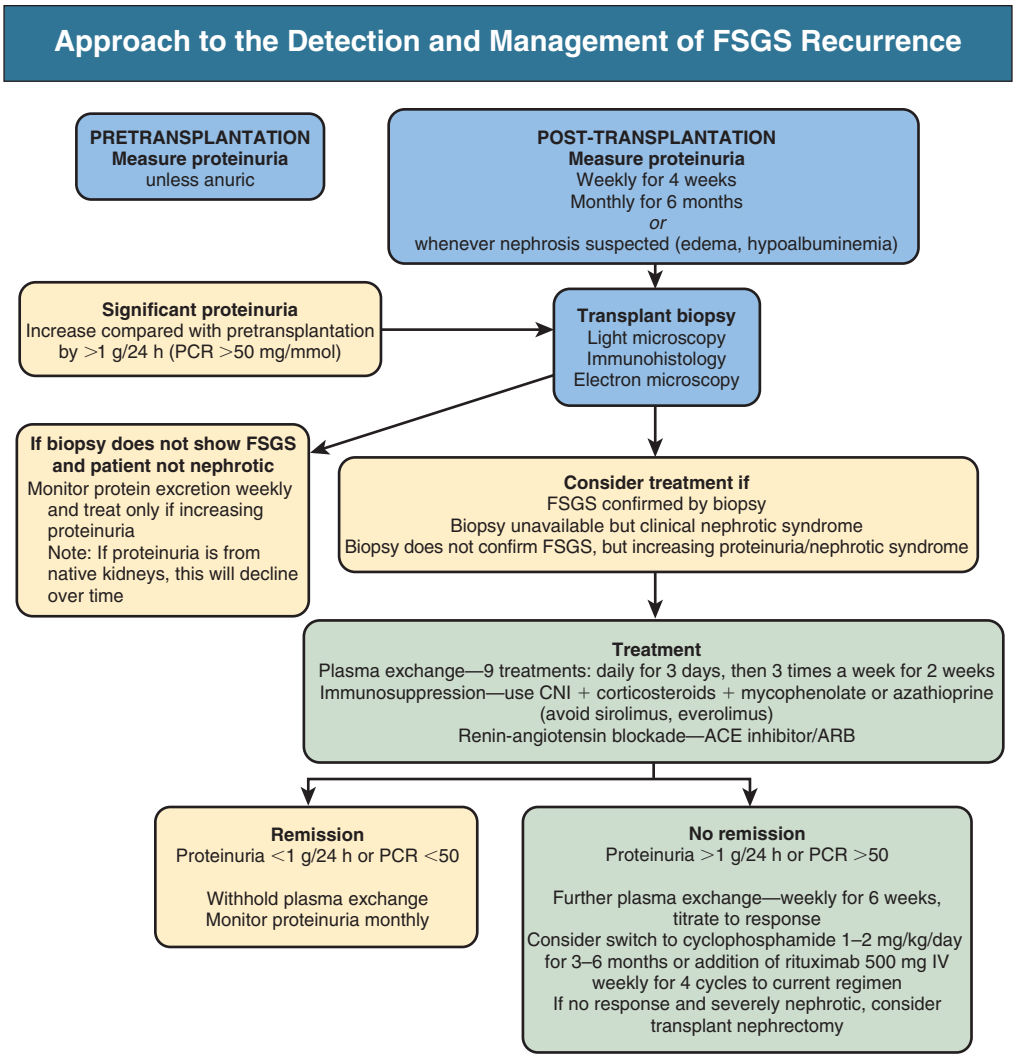

Figure 108-4 Approach to the detection and management of focal segmental glomerulosclerosis (FSGS) recurrence. Author's recommendation based on Davenport.[30] *ACE,* Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *CNI,* calcineurin inhibitor; *PCR,* urine protein-creatinine ratio, mg/mmol.

Minimal change disease is a far less frequent cause of ESRD. Recurrence of disease after transplantation has been reported; however, it is difficult to be sure that the underlying disease was not FSGS.

Membranoproliferative Glomerulonephritis

Recurrent MPGN bears major clinical and histologic similarities with the subgroup of patients with CAN who have transplant glomerulopathy, and comprehensive assessment of transplant biopsy specimens (see Fig. 108-3 and compare Figs. 107-4 and 107-5) as well as accurate diagnosis of the native kidney disease is crucial in making this distinction (see Table 108-1). MPGN type I, rather than transplant glomerulopathy, is suggested by the presence of crescents on light microscopy, stronger staining for C3 and weaker staining for IgM on immunohistology, and subendothelial electron-dense deposits on electron microscopy.[17] This distinction has important clinical implications, particularly because a recurrence carries a higher risk of subsequent recurrence should retransplantation be considered. A retrospective analysis of renal biopsies that included 70 patients with MPGN suggests that the severity of histologic lesions is predictive of recurrence.[33]

Membranoproliferative Glomerulonephritis Type I

Membranoproliferative glomerulonephritis type I appears to be mediated by glomerular deposition of immune complexes, triggered by exposure to endogenous or exogenous (e.g., hepatitis C virus [HCV]) antigens. Because the antigens are not necessarily removed by transplantation, recurrence of disease is possible and is seen in 20% to 33% of graft recipients.[34] Graft loss has been reported in up to 40% of those with recurrence, and the risk of recurrence in subsequent grafts approaches 80%.[35] Significant geographic diversity in the risk of recurrence is evident, largely linked to the prevalence of HCV, with much higher rates of graft loss resulting from recurrence being reported in areas where the majority of patients with MPGN are HCV positive, such as Spain,[34] as compared with low–HCV prevalence areas, such as Australia.[3] Patients receiving HLA-identical grafts appear to be at increased risk of recurrence in some series[34] but not in others.[3]

No form of treatment is proven, and the underlying cause of recurrent MPGN should be considered in each patient. Prevention may be effective in HCV-associated MPGN, because interferon-based therapy appears to be effective for virus elimination if undertaken while the patient is on maintenance dialysis, and this provides substantial protection from HCV viremia and MPGN recurrence

after subsequent transplantation.[36] By contrast, the use of interferon after transplantation may precipitate acute rejection and should be avoided. Other antivirals, such as ribavirin, may have a role; however, proof is awaited. Other forms of MPGN type I have been treated with immunosuppression or plasma exchange with success in single patients.

Dense Deposit Disease

Dense deposit disease (formerly known as MPGN type II) also has clinical and histologic similarities to transplant glomerulopathy. DDD is suggested by granular staining for C3 on capillary loops without immunoglobulin deposits, and the characteristic ribbon-like intramembranous dense deposits on electron microscopy (see Fig. 22-1).[17] DDD has been found to recur in 50% to 80% of grafts, typically presenting with proteinuria, hematuria, and slowly progressive loss of kidney function.[37] The disease course tends to be slow, and whereas graft loss caused by recurrence is ultimately seen in approximately 20% of patients, this generally occurs beyond the first 10 years after transplantation.[3,37] Graft loss has been associated with male gender, crescents on biopsy, and heavy proteinuria.[37] No effective therapy is known, and although plasma exchange and immunosuppression have been described, these are not warranted in our opinion, and control of blood pressure and proteinuria with renin-angiotensin blockade is the preferred therapy. Given the emerging role of alternate complement pathway mutations in DDD (see Chapter 22), plasma infusion or administration of eculizumab may prove useful in the future.

Membranoproliferative Glomerulonephritis Type III

Recurrence of membranoproliferative glomerulonephritis type III, a rare disease, has been reported and has resulted in graft loss in the longer term.[38]

Congenital Nephrotic Syndrome

Congenital nephritic syndrome of the Finnish type has, in small case series, been reported to recur after transplantation and to cause graft loss; however, it is likely that the mechanism of kidney damage is quite different between primary and recurrent disease. The primary disorder is caused by a mutation of the *NPHS1* gene that results in complete absence of nephrin, and therefore transplantation causes *de novo* exposure to nephrin in the transplanted kidney. Neoantigen exposure causes antibody development and deposition that damages the slit diaphragm and produces a type of MN with podocyte fusion on electron microscopy and a clinical picture of heavy proteinuria and ultimately graft failure. Cyclophosphamide-based rescue therapy may be successful.[39]

Antineutrophil Cytoplasmic Antibody–Associated Pauci-immune Vasculitis

A pooled analysis of all reported case series examining recurrence of ANCA-associated vasculitis, incorporating 127 patients, has largely clarified the behavior of this group of disorders after transplantation.[40] Disease recurrence was detected in 17% of patients after 4 to 89 months of follow-up, with renal involvement demonstrated in approximately 60% of these recurrences and graft losses reported in 25% of these. Clinical parameters were not useful in predicting those patients likely to experience a relapse after transplantation. Pretransplantation disease course, duration of dialysis, ANCA titers at time of transplantation and during follow-up, cytoplasmic ANCA (c-ANCA) or perinuclear ANCA (p-ANCA) pattern, antigen specificity, disease subtype (granulomatous polyangiitis [Wegener granulomatosis], microscopic polyangiitis, or renal-limited vasculitis), and donor source had no significant impact on recurrence rate.[40]

The prevention and management of relapse has not been prospectively examined. In most reports, patients did not receive a transplant until they were in clinical remission; however, successful transplantation in the face of persisting ANCA positivity is well recognized. In the absence of firm evidence, we recommend that clinical remission be maintained for at least 6 months before transplantation to reduce the risk of recurrence and also to avoid the risks associated with performing transplantation in a debilitated patient, especially if ESRD has occurred soon after presentation with systemic vasculitis. Patients with renal relapses have generally been managed with cyclophosphamide-based regimens as used for renal vasculitis in native kidneys, reported to be successful in inducing a remission in 11 of 16 (69%) cases.[40] The negative impact of use of cyclophosphamide to treat relapse has not been reported, but would clearly include a significant increase in the risk of bladder cancer.

Kidney transplantation for ANCA-associated vasculitis is associated with a reduction in the frequency of disease relapse by approximately 50% compared with patients remaining on dialysis, and patient and graft survival post-transplantation is similar to that in other transplant recipients.[40]

Goodpasture Disease

Histologic recurrence of anti-GBM disease (Goodpasture disease) is seen in 50% of patients who receive a transplant while circulating anti-GBM antibodies persist, but rarely when patients undergo transplantation 6 months or more after the disappearance of anti-GBM antibodies. With delayed transplantation, the rate of clinical recurrence is very low, and since the implementation of this practice in Australia, no grafts were lost after transplantation in 47 patients followed for up to 10 years.[3] Rare episodes of recurrence should be treated as for native kidney disease with corticosteroids, cyclophosphamide, and aggressive plasma exchange (see Chapter 24).

Recurrent anti-GBM disease is distinct from *de novo* anti-GBM disease, which is seen in up to 15% of transplant recipients with Alport syndrome who develop anti-GBM antibodies in response to neoantigen exposure (α chain of type IV collagen) via the transplant.[41] This is also discussed further in Chapter 24.

Lupus Nephritis

The reported recurrence rate of LN has varied from 2% to 54% depending on the diagnostic criteria used.[42,43] Recurrence has been reported early (days) and late (years) after transplantation, with a median time to recurrence of approximately 4 years.[42] The clinical and histologic pattern of recurrence is variable but is typically more benign in histology and clinical expression than the patient's original disease. Whereas the majority of patients with ESRD caused by lupus have had diffuse proliferative (class III or IV) LN, mesangial proliferative (class II) LN is the most commonly described lesion post-transplantation, followed by class III and membranous LN (class V).[43] Duration of dialysis and serologic activity before transplantation do not predict recurrence, and antinuclear antibody titer and complement levels are unreliable markers of disease recurrence. There is no consistent relationship between recurrence of nephritis and activity of extrarenal lupus after transplantation.

The long-term outcome for lupus patients after transplantation is controversial but appears similar to that of the general post-transplantation population.[42,44] Although recurrence is an uncommon cause of graft loss within the first 10 years after transplantation, with no cases of graft loss reported from 86 recipients in one registry

analysis,[3] late graft losses do occur. It is clear that lupus patients, particularly those with a lupus anticoagulant, are at increased risk of thrombotic events after transplantation including graft thrombosis.[45]

Management of recurrent LN has not been systematically studied; corticosteroids, cyclophosphamide, mycophenolate, and plasma exchange have been used, with variable results reported. Anticoagulation during the perioperative and early post-transplantation phases should be considered for those with a past history of thrombosis or lupus anticoagulant positivity. Successful retransplantation has been reported after graft loss caused by recurrence.[45]

Thrombotic Microangiopathy and Hemolytic Uremic Syndrome

The diagnosis of recurrent thrombotic microangiopathy (TMA), including HUS, is complicated by the fact that *de novo* TMA is seen in 1% to 5% of kidney transplant recipients, most commonly associated with the use of calcineurin inhibitors (both tacrolimus and cyclosporine carry a similar risk), sirolimus, or OKT3 or with acute vascular rejection. Drug-induced *de novo* TMA is generally observed within 14 days of drug commencement. A meta-analysis that examined 10 reports covering 159 grafts in 127 patients reported recurrence in 28% of grafts, and this was strongly associated with a poor outcome: 1-year graft survival was 33% for those with recurrence versus 77% in those free from recurrence ($P < .001$).[46] Recurrence risk is clearly associated with the underlying cause of TMA. Typical childhood Shiga toxin–associated HUS seldom recurs, whereas recurrence of atypical HUS is frequent and, particularly in hereditary forms associated with mutation of complement components or complement regulatory factors, occurs in up to 80% of patients.[47]

Our understanding of atypical HUS has increased substantially in recent years with the identification of the alternate complement pathway as the central player in its pathogenesis. The risk of atypical HUS recurrence and its impact on graft survival are dependent on the mutation responsible. Mutations in factors H and I are associated with a recurrence risk of approximately 75%, and more than 90% of those with recurrence incur graft failure, typically within the first year.[48] In contrast, mutations of membrane cofactor protein are associated with a recurrence rate of 20% and substantially better survival rates than in patients with factor H or I mutations.[49] Given the variation in risk of recurrence associated with mutations of different complement components, genotypic evaluation of the recipient and any potential living donors before transplantation is advisable for all patients with ESRD caused by atypical HUS.[50] Combined liver-kidney transplantation may be considered in selected candidates with defined mutations.[51] Recurrence is also associated with an older age at onset, rapid progression of the original disease, earlier transplantation, living-related transplantation, and the use of calcineurin inhibitors.[46] Recurrence is generally within the first 6 months after transplantation; however, late recurrences have been reported.[46] The clinical presentation may be gradual or abrupt, with thrombocytopenia, hemolysis, and progressive renal dysfunction.

Whereas *de novo* disease may respond to withdrawal of the inciting agent, management of recurrent disease is uncertain. We recommend withdrawal of any potential causative agent such as calcineurin inhibitors, and if this is not effective after 48 hours, a trial of plasma exchange should be initiated with three half-plasma volume exchanges performed on 3 consecutive days with fresh-frozen plasma used for replacement. Because an increased incidence of acute rejection has been reported in patients with recurrence,[47] inadequate immunosuppression after calcineurin inhibitor withdrawal should be prevented with a temporary increase in the dose of corticosteroids. In patients with life-threatening thrombocytopenia or hemolysis, hematologic stability may be restored by transplant nephrectomy. Eculizumab, a humanized monoclonal antibody targeting C5 of the complement membrane attack complex, is emerging as an effective therapy in the treatment of atypical HUS. In case reports, eculizumab has been reported to be successful in both the treatment of recurrence and prophylaxis pretransplantation. Multicenter Phase II trials are currently under way to evaluate its efficacy. Plasma exchange may be effective in patients with mutations in factors H or I, as well as those who have autoantibodies directed against factor H. However, it may be less effective in patients with mutations of membrane cofactor protein or thrombomodulin, in which the protein is membrane bound. The prognosis with recurrent disease is poor. More than 50% of grafts are lost within the first year, and graft survival beyond 5 years is quite uncommon.[46] There is no evidence that calcineurin inhibitor avoidance is useful in preventing recurrence.

Scleroderma

Limited literature exists because of the rarity of scleroderma. An analysis of 86 patients reported to the UNOS registry after receipt of a kidney transplant because of scleroderma from 1987 to 1997 demonstrated graft survival of 62% at 1 year and 47% at 5 years after transplantation; 24% of recipients died during the 10-year observation period.[52] The recurrence rate could not be accurately determined; however, recurrence was responsible for graft loss in 21% of patients in whom the cause was identified, which is consistent with previously accepted recurrence rates. A recent review of the literature suggests that rapid loss of renal function after diagnosis may predict recurrence in the graft.[53] The effect of transplantation on the extrarenal manifestations of scleroderma has not been well documented. The management of scleroderma after transplantation is unstudied; however, the use of RAS blockade after transplantation to treat hypertension would seem appropriate. Overall, renal transplantation appears to be an appropriate treatment for those with scleroderma and ESRD.

AMYLOID, LIGHT-CHAIN DISEASE, AND FIBRILLARY AND IMMUNOTACTOID GLOMERULOPATHIES

Amyloidosis

The risk and impact of recurrence for patients who undergo transplantation because of systemic amyloidosis are dependent on its cause. Management of AL amyloid is primarily directed at treating the underlying plasma cell dyscrasia, most commonly by high-dose chemotherapy and autologous stem cell or allogeneic bone marrow transplantation. Recurrence after transplantation is likely to occur if the malignancy is not fully controlled but may be susceptible to further chemotherapy. The largest reported series includes 25 patients who received a kidney transplant for AL amyloid–induced renal failure, of whom 22 had received chemotherapy which placed three patients in complete remission and 13 patients in partial remission at the time of the kidney transplant.[54] Five-year and 10-year graft survival rates were 74% and 25%, respectively. Recurrence in the graft was documented by iodine 123 (^{123}I)–labeled serum amyloid P component scintigraphy in 28% at a median of 5 years after transplant, although no grafts were lost through recurrence. Myeloma recurred in five patients (28%), of whom three achieved complete remission with further chemotherapy. The major cause of graft failure was the death of 13 patients (52%), most commonly caused by sepsis. Cardiac involvement on echocardiogram was noted in five patients before transplantation, and one died of cardiac failure after

transplant. Thus, transplantation appears to be a viable option for patients with ESRD caused by AL amyloidosis, provided they have achieved at least a partial remission after chemotherapy and have little or no cardiac involvement.

Secondary (AA) amyloidosis is typically a more insidious disease; renal failure is a relatively frequent complication, and renal transplantation is frequently effective.[54] The risk of recurrence of AA amyloid depends on the ability to eradicate the underlying cause of chronic inflammation. In AA amyloid, recurrence as a result of chronic infection is unlikely if the infection can be eradicated pretransplantation, whereas conditions such as rheumatoid arthritis may persist after transplantation and lead to recurrent amyloid in the graft. Less than 5% of patients with AA amyloid associated with familial Mediterranean fever, which can be managed with colchicine after transplantation, have recurrence at 10 years after transplantation.[55] A Norwegian series of 62 transplants in patients with AA amyloid, mostly secondary to rheumatic diseases, demonstrated a recurrence rate of 10% at an average of 5 years of follow-up, with recurrence causing graft loss in two patients only. Overall, patient and graft survival rates were 65% and 62%, respectively, at 5 years, with most losses resulting from infection.[56]

Light-Chain Nephropathy

Patients with light-chain nephropathy have occasionally received transplants and recurrence is common; one case series reported recurrence in five of seven patients at a range of 2 to 45 months after transplantation. Those with recurrence developed proteinuria, hypertension, and progressive graft dysfunction. One of seven has had long-term graft function, and one died soon after transplantation because of myeloma.[57] Kidney transplantation is therefore generally inadvisable for patients with this disease, unless performed in conjunction with bone marrow transplantation as a means of curing the underlying disease. Rituximab and bortezomib have been used with success in patients with light-chain nephropathy recurrence in the graft, but insufficient evidence exists to recommend either agent as a standard of care.

Fibrillary and Immunotactoid Glomerulopathies

Fibrillary and immunotactoid glomerulopathies are known to recur in approximately 50% of those undergoing transplantation for these diseases, and although early graft loss as a result of recurrence has been reported, decline in graft function is most commonly slow and does not appear to have an impact on 5-year graft survival rates.[58]

RECURRENCE OF METABOLIC DISEASES AFFECTING THE KIDNEY TRANSPLANT

Diabetes Mellitus

Diabetes mellitus is the most common cause of ESRD in most parts of the world; however, these patients undergo transplantation less commonly than those with GN because of a higher prevalence and severity of cardiovascular comorbidity. Recurrence of diabetic nephropathy is well recognized both histologically and clinically, affecting at least 25% of recipients at an average follow-up of 6 years and with some patients diagnosed within 3 years of transplantation.[59] Histologic and clinical features are similar to those of native kidney diabetic nephropathy. The risk of graft loss from recurrence has not been well documented but appears to be significantly less than with GN, probably because of the competing risk of death from cardiovascular disease. NODAT is also common and has been reported to cause nephropathy in the graft in a similar proportion of patients, also commonly manifesting within 5 years of transplantation. The extent to which this contributes to graft loss also awaits clarification, although a recent analysis of registry data suggests that the impact on graft failure is insignificant in comparison with the impact on premature death with a functioning graft.[5]

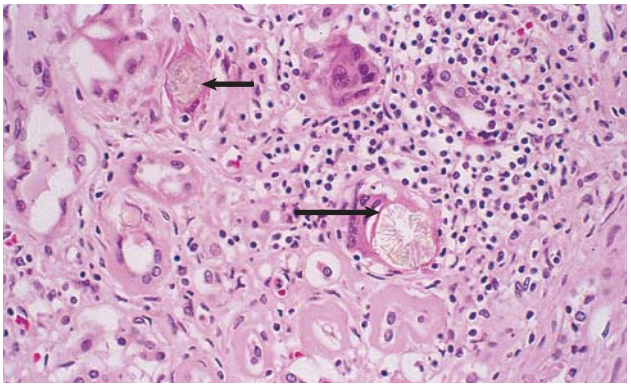

Figure 108-5 Recurrent primary hyperoxaluria. Light microscopy demonstrates oxalate crystals within the tubular lumen *(arrows)* with a secondary interstitial inflammatory infiltrate.

Primary Hyperoxaluria

Primary hyperoxaluria (see Chapter 59) is a rare autosomal recessive disease caused by defective or absent hepatic production of alanine glyoxylate aminotransferase, resulting in systemic accumulation of calcium oxalate (oxalosis). Kidneys and blood vessels in particular are affected. Kidney transplantation alone is frequently complicated by hyperoxaluria and consequent recurrence in the graft and ultimately graft loss (Fig. 108-5). By contrast, combined liver-kidney transplantation corrects the underlying metabolic deficit and permits long-term kidney graft survival. In an analysis of the USRDS that included 190 adults with oxalosis who went on to undergo renal transplantation, 134 patients who received a kidney transplant alone experienced 48% 8-year death-censored graft survival. This was inferior to 56 patients who also received a liver (76%) and inferior to a control group with a primary diagnosis of GN (61%).[60] Aggressive removal of residual oxalate before transplantation by dialysis and after transplantation by pyridoxine supplementation and maintenance of high urine volumes may also decrease the risk of graft damage.

Fabry Disease

Fabry disease results from a defect in lysosomal α-galactosidase A enzyme, which results in tissue accumulation of trihexosylceramide, eventually causing ESRD (see Chapter 48). Recurrent Fabry disease has been documented within the graft; however, graft survival does not appear to be affected. Treatment with recombinant α-galactosidase A, should this become widely available, is likely to reduce the risk of ESRD and also that of recurrence.

RECURRENCE OF VIRUS-ASSOCIATED NEPHROPATHIES AND TUMORS IN THE TRANSPLANTED KIDNEY

Virus-associated kidney diseases may recur following transplantation. Hepatitis B and C virus–associated MPGN and MN are known

to recur; however, the risk of this can be substantially decreased by successful antiviral therapy before transplantation (see Chapter 57).

Retransplantation has been reported in patients experiencing graft loss because of BK virus nephropathy. In the largest series, recurrence was documented in 1 of 10 transplant recipients at an average follow-up of 3 years.[61] Measures to decrease the risk of recurrence included delay in retransplantation by an average of 13 months and transplant nephrectomy in seven patients. Calcineurin inhibitor–based triple immunosuppressive therapy was used in all patients, and the one patient with recurrence experienced stabilization of graft function after a reduction in immunosuppression.[61] Thus retransplantation, ideally delayed until BK virus is not detectable in serum by polymerase chain reaction, appears to be safe and effective.

Patients who develop post-transplantation lymphoproliferative disease and incur graft loss as a result of direct infiltration or rejection after the withdrawal of immunosuppression may safely and successfully undergo retransplantation after a substantial period of recovery. There was no evidence of recurrence reported in one series of five cases.[62]

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CHAPTER 109

Outcomes of Renal Transplantation

Jeremy R. Chapman and Deepa Usulumarty

Improving the outcome for patients with end-stage renal disease (ESRD) is the only justification for renal transplantation. If there were not objective and relevant data on outcomes that are meaningful to the patient, then few would take on trust the benefits of a procedure that has the risk of multiple adverse events. The first patients in the 1950s were comparing the potential benefits of transplantation with certain death from ESRD at that time in the absence of dialysis therapy[1]; some chance of life was better than no chance. Today's patients face a more complex decision with excellent dialysis treatment available in many parts of the world, and an improving and much better understood alternative in the form of renal transplantation.

The field of renal transplantation is rich with data, and increasingly sophisticated outcome measures and analyses are available to inform patient decisions. Nevertheless, when a patient is faced with a particular clinical problem, it is still common that the evidence base is insufficient to inform a specific decision. Transplantation guidelines that have been created by a number of societies and by Kidney Disease: Improving Global Outcomes (KDIGO) demonstrate through the grading of evidence that many specific decisions can be informed only by "consensus opinion." At the very least this emphasizes that there is often no right answer; but it also provides a challenge to prove more about the assumptions that are made in clinical practice every day.

This chapter reviews the techniques and factors that deliver the outcome measures available today to inform patients' decision making about renal transplantation.

METHODS OF MEASUREMENT AND ANALYSIS

Types of Outcome Analyses

If the outcomes of 1000 people undergoing transplantation at different times and in different places are measured, some of the patients will inevitably die over the succeeding years. They may die because of the transplant, they may have an accident, or some other intervention may lead to death. How can this be related to the success or failure of the transplant? The most conventional method is to use a Kaplan-Meier plot that yields an actuarial estimate of outcome, as opposed to an actual measure.[2,3] Events—deaths in this case—are recorded and the time to that event from the transplant is measured. The Kaplan-Meier method then uses the time of follow-up for each individual to contribute to the analysis, resulting in a better estimate of what will happen to the entire group of patients and not just the small group of patients who have reached a particular time point. An example of such an analysis is shown in Figure 109-1.[4] When one is comparing two groups of individuals, there may be issues that should be taken into account such as age. For example, if one group had an average age of 30 years and the other 60 years, differing death rates would be predicted from expectations of what would happen in the general, non-ESRD population. Thus it may be important to show "adjusted" results—for example, adjusted for age and gender—to get appropriate comparisons—for example, between the results in different transplant programs. A multivariate analysis will provide the opportunity to adjust the results for all of the factors that, on their own, appear to affect the outcome. In the 1000-patient example, it may be that there are statistically significant differences in death rates if the group is divided based on age, the presence or absence of diabetes, gender, or the center where the patients underwent transplantation.[5,6] With a multivariate analysis, it is possible to see which of these outcomes is influenced by the particular distribution of the others. It may be that one transplant center that appears to have worse results performs transplants mostly on older patients and those with diabetes, whereas another center with excellent results selects only young nondiabetic recipients for transplantation. The multivariate analysis may indicate that both centers would likely achieve the same results if they performed transplants in similar patients.

Half-Life Analysis

The half-life analysis is the second type of analysis that is used to extrapolate results beyond where the data stop. In the 1000-patient example it may be that no one has passed the 10-year mark, yet patients seek an estimate of how long their kidney may last. Actuarial analysis may indicate an 80% chance of a transplant lasting 10 years but does not provide information about what happens after 10 years. A half-life analysis allows extrapolation from the known data. There are two different half-life calculations in the literature: the median survival, which is the time for which the middle patient in the series has survived; and the conditioned half-life, which is the median survival of the patients who have survived 1 year or more. Figure 109-2 provides an example of the use of half-life calculations to demonstrate the difference in outcomes related to human leukocyte antigen (HLA) matching between donor and recipient.[7]

Graft Survival

Graft survival may be presented in two different ways, each valid in its own right, but yielding quite different answers. One of the problems in the field is that many graft survival analyses do not make clear which is being used. It is possible to understand the problem using the 1000-patient example. Assume that 100 patients have died with their transplant still functioning at the time of death and 80 have lost their grafts from rejection and other causes. If one counts death as a cause of graft loss, then 180 of the 1000 patients have lost their grafts; if one ignores death as a cause, then only the 80 have lost their grafts. The latter calculation is best described as *death-censored graft survival,* whereas the inclusive analysis is described as *patient and graft survival.* When the analysis is not specified, the

findings can be misleading and may make no sense. For example, in the illustrative analysis, the actual patient survival would be 90% (100 deaths in 1000 patients) and the death-censored graft survival would be 92% (80 grafts lost in 1000 transplants), so it might be concluded that 2% or 20 kidneys somehow survive in the absence of the recipient! Both approaches are of course relevant to different situations—on the one hand to understand what causes kidneys to fail, and separately to understand what causes patients to die—but there must be methodologic clarity.

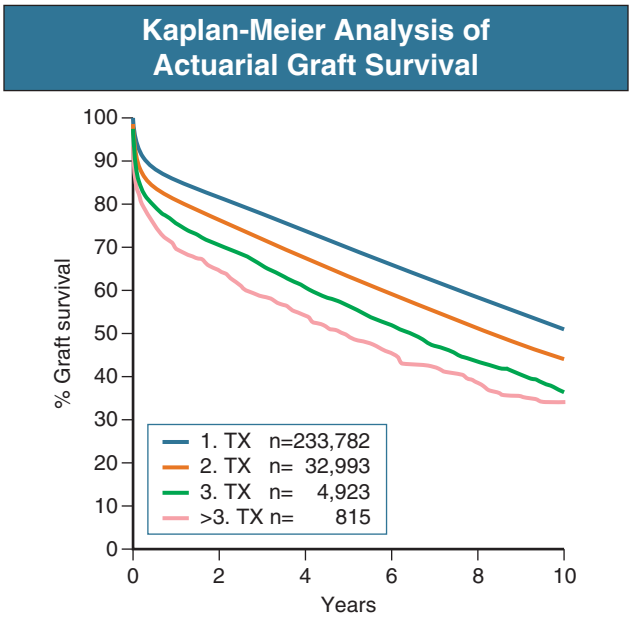

Figure 109-1 Kaplan-Meier analysis of actuarial graft survival. Collaborative Transplant Study analysis of actuarial survival of deceased donor renal transplants 1985 to 2011 by recipient graft number (1, 2, 3, and >3). *(From the Collaborative Transplant Study, University of Heidelberg, Department of Transplantation Immunology. CTS outcome graphs. Available at www.ctstransplant.org/public/graphics.shtml. Accessed January 7, 2013.)*

Randomized Controlled Trials

Randomized controlled trials (RCTs) are a conventional way of determining differences between two or more therapies and are used in transplantation especially to evaluate new pharmaceutical products, which require testing in randomized studies before they can be registered for use. The majority of RCTs therefore compare two drug regimens—one with and one without the new agent. Two critical problems compromise the value of RCTs in renal transplantation: First, the relatively small number of transplants performed in any one center means that it is hard to mount studies with sufficient power to detect significant differences; and second, good early surrogate markers for long-term outcomes are lacking. In cardiovascular studies, in contrast, it is often possible to randomize many thousands of patients and detect differences in meaningful outcomes other than death; and in cancer studies it is possible to use short-term evidence of tumor response as a surrogate for longer-term outcomes. In an earlier era of renal transplantation, relatively small studies could be highly informative. An example of an RCT from the 1980s is the Oxford cyclosporine trial,[8] in which azathioprine and prednisolone could be compared with cyclosporine with sufficient power to detect a difference with less than 100 patients randomized to each group. This was because the survival rates in the control arm were susceptible to large improvements—5-year graft and patient survival improved by 20% from a baseline around 47% to 67% with the addition of cyclosporine. Today the results of standard of care therapy are so high that recruitment of sufficient patients to detect either graft or patient survival differences at 1 or 2 years is not only extremely expensive but, unless the trials are very large, likely to founder on small random variations in such issues as surgical complications.

In the 1990s the introduction of the composite end point controlled the required size of RCTs. The composite end point is an acceptable indicator of benefit for the U.S. Food and Drug Administration (FDA) and other regulatory authorities to register a drug for therapeutic use. The composite end point includes patient death, graft loss, acute rejection episodes, and loss to follow-up (the last index conservatively defaults the patients who are lost to follow-up as having failed the therapy). Analysis is by intention to treat—in

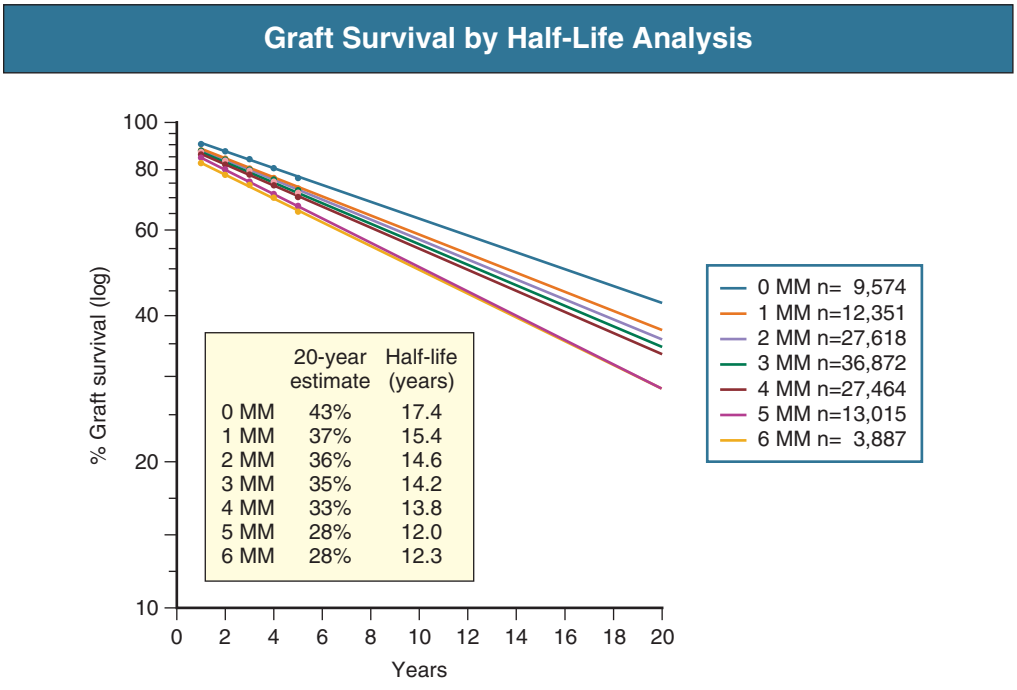

Figure 109-2 Graft survival by half-life analysis. Collaborative Transplant Study analysis of survival of first deceased donor renal transplants performed from 1985 to 2011 by human leukocyte antigen (HLA) mismatch *(MM)* showing the half-life calculation and 20-year estimates of survival. *(From the Collaborative Transplant Study, University of Heidelberg, Department of Transplantation Immunology. CTS outcome graphs. Available at www.ctstransplant.org/public/graphics.shtml. Accessed January 7, 2013.)*

other words, for outcome analysis the patient is assigned as randomized whether or not the patient ever received the assigned treatment. Three key studies confirming the benefit of mycophenolate mofetil (MMF) were conducted using this approach and recruited around 500 patients allocated randomly into three study arms.[9,10]

Moving forward another 10 years, the largest transplant RCT undertaken to date (the Symphony trial[11]) required more than 1500 patients to be randomized, and even then was powered only for a surrogate marker of long-term outcome, differences in renal function. It is now accepted that transplant RCTs cannot be sufficiently powered to detect differences in the "hard" end points of patient and graft survival and must all be powered for a composite end point and surrogates of long-term outcomes. Which short-term surrogates provide good predictors of long-term outcomes has yet to be determined. Acute cellular rejection was, in the 1990s, a short-term measure of importance for long-term results, but perhaps not when current immunosuppressive regimens are used.[12]

Cohort Studies

Some clinical issues are not susceptible to testing by RCT. For example an RCT design will never be able to test whether cancer is more prevalent in patients on dialysis compared with patients after transplantation, first because randomization to dialysis or transplantation is ethically unachievable, and second because the numbers required to power such a study would exceed global transplant capacity. However, it is still important to understand whether the risks change between dialysis and transplantation and thus to understand whether there is any action that can increase or decrease death from cancer after transplantation. An example of an analysis addressing these questions is the Australian cancer study in which data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry on a cohort of patients who were first treated for ESRD between 1982 and 2003 were linked to data from the national cancer registries.[13] It is critical to ensure the selection of the cohort is appropriate to the question being asked. All too often a cohort study is selected from a convenience sample and thus has critical systematic flaws. A typical convenience sample is "all patients being followed by a particular transplant unit." The analysis becomes an assessment only of patients still alive and still coming to the transplant unit for follow-up. The cohort has been distorted, the flaw being that the patients not being followed, because of death or graft failure, may be crucial to the analysis.

Meta-Analyses

Some areas of transplantation are rich in both RCTs and nonrandomized studies of a particular intervention—for example, interleukin-2 (IL-2) receptor blockade for induction in renal transplantation. Because the studies have produced variable results, which one should be believed? This issue is approached by meta-analysis of available studies and exemplified by the work of the International Cochrane Collaboration.[14] An example of a Cochrane review is shown in Figure 109-3.[15] These types of analysis combine the results from patients who have undergone the same interventions from all similar studies, which thus gives much greater statistical power than each study alone can provide. The methodology requires searching for all studies of the question and especially capturing unpublished studies. The problem of publication bias plagues the field; studies with a positive finding for the intervention are more likely to be published than negative studies. The compulsory preregistration of all trials of a drug by commercial entities in a public database such as

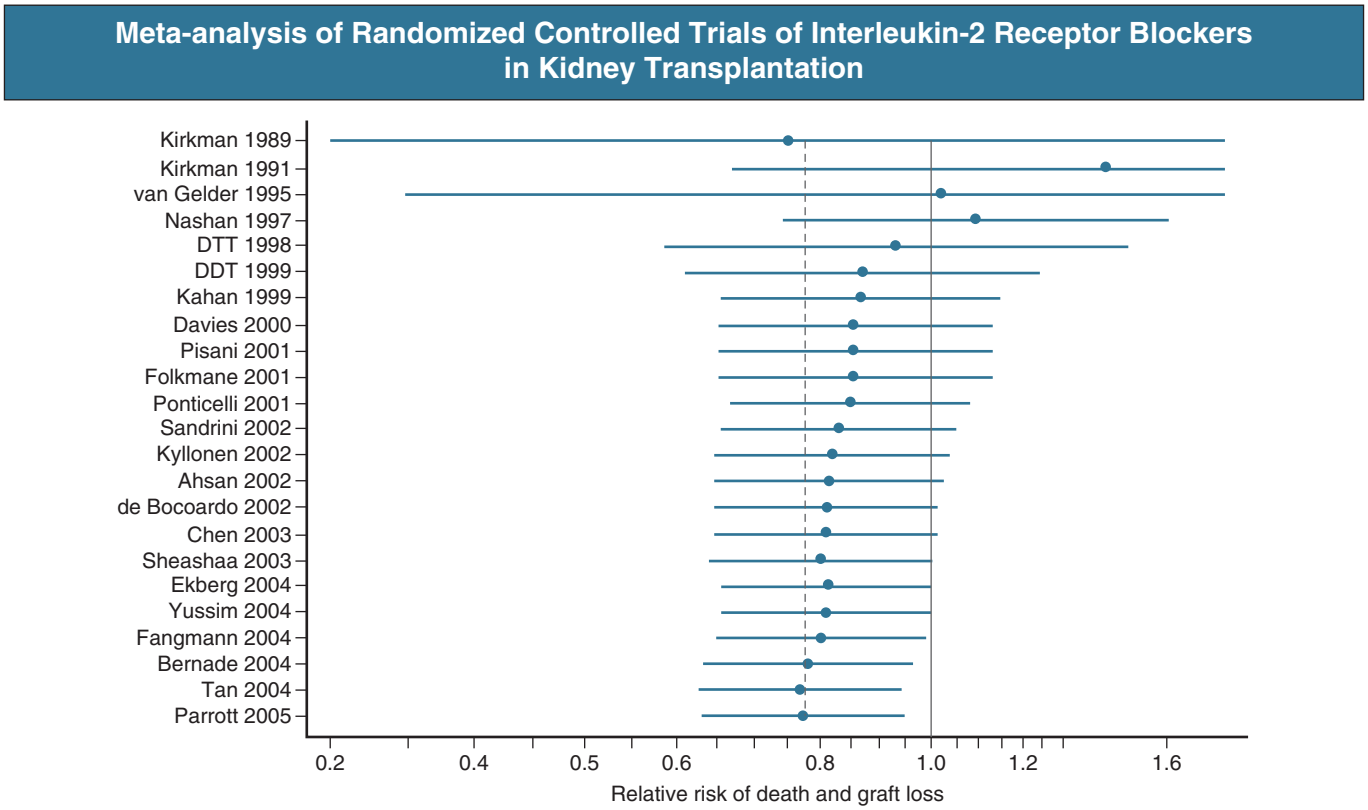

Figure 109-3 Meta-analysis. A cumulative meta-analysis showing the effect of increasing numbers of trials on the confidence intervals of the outcome of death and graft loss in patients receiving interleukin-2 receptor blockers compared with placebo in all randomized controlled trials published from 1989 to 2005. *(Data reproduced with permission from and courtesy A. Webster, presented at the World Transplant Congress, Boston, 2006.)*

www.clintrials.gov is designed to avoid this publication bias, and it is now widely accepted that nondisclosure of data by commercial sponsors of clinical trials is neither scientifically acceptable nor tolerated by the regulators.

Case Reports

Can a case report provide valuable information about outcomes after transplantation? There are some instances of rare events where the knowledge from a case report has proved important. One example is the early anecdotal reports of hepatitis B transmission from hepatitis B surface antigen (HBsAg)–negative donors to recipients of their livers.[16] A few case reports led to a cohort analysis, which in turn led to an understanding that hepatitis B can be transmitted from a donor who tests negative for HBsAg but positive for hepatitis B core antibody. The surveillance and vigilance strategy for the safety of cells, tissues, and organs of human origin is based on this concept—identifying and publicizing the rare cases so that the problems can be recognized (see www.notifylibrary.org).

Expert Opinion Guidelines

The final type of analysis that is pervasive in the transplantation literature is expert opinion, sometimes leading to clinical practice guidelines. Only the major questions have answers in RCTs, meta-analyses, or cohort studies. The clinician is faced with unanswered questions in day-to-day clinical decision making. Guidelines rate the available evidence on particular questions from good to nonexistent. An example of a widely disseminated set of guidelines is the KDIGO guidelines for the care of a transplant recipient,[17] which clearly set out the limits of knowledge in the area. Much of the guidance provided on how to maximize outcomes for particular patients is based on the combined wisdom and experience of clinical practitioners and not on RCT or other data analyses.

Qualitative Studies

Some questions are not amenable to quantitative data collection yet are of great importance to the field. What causes potential living donors to decide to donate? What do physicians consider most important in assessment of living donors? Why does a particular community not donate many organs after death? These questions are amenable to qualitative research and can be assessed and measured, not to produce proof related to a particular question, but to generate testable hypotheses. Qualitative studies create insights into behaviors and attitudes and do not assume that there is a single reality to be discovered; people have different views on organ donation, and any system of measurement that expects everyone to be driven by the same perspectives is going to be disappointed. A guide to the approach of qualitative studies in transplantation has been published to assist scientists familiar mostly with quantitative studies.[18]

Types of Data Collection

All analyses of data are dependent on the methodology of data collection and completeness of the data. Clearly if the data entered into an analysis are flawed in some way, then the analysis will simply embed those flaws and provide spurious confidence in the outcomes of the analysis. Once the flaws of data collection have been hidden by an analysis, it is all too often that they are never again identified and clinical practice is influenced on the basis of a false assumption. It is thus essential that the reader of any analysis verify for himself or herself whether the data were collected in a manner that is trustworthy and relevant to the question. There are many ways to collect data, all of which have their usefulness when applied in the right manner.

Registries

The methodology of registry data collection varies from voluntary to compulsory and from automated to manual. The completeness of data is related to the amount collected, the frequency with which it is updated, and the methods used. National transplantation registries, such as the ANZDATA registry in Australia and New Zealand[19] or the similar Malaysian Dialysis and Transplant Registry, are often voluntary. Some, such as the North American UNOS (United Network for Organ Sharing), database are mandatory, in that financial penalties are threatened for failure to fill in critical data elements.[20] The largest international registry is the Collaborative Transplant Study run from Heidelberg, Germany, which uses voluntary data collection on the repeatedly stressed basis that all sequential transplants are entered and followed.[4] Donor registries tend to be complete because they capture all data at the time of organ donation as a part of the process of donation.[21] Registries that collect their data in a manner that is integrated into the process they are measuring, such as taking data directly from the patients' medical records, as in Hong Kong, tend to have the most reliable data. In the United States, the Scientific Registry of Transplant Recipients (SRTR) has the opportunity to use data linkage between databases to increase its accuracy.[22] Data available to SRTR include deaths in the United States and Medicare billing data to cross-check whether a transplant recipient is being billed for dialysis—both useful pieces of information to construct an accurate view of survival of either the patient or graft.

Incompleteness of follow-up data is a weakness of many transplant registries and depends on the ability of transplant programs to follow their patients and to report outcomes. Both steps are fraught with failure. Many patients move among physicians and thus lose contact with the transplanting center; and of course, many transplant centers are pressed for resources, so the voluntary and unpaid activity of completing data returns receives minimal attention. Regrettably, successful outcomes can be artificially inflated by centers that assume patients are alive and well unless they have heard otherwise: bad data thus produces apparently good results.

Registries usually seek at least one data point annually that confirms the patient has been seen and the graft is still functioning; failing that, they define the patient as lost to follow-up at the point of last contact. This technique yields the most benefit from the data that are known about any one individual but does not allow uncertain data to contribute to analyses.

International Statistical Collections

The most useful international statistics collections are those conducted by the World Health Organization and published on the Global Observatory on Donation and Transplantation (GODT) website (www.transplant-observatory.org). These data are contributed by all national governments and represent probably the best estimates of global transplantation activity, but little or nothing regarding outcomes is available from that source. The GODT does allow analysis of relationships between donation and transplantation indices on the one hand and national health and financial statistics on the other, as in Figure 109-4.

Randomized Controlled Trials

The techniques of data management for commercially sponsored clinical research probably supply the most robust of all the data that are available, because the primary data source is the patients' medical records, which are used to record specific items of carefully predefined data and most crucially are audited for accuracy. These three elements—primary data source, predefined information, and auditing—deliver the most trustworthy data. There is, however, one

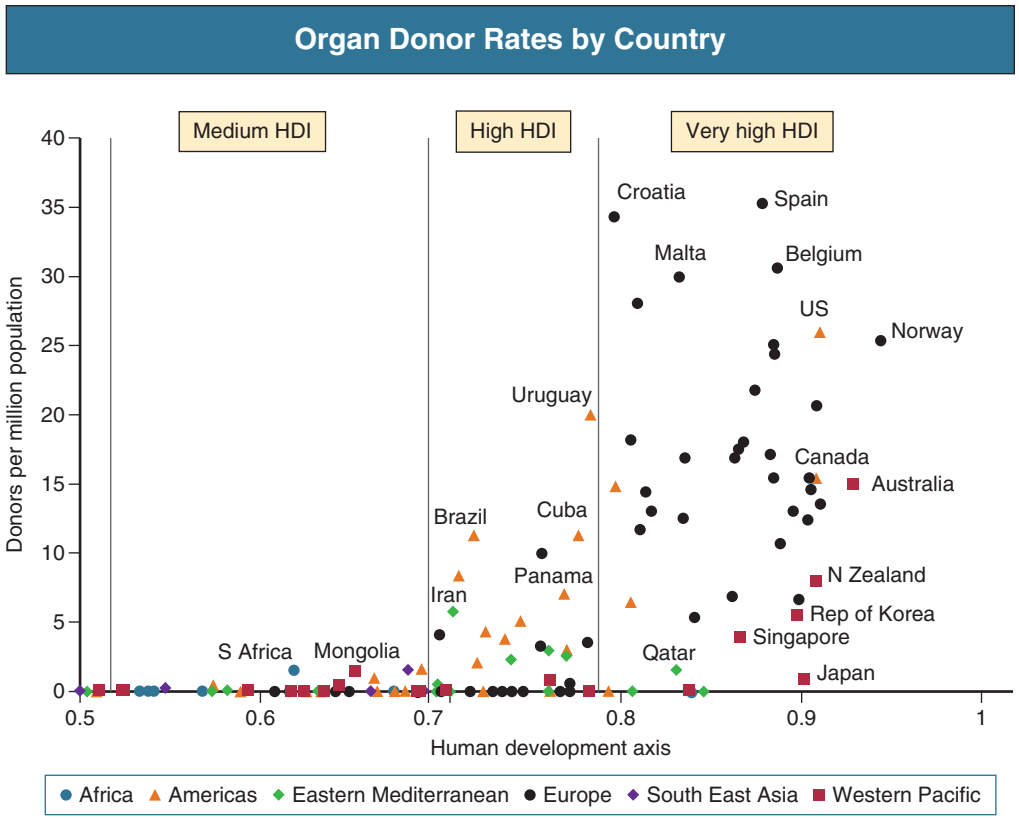

Figure 109-4 Organ donor rates by country. World Health Organization (WHO) analysis of the number of organ donors plotted against the Human Development Index (HDI) for each member state. *(Data reproduced with permission from the Global Observatory on Donation and Transplantation.)*

major drawback: The predefined duration of the studies ensures that data needed to answer questions about the long-term outcomes are almost always missing. The longest clinical trial data collections are usually for only 5 years. An exception, in Australia, is the case of two RCTs in which patients have been followed for up to 20 years through the use of the ANZDATA registry.[23,24]

Structured Reviews

Structured literature reviews are derived from medical reference literature search engines such as PubMed and Embase. There are also two transplantation-specific databases of published clinical trials in the Cochrane Collaboration[14] and the Transplantation Library.[25] These databases contribute the majority of information for the structured literature reviews needed for meta-analyses and guideline development, but nonautomated searching of conference proceedings and abstracts is also needed to ensure complete data identification. The final source of data for questions related to registered therapeutic products is pharmaceutical companies.

VARIABLES AFFECTING THE OUTCOMES OF TRANSPLANTATION

Deceased Donor Variables

The best transplant outcomes have been assumed to come from transplantation of kidneys from young adult male donors with simple trauma as the cause of brain death and with no other medical conditions. These were the donors with which the majority of transplant programs commenced and which have become increasingly rare as road safety, accident retrieval, and neurosurgical interventions have all improved. The older recipient with previous medical conditions who finally dies from a cerebrovascular accident after many years of uncontrolled hypertension has had organs transplanted warily and somewhat reluctantly, usually into an older recipient. An analysis in the United States demonstrated that these extremes yield a twofold difference in graft survival.[26] Four donor factors provide the clearest distinction of outcome: donor age, cerebrovascular cause of death, a history of hypertension, and renal function at the time of donation. These criteria provide a matrix of relative risk of graft failure that ranges from 1.00 for a 10- to 35-year-old donor with no adverse features to a nearly threefold increased risk of failure (2.69) for a donor over age 60 with a cerebrovascular accident, a history of hypertension, and a terminal serum creatinine over 1.5 mg/dl. These criteria were grouped to simplify the definition of a donor kidney likely to be associated with worse graft outcomes as the expanded-criteria donor (ECD) using a cutoff of a 1.7-fold worse outcome; all other donors are classified as standard-criteria donors (SCDs) (Table 109-1).

Expanded-Criteria Donors and Graft Failure

				Donor Age 50-59 yr	Donor Age ≥60 yr
No comorbidity	—	—	—	1.41	1.90
One comorbidity	CVA	—	—	1.61	2.17
	—	HTN	—	1.60	2.16
		—	Creat	1.53	2.04
Two comorbidities	CVA	HTN	—	1.83	2.47
	CVA	—	Creat	1.75	2.37
	—	HTN	Creat	1.75	2.37
Three comorbidities	CVA	HTN	Creat	1.99	2.69

Table 109-1 Expanded-criteria donors and graft failure. Relative risk of graft failure with expanded-criteria donors in the United States, 1999 and 2000. Relative risk is compared with graft failure with donors aged 10 to 39 years with no adverse factors: relative risk = 1.00. Relative risk increases with increasing donor age and presence of one or more of three comorbidities: death from a cerebrovascular accident *(CVA),* donor history of hypertension *(HTN),* or terminal predonation serum creatinine >1.5 mg/dl *(Creat).*

Patient Survival After Transplantation with Expanded-Criteria Donor and Standard-Criteria Donor Kidneys

Recipient Age	ECD		SCD	
	1 Year (%)	5 years (%)	1 Year (%)	5 Years (%)
35-49	96	78	97	85
50-64	89	63	92	75
65+	86	55	89	59

Table 109-2 Patient survival after transplantation with expanded-critera donor (ECD) and standard-criteria donor (SCD) kidneys. Patient survival (percent) after receiving an ECD versus an SCD kidney in the United States, 1999 and 2000. *(Based on data from reference 26.)*

The survival of recipients who received ECD grafts was 91% at 1 year compared with 95% for SCD grafts, but because these kidneys had been allocated to older recipients, the results were not directly comparable. However, by comparing within age cohorts it can be seen that there was a reduced patient survival after transplantation of a kidney from an ECD (Table 109-2). In a separate analysis it has been shown that the mean creatinine clearance 6 months after transplantation declines from approximately 65 ml/min if the donor was 20 to 25 years old to only 35 ml/min for donors older than 70 years.[27]

The approach to allocation of such ECD kidneys varies around the world. The Eurotransplant policy is to allocate older donors to older recipients.[28] In contrast, the Australasian allocation policy does not distinguish among donor ages, but refusal of offers by younger patients leads to organs being accepted only by older recipients, unless a particularly beneficial HLA match or a negative crossmatch occurs in a highly sensitized patient and motivates a younger patient to accept an ECD offer.[29]

Donation after circulatory arrest (donation after cardiac death [DCD]) rather than after a diagnosis of brain death (donation after brain death [DBD]) now accounts for up to 20% of kidney donations in some countries. It has thus become important to determine the impact of DCD on short- and long-term outcomes. The data are reassuring in that although DCD kidneys more often suffer delayed graft function, neither graft survival, patient survival, nor renal function is different from that in transplantation of DCD kidneys from donors under the age of 45 years compared with donation after brain death.[30] Markov modeling has demonstrated that the combination of DBD and DCD donation is economically superior to a simpler strategy that focuses only on the use of DBD kidneys.[31]

Living Donor Variables

The assessment of the living donor is primarily directed at donor safety to ensure the risk to the donor is minimized as much as possible. The secondary assessment is of factors that may affect the recipient's chances of a successful outcome. Impaired renal function and significant donor hypertension and diabetes are, for example, usually exclusion criteria based on donor safety rather than recipient outcomes.[32] Assessment of the living donor is further discussed in Chapter 102. The cumulative data from almost all studies show that transplantation of a living donor kidney offers superior outcomes to deceased donation, though the precise reason for this is probably a mixture of recipient and donor factors including the ability to perform preemptive transplants with living donors. A long-term analysis performed by ANZDATA shows there was a 10% advantage to living donation at 1 year stretching to a 14% advantage by 20 years after transplantation (Table 109-3 and Fig. 109-5).[33]

Graft Survival After Living and Deceased Donor Transplantations

Years	1	5	10	15	20
Living donor	91	75	61	45	35
Deceased donor	81	66	47	33	21

Table 109-3 Graft survival after living and deceased donor transplantation. Percentage of actuarial non–death-censored graft survival after living and deceased donor transplantation, 1985 to 1989. *(Based on data from reference 19.)*

Comparison of the Long-Term Outcomes of Transplantation by Era in Australia and New Zealand After Living and Deceased Donation

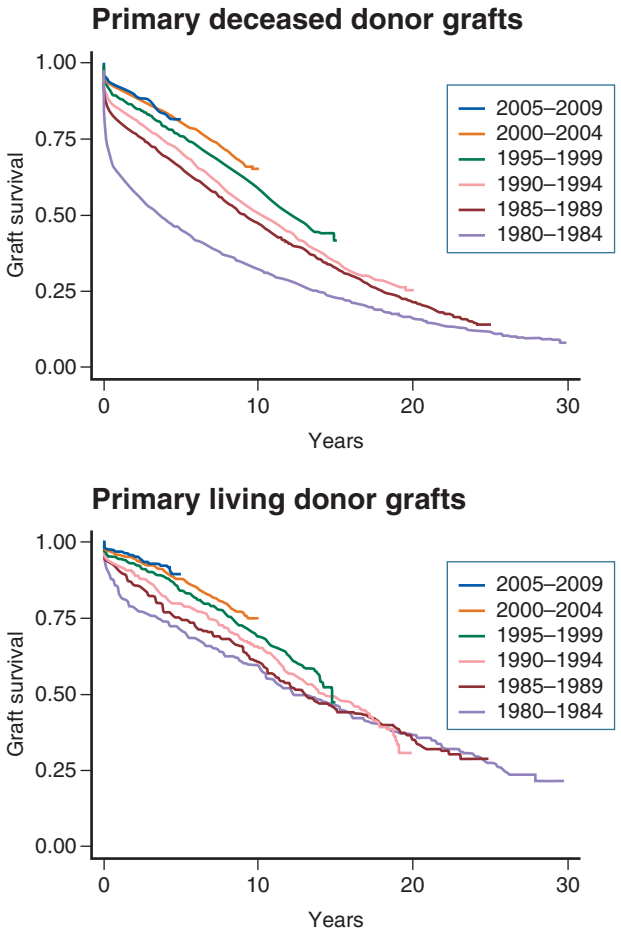

Figure 109-5 Comparison of the long-term outcomes of transplantation by era in Australia and New Zealand after living and deceased donation. *(From reference 19.)*

Other Donor Variables

Additional donor-related factors are known to affect both long- and short-term graft and patient outcomes, such as those that lead to initial nonfunction and determine whether or not the recipient will need dialysis postoperatively (Box 109-1).

Recipient Variables

Many factors that affect both patient and graft outcomes relate directly to the recipient, some of which may be modifiable and some of which are intrinsic. Perhaps the most modifiable factor in theory would be when to get a transplant—before the need for dialysis (preemptive transplantation) or after dialysis has commenced. The analysis of the benefit of preemptive transplantation is complex because the comparison cannot be between people receiving preemptive transplants and those who undergo transplantation after dialysis, because the delayed patients have to survive long enough to be offered a transplant. Despite these complexities of lag time in analysis, there is both an economic argument (it is cheaper to avoid dialysis) and a survival advantage (patients with preemptive transplants have 5% to 10% better 5-year survival after transplant). Equity of access to preemptive deceased donor and living donor transplants is another important factor. Figure 109-6 shows the Australian experience with access to a living donor transplant; people in the higher socioeconomic demographics have a greater chance of a preemptive transplant and greater total access to living donor transplants.

The variously modifiable and unmodifiable factors influencing graft outcomes are shown in Box 109-2, with body mass index (BMI) illustrated in Figure 109-7.[34] In assessment of individual outcomes, there are unfortunately no simple tables of risk analogous to cardiovascular risk profiles for the general population, but the dominant features affecting outcomes are recipient age and cardiovascular comorbidities.

Donor Factors Influencing Recipient and Graft Outcomes

- Deceased versus living donor
- Donation after cardiac arrest (DCD) compared with donation after brain death (DBD)
- Increasing donor age
- Prior donor history of hypertension or diabetes
- Cause of donor death—cerebrovascular disease or prolonged anoxia or drowning
- Female gender compared with male
- Nephron mass (donor-recipient weight ratio)
- Histology (% sclerosed glomeruli)
- *Ex vivo* perfusion not used
- Transmissible disease (infection, malignancy)
- Worse terminal renal function
- Use of inotropes before donation
- Duration of final intensive care admission

Box 109-1 Donor factors influencing recipient and graft outcomes. These donor factors are known to worsen graft and/or patient outcomes after renal transplantation.

Effects of Immunosuppression on Transplant Outcome

There are many examples of the use of outcome analysis to determine alternatives for immunosuppressive therapy after renal transplantation.[8-11,35,36] The proliferation of alternative immunosuppressive therapeutic regimens has yet to be resolved in the way that

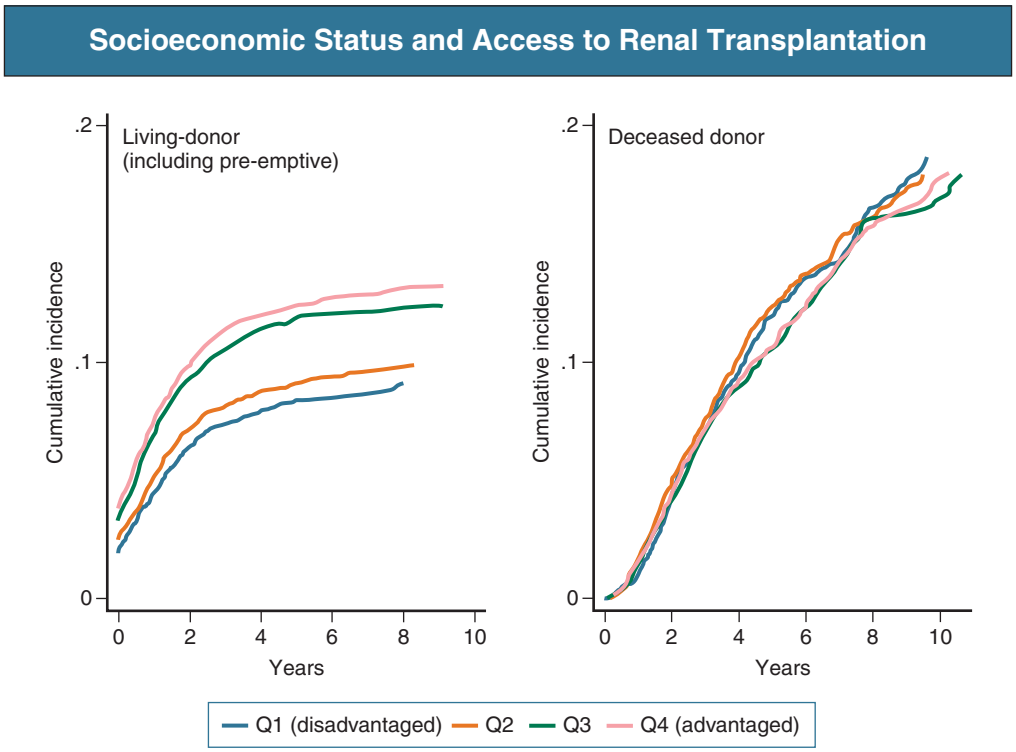

Figure 109-6 Socioeconomic status and access to renal transplantation. Access to transplantation in Australia and New Zealand, 2000 to 2010, by socioeconomic status expressed in four quartiles (*Q1,* most disadvantaged, to *Q4,* most advantaged). Living donor transplants were accessed more frequently and sooner by the top two socioeconomic groups *(Q1, Q2);* approximately 25% of living donor grafts were preemptive. There was no effect of socioeconomic status on deceased donor outcomes (no preemptive deceased donors included). *(From reference 19.)*

Recipient Factors Affecting Graft and Patient Survival After Renal Transplantation

Patient-Related Factors

Age

Adults: Outcome worse with increasing age

Children: Outcome worse <7 kg

Gender: Better outcomes from male donor to female recipient, presumably based on nephron mass.

Race: Worse outcomes compared with whites in United States for African Americans, but better for Asians. Variable effects in other countries but generally worse for indigenous races.

Anti-HLA antibodies: Worse with increasing sensitization because of previous blood transfusions, pregnancies, grafts.

Previous transplants: Worse outcomes with second and subsequent grafts.

Primary renal disease: Specific risks of recurrent disease by type of primary disease.

Comorbidities: Worse outcome with cardiovascular disease, chronic respiratory disease, diabetes mellitus, hepatitis B, or hepatitis C.

Body mass index: Worse outcomes at extremes of BMI: below 20 and above 35 (see Fig. 109-7).

Medication and clinical follow-up adherence: Worse outcome with poor adherence to follow up and medication protocol.

Transplantation-Related Factors

Surgical experience: Worse outcomes with inexperienced surgeons.

Graft and patient vascular anatomy: Worse outcomes with multiple arteries and veins.

Warm ischemia time: Worse outcome with prolonged time.

Cold ischemia time: Worse outcome with prolonged time.

Transplant center experience and results: Most apparent center effects are related to patient and donor selection criteria rather than center expertise. However, some centers in some countries do produce worse outcomes based on multivariate analysis of all relevant factors, leaving center expertise the most likely remaining outcome variable.

HLA matching: Worse outcome with poor matching.

Donor-specific antibodies: Easily detected high-titer anti-HLA class I and class II antibodies detected by cytotoxicity crossmatch tests are associated with hyperacute, accelerated, and acute rejection. Anti-HLA antibodies detected only by solid phase assay depending on their titer are associated with worse long-term outcomes.[42]

Box 109-2 Recipient factors affecting graft and patient survival after renal transplantation. There is significant variation in some of these factors in different countries. *BMI,* Body mass index; *HLA,* human leukocyte antigen.

cancer chemotherapeutic regimens have been defined with specific strategies for specific indications. The standard immunosuppressive therapy against which comparisons must be made in current practice includes a calcineurin inhibitor—generally assumed to be tacrolimus, despite some reluctance by the FDA to accept it over cyclosporine; MMF or mycophenolate sodium; and corticosteroids. The choice of immunosuppressive regimens is discussed further in Chapter 104.

The adverse outcomes of immunosuppression such as excess cancer risk[13] and observations of reduced cancer risk with inhibitors of the mammalian target of rapamycin (mTOR),[37] have led to the individualization of therapy for those with a high risk of skin cancer.[38] This is discussed further in Chapter 105.

Body Mass Index and Graft Loss

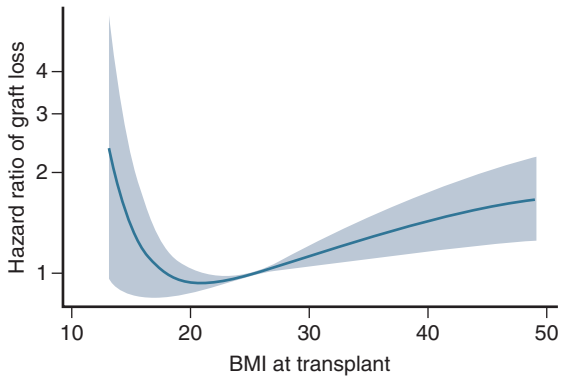

Figure 109-7 Body mass index *(BMI)* and graft loss. Univariate analysis of graft loss by body mass index in 5684 patients in ANZDATA from 1991 to 2004. *Blue line* shows hazard ratio of graft loss; *shaded area* shows confidence intervals. Obesity was not associated with cardiovascular disease (CVD)–related mortality and was associated with age, male gender, smoking, diabetes, CVD, and long-term dialysis ($P < .001$). *(From reference 34.)*

Transplant Center Variables

The outcome of transplantation in different transplant centers is largely, but not entirely, driven by patient selection. In the United States a center-based report card has been used to identify low-performing centers (which have statistically significant worse outcomes than predicted from their case mix). Some of these centers remain low performing and perform fewer transplants after a low-performance report, suggesting that the information about poor outcomes assists both patients and administrators in identifying problems and avoiding transplantation at those centers, but sadly not that the report leads to changes in a low-performing center to turn it into a high-performing center.[6,39]

Transplantation Matching Variables

Human leukocyte antigen matching is perhaps the most dominant feature of individual patient outcomes, with 15% 5-year differences in graft survival quite common across different analyses (see Fig. 109-2).[7,40] The advent of specific definition of anti-HLA antibodies through solid phase assays—especially those using beads read by dual-laser flow cytometry[41]—has increased the precision of HLA typing and HLA matching. However, a critical question remains that has not yet been amenable to long-term outcome analysis: At what sensitivity level and against which HLA antigens should an anti-HLA antibody be avoided? A recent consensus meeting helped to define the knowns and unknowns but has not yet led to a conformity of HLA matching and crossmatching criteria.[42] Desensitization of patients with anti-HLA antibodies has been shown to be a successful way of performing transplantation in patients who would otherwise not be candidates for the procedure,[43] and is discussed further in Chapter 104.

The blood group barrier, once thought immutable, is like the HLA antibody barrier—amenable to intervention providing the titer of anti-ABO antibody is known and reduced by physical removal to a low level at the time of transplantation.[44] The data support the view that antibodies to both HLA and blood group substances may be tolerated once the graft is *in situ* because continued activation of complement is seen in ABO-incompatible grafts but without obvious pathologic graft damage.[45]

OUTCOMES INFORM THE RECIPIENT DECISION

Each patient with progressive end-stage chronic kidney disease must decide whether he or she wishes to commence dialysis, receive a transplant, or elect not to be treated. The outcomes of the alternatives are obviously critical to that decision, and thus it is the responsibility of the treating physician and team to ensure that each patient is properly informed to make that choice. The components of that decision, of course, extend beyond the medical facts and in many countries involve financial and other social factors such as availability of therapy. The medical decision for each individual revolves around prognosis related to comorbidities, organ availability (of both living and deceased donor kidneys), and alternative dialysis therapies. The advantages are not all exactly as might be predicted. For example a 25- to 35-year-old adult with no comorbidities can be predicted to do well after transplantation with either a living or a deceased donor, but such an individual will also do well on dialysis, so the life-year gain from transplantation may not be as much as expected. On the other hand, a 55-year-old diabetic patient may have a poor prognosis with a transplant but will do even worse on dialysis and thus may wish to seek the added life-years from transplantation. This question has been addressed with use of the UNOS databases. Analysis of the additional donor and allocation factors related to prognosis after transplant show that the most life-years accrue when a simultaneous pancreas and kidney transplant is performed in a younger type 1 diabetic recipient and that even an SCD kidney given to an older patient may result in only an additional 2 or 3 years of life compared with dialysis.[46]

These analyses inform the debate about the use of a donated kidney either with or without a pancreas and to whom it should be offered. Outcome data and data analysis are there to assist the transplant community to make judgments about who gets which opportunities—and for the individual, when the opportunities are offered, whether he or she should accept them.

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CHAPTER 110

Pancreas and Islet Transplantation

Jonathan S. Fisher, Jonathan R. T. Lakey, and Christopher L. Marsh

Pancreas transplants are performed for the amelioration of insulin-requiring diabetes. Initially, pancreas transplants were performed only in those diabetic patients with chronic kidney disease who needed kidney transplants; these patients underwent simultaneous pancreas-kidney transplantation (SPK). Today, pancreas transplantation alone (PTA) or pancreas transplantation after living or cadaveric renal transplantation (pancreas-after-kidney [PAK] transplant) is increasingly common. SPK accounted for 72% of all pancreas transplants in 2010 (Fig. 110-1). There were approximately 3400 people in the United States waiting for pancreas transplants in 2013.[1] The 2011 Annual Report of the Organ Procurement and Transplantation Network (OPTN) and the Scientific Registry of Transplant Recipients (SRTR) reveals that the number of new registrations as well as of pancreata recovered and transplanted in the United States steadily increased from 1997 to 2004, but there has been some decline since then.[2] Although there is less complete data for pancreas transplants outside the United States, the trends are similar with a decline in non-U.S. transplants performed since 2007. Several factors are thought to play a role. New insulin formulations and delivery systems in the form of insulin pumps have reduced the need for transplant in some patients. Selection criteria for potential recipients have become increasingly stringent as the average age of recipients has increased as well as the number of transplants being done in type 2 diabetic patients. Simultaneously, there has been a trend over time toward tighter donor criteria. Last, there have been recent downward trends in numbers of patients registered for pancreas transplants. New SPK registrations rose from 1412 in 1997 to a high of 2007 in 2000 and declined to 1671 in 2006. Some of this reduction may be the result of an increase in the number of patients receiving islet cell transplants. The relative roles of pancreas and islet cell transplantation remain controversial.

PATIENT SELECTION CRITERIA FOR PANCREAS OR ISLET TRANSPLANTATION

Indications for Transplantation

Indications for pancreas or islet transplantation include (1) insulin-dependent diabetes with associated diabetic complications (nephropathy, neuropathy, and retinopathy) and (2) diabetes with episodes of hypoglycemic unawareness.

A number of factors influence the choice between pancreas transplant and islet transplant. Because giving sufficient islets remains a limiting factor, islet transplants are more appropriate for patients with smaller insulin requirements, typically slender women. Larger patients (usually with higher insulin requirements) are more reliably served with whole-organ pancreas transplants. Islet transplantation is performed with a radiographic procedure and therefore is better suited for patients who cannot tolerate the surgical stress of whole-organ transplantation, such as older patients with severe coronary heart disease.

Pancreas or islet transplantations have not routinely been performed for type 2 diabetes mellitus because the primary defect in type 2 diabetes is insulin resistance, not insulin deficiency. There may be a role for pancreas transplantation in type 2 diabetic patients who develop islet failure after years of insulin resistance or those who have deficiencies in beta cell function such as maturity diabetes onset of the young (MODY, types 1 to 6) or mutations of the insulin receptor gene (e.g., type A insulin resistance or Rabson-Mendenhall syndrome).[3] A recent review of the United Network for Organ Sharing (UNOS) registry from 2000 to 2007 revealed that after adjustment for a variety of factors (e.g., age, race, weight, time on dialysis, cardiovascular disease), there were no differences in risk for death or kidney or pancreas failure according to diabetes classification.[4] The analysis suggested that insulin-requiring patients who have type 2 diabetes, are younger than age 50 years, and have a body mass index (BMI) below 30 kg/m^2 will become insulin independent with a pancreas transplant. The proportion of pancreas transplants that are performed in type 2 diabetics increased from 2% in 1995 to 7% in 2010.[5]

Most pancreas organs for transplantation come from deceased donors. However, one approach to increasing the donor supply has involved living donor laparoscopic distal pancreatectomy with or without simultaneous laparoscopic nephrectomy.[6]

Should living kidney donor recipients be offered a PAK transplant? An analysis of the UNOS database revealed no difference in survival of SPK recipients and living kidney donor recipients at up to 8 years of follow-up.[7] However, a European study showed an improved 10-year patient survival (83% in SPK versus 70% in kidney transplants alone) and noted a significantly lower progression of macrovascular disease (cerebrovascular, coronary, and peripheral vascular) with SPK transplants.[8] A review of the UNOS registry from 1997 to 2007 divided recipients with type 1 diabetes who received a living donor kidney transplant into two groups: (1) those who subsequently received a PAK transplant within a year of the kidney transplant (n = 1026) and (2) those who did not (n = 3528). At the end of the eighth year, the patients who subsequently received a PAK transplant had superior patient (85% versus 75%) and kidney graft survival (75% versus 62%).[9] Therefore the two-stage approach of PAK after a living donor kidney transplant should perhaps be offered to patients who have a living kidney donor and in whom the cardiovascular risk of the extended procedure required for SPK is considered too great.

The role of PTA in those with preserved renal function has recently been questioned. A single-center study of 131 PTA recipients revealed that PTA is an independent risk factor for the development of renal failure, presumably because of the nephrotoxicity of long-term immunosuppression.[10] An analysis of the UNOS database demonstrated worse survival for those with diabetes and preserved kidney function receiving a PTA than for those who remained on the waiting list and received conventional therapy.[11] The recent SRTR data reveal 1-year patient survival rates similar for PAK, SPK, and

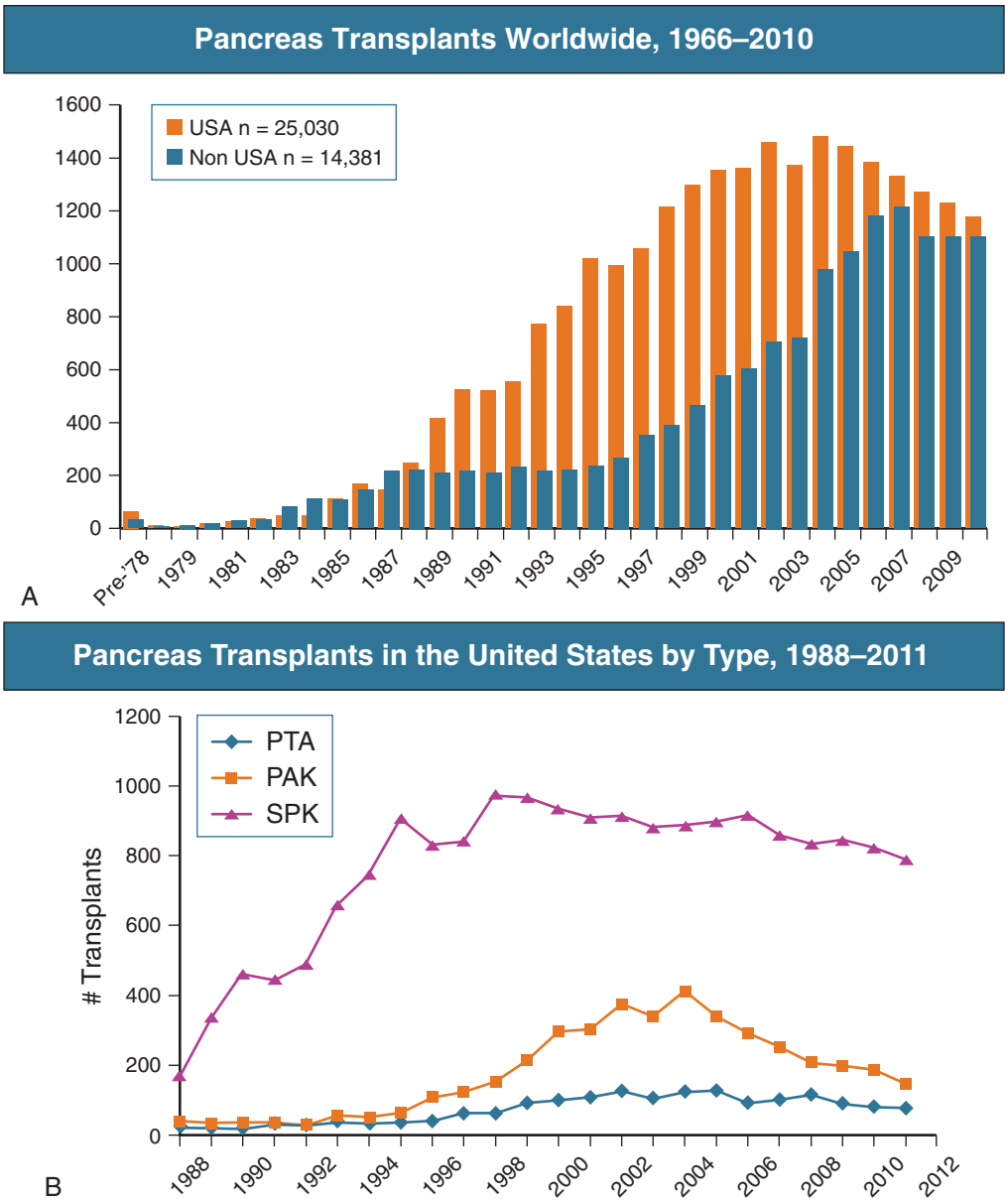

Figure 110-1 Pancreas transplantation. A, Number of pancreas transplants worldwide, 1966 to 2010. **B,** Pancreas transplants in the United States by type, 1988 to 2011. *PAK,* Pancreas transplantation after living related or unrelated kidney transplantation; *PTA,* pancreas transplantation alone; *SPK,* simultaneous pancreas-kidney transplantation. *(From reference 5.)*

PTA recipients (ranging from 95% to 97%). However, the 10-year patient survival rate was lowest for PAK recipients at 77% and similar for SPK and PTA recipients with rates of 82% and 71%. SPK resulted in the best pancreas graft survival rates, 86% at 1 year and 52% at 10 years. Graft survival rates for PAK and PTA recipients were slightly worse and similar to each other, with 1-year rates of 79% and 75%, respectively, and 10-year rates of 37% and 35%, respectively (Fig. 110-2).[1] Further close study is warranted, keeping in mind that a prospective, randomized trial of pancreas transplantation versus conservative therapy is not practical.

Medical Evaluation

The medical evaluation of the prospective pancreas transplant candidate is similar to that of the kidney-only recipient (see Chapter 102), although the cardiac workup is more extensive. The best candidates for transplantation are younger than 50 years and have a limited number of major complications of diabetes, such as hypoglycemic unawareness or diabetic neuropathy. Additional complications, such as vascular disease, orthostatic hypotension, and severe gastroparesis, put patients at higher risk of post-transplantation complications, but none of these factors by themselves exclude a patient from transplantation. Cardiovascular status is the primary deciding factor for transplantation eligibility because the surgery, infections, risk of thrombotic complications, and, until recently, rejection are more severe in the pancreas transplant recipient, demanding that the cardiovascular system be able to withstand multiple prolonged, hemodynamically stressful events. All patients require noninvasive cardiac stress evaluation because of the limited exercise capabilities of many patients. Cardiac catheterization is performed on the basis of the results of noninvasive testing or performed first for high-risk patients, typically those older than 45

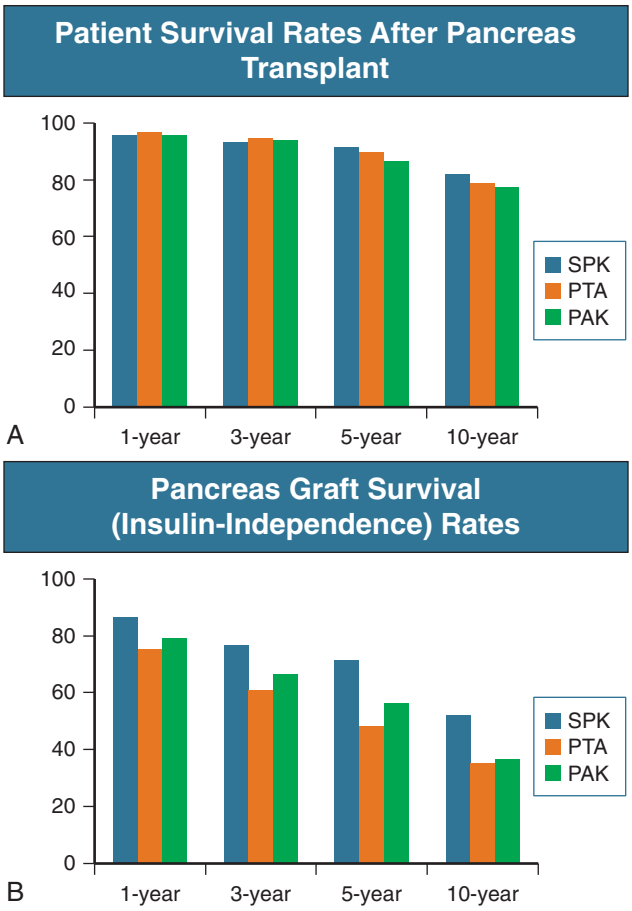

Figure 110-2 Patient and graft survival after pancreas transplantation. Unadjusted 1-, 3-, 5-, and 10-year pancreas patient and graft survival by type. **A,** Patient survival rates. **B,** Pancreas graft functional survival (insulin-independence) rates. *PAK,* Pancreas transplantation after living related or unrelated kidney transplantation; *PTA,* pancreas transplantation alone; *SPK,* simultaneous pancreas-kidney transplantation. *(Modified from reference 2.)*

years, those with diabetes duration of more than 25 years, smokers of more than 5 pack-years, and those with an abnormal electrocardiogram. Peripheral vascular disease is evaluated by clinical examination and by arterial duplex ultrasound. Patients with limb-threatening ischemia are typically poor pancreas transplant candidates. The medical evaluation for islet transplantation is similar to that for pancreas transplantation, but exclusion criteria are fewer because of lower surgical and inflammatory risks.

The last criteria for transplantation are that the donor and recipient match for ABO blood group and that the recipient sera are crossmatch negative against donor T cells by either the standard antiglobulin or flow cytometry crossmatch.

PANCREAS TRANSPLANTATION

Patient and Graft Survival

Pancreas graft survival rates have increased as a result of improved surgical techniques, donor selection criteria, and improvement in the composition of the preservation fluid, as well as more effective immunosuppressive regimens, despite an increasing proportion of high-risk patients.

There has been a trend toward tighter donor selection criteria. The ideal donor can be defined as 10 to 40 years of age, with a BMI

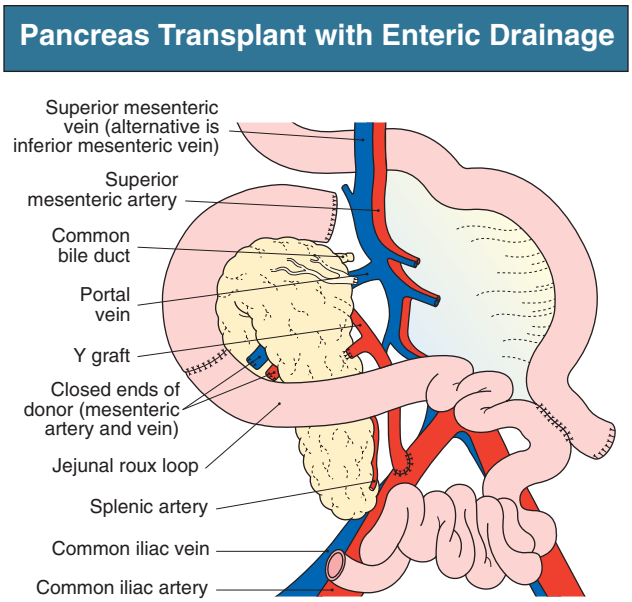

Figure 110-3 Pancreas transplant with enteric (portal) drainage.

less than 27.5 kg/m^2 and a cause of brain death that is other than cerebrovascular.[12] The UNOS database shows that over the past 5 years more than 60% of donors have had a cold ischemic time of less than 12 hours.[2]

The most commonly used cold storage solution is the University of Wisconsin (UW) solution, which has increased early pancreas graft function and reduced the occurrence of preservation pancreatitis. A second cold storage solution, histidine-tryptophan-ketoglutarate (HTK), offers the advantages of better tissue perfusion because of lower viscosity, less reperfusion hyperkalemia, and significantly lower cost. However, studies have suggested a higher incidence of graft pancreatitis and an increased rate of graft loss with HTK, particularly with longer cold ischemia.[13,14] Approaches using either a two-layer storage method with UW or an HTK solution and a second layer of highly oxygenated perfluorocarbon or the attachment of the pancreas to a low-pressure pulsatile perfusion system are being investigated.

The current gold standard immunosuppression for pancreas transplants is antibody induction therapy, tacrolimus, mycophenolate mofetil (MMF), and corticosteroids; this has led to a 40% decrease in incidence of rejection and an increase in 1-year graft survival to more than 90%. UNOS registry data show that human leukocyte antigen (HLA) matching has no effect on the outcome in SPK, whereas for PAK and PTA, a beneficial effect is seen by matching at the A and B loci. The reported 1-, 3-, and 5-year patient and graft survival rates with use of these techniques and criteria are shown in Figure 110-2.[1]

Enteric Drainage of the Pancreas Transplant

Current practice is to transplant the whole pancreas with a cuff of duodenum, which preserves the blood supply of the head of the pancreas and provides a means to drain exocrine secretions into either the small bowel (enteric drainage) or the bladder (Figs. 110-3 and 110-4).[1] From 2004 to 2008, the majority of the pancreas transplants in the United States were enterically drained (Fig. 110-5).[1] The graft may be placed in the right iliac fossa like a kidney, intraperitoneally, and vascularized from the common iliac vessels so that the secreted insulin enters the systemic circulation. The right side is

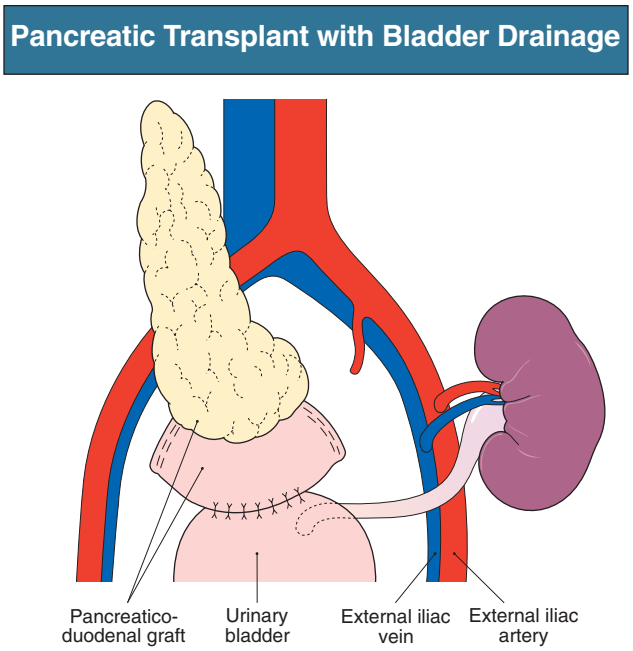

Figure 110-4 Pancreas transplant with bladder drainage. The pancreas may be placed in either the intraperitoneal or the extraperitoneal position.

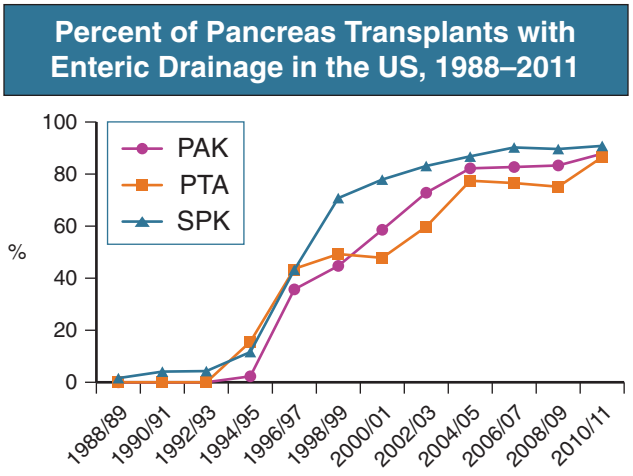

Figure 110-5 Percentage of U.S. primary pancreas transplantations with enteric drainage, by recipient category and era, 1988 to 2008. There has been a shift toward enterically drained compared with bladder-drained pancreas transplantation. *PAK,* Pancreas transplantation after living related or unrelated kidney transplantation; *PTA,* pancreas transplantation alone; *SPK,* simultaneous pancreas-kidney transplantation. *(Modified from reference 5.)*

preferred to the left because the vessels are somewhat more shallow on the right side and consequently the anastomoses are easier to perform. However, an alternative is to construct the venous anastomosis to the superior mesenteric vein, allowing more physiologic insulin output through the portal circulation. Currently, 15% to 20% of enterically drained transplants use portal drainage. In either approach, an interposition graft from the donor (typically a Y graft containing common iliac with external and internal branches) is used to provide inflow from the recipient common iliac artery to the graft superior mesenteric and splenic arteries. Some surgeons have advocated reconnection of the graft gastroduodenal artery if the

Causes of Pancreas Graft Dysfunction

Rejection
Ductal obstruction
Vascular: arterial or venous thrombosis (partial or complete), arteriovenous fistula
Volume depletion
High calcineurin inhibitor levels
Graft pancreatitis (preservation, viral, bacterial, or fungal)
In cases of bladder drainage
- Reflux pancreatitis
- Urinary tract infection
- Anastomotic leak
- Bladder outflow obstruction

In cases of enteric drainage
- Anastomotic leak
- Bowel obstruction

Box 110-1 Causes of pancreas graft dysfunction.

pancreaticoduodenal arcades are not intact. Pancreas transplants with venous outflow to the superior mesenteric vein can be placed either anterior to the small bowel mesentery or in a retroperitoneal position behind the ascending colon, where the superior mesenteric vein is reached from the side. Surgical outcomes have not differed whether the venous drainage is systemic or portal. Although portal drainage is considered more physiologic and avoids hyperinsulinemia, these apparent benefits are not well confirmed.

Immunosuppression

Most centers use antibody induction therapy during the first 1 to 2 weeks after transplantation. OKT3 has largely been replaced by antithymocyte globulin (ATG).[15] Other centers use an interleukin-2 receptor antagonist (basiliximab) or, most recently, an anti-CD25 antibody (alemtuzumab).[16,17] Antibody-mediated rejection may be more common than acute cellular rejection in patients receiving alemtuzumab.[18] Most centers use triple-drug maintenance immunosuppression with tacrolimus (or less commonly cyclosporine), MMF (or rarely azathioprine), and corticosteroids. There is increasing evidence of equivalent success with rapid corticosteroid elimination or corticosteroid avoidance protocols. Some centers replace the calcineurin inhibitor or MMF with sirolimus. With the more profound immunosuppressive induction produced by the newer antibodies (particularly alemtuzumab), there have been reports of immunosuppression protocols limited to a depleting antibody and a single additional agent.[17,19,20] Fortunately, cytomegalovirus (CMV) infection rates appear to be lower in corticosteroid-free regimens,[17] although there has been some increase in CMV infection in those receiving depleting antibody therapies.[16]

Graft Monitoring

The causes of pancreas graft dysfunction and the evaluation process are shown in Figure 110-6, Box 110-1, and Table 110-1.

During the immediate perioperative phase, intravenous insulin is used to decrease the stress on the transplanted pancreas by maintaining serum glucose concentration around 100 to 120 mg/dl (5.5 to 6.6 mmol/l). Serum glucose values are not an early marker of pancreas dysfunction; elevations are observed only after significant parenchymal pancreatic damage has occurred. With bladder

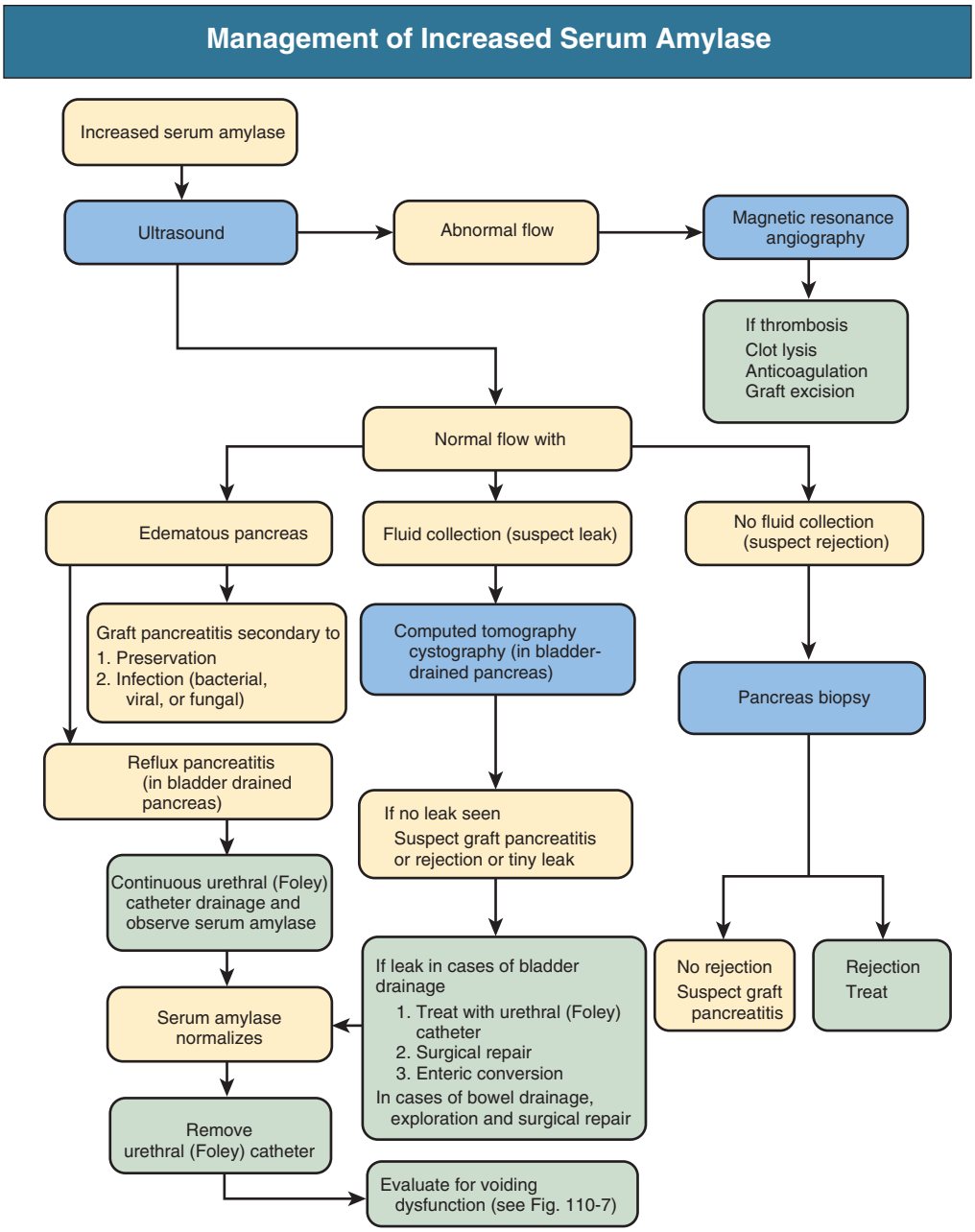

Figure 110-6 **Management of increased serum amylase after pancreas transplantation.**

drainage, urinary amylase excretion is measured on 12-hour collections and reported as units per hour. During the first 1 to 2 weeks after transplantation, serum amylase may be elevated as a result of pancreatic preservation injury. Trends are followed rather than absolute values, taking into consideration factors such as length of cold ischemic time and degree of organ edema. Stable serum levels are usually attained within 2 weeks after transplantation. Rising serum amylase or lipase concentration indicate possible graft injury, because both are moderately sensitive markers of pancreas rejection. However, other conventional causes of pancreatitis can still occur. Elevated fasting glucose and 2-hour postprandial glucose levels are relatively late indicators and only indicate dysfunction without revealing cause.

Ultrasound examination of the pancreas transplant is performed frequently in the early post-transplantation period to rule out vascular thrombosis. If the pancreas cannot be well visualized on

Evaluation of Pancreas Graft Dysfunction

Assessment	Tests
Laboratory tests	Serum amylase, blood glucose human anodal trypsinogen, cyclosporine or tacrolimus levels, C peptide In bladder-drained cases, urinary amylase and urine culture
Doppler ultrasound	Pancreatic blood flow, peripancreatic fluid collection, pancreatic ductal dilation In bladder-drained cases, evidence of bladder outlet obstruction
Computed tomography with or without cystography	Looking for leak and collections; this is performed by cystography in bladder-drained cases

Table 110-1 **Evaluation of pancreas graft dysfunction.**

ultrasound scan, magnetic resonance imaging and angiography may be informative. Any inflammatory state can also yield images of an edematous pancreas; however, other than for vascular thrombosis, imaging generally cannot reveal the cause of the dysfunction.

Biopsy of the pancreas transplant remains the gold standard for diagnosis of acute or chronic rejection. A biopsy may be performed at certain time points by protocol or at times of graft dysfunction to identify rejection or other causes of pancreatic injury before irreversible tissue damage has occurred. The easiest approach is a percutaneous biopsy with ultrasound or computed tomography guidance. The most frequent complication of percutaneous biopsy is a perigraft hematoma or transient hematuria, but rarely seen are pancreatitis, arteriovenous fistula, abdominal hemorrhage, bowel perforation requiring exploration, and even graft loss. Because of the risks associated with biopsy, if the clinical picture is consistent with a mild case of rejection, patients may be treated for rejection without biopsy confirmation.

Treatment of pancreas rejection is similar to that of kidney rejection and generally involves pulse intravenous corticosteroids or antilymphocyte antibodies (see Chapter 104).

Treatment response is achieved by following the return of serum amylase and lipase to baseline values. Imaging can be used to show resolution of edema and inflammation. Repeated biopsy, usually after a 2-week interval, is required to show resolution of more moderate or severe rejections and to look for histologic signs of the development of chronic rejection.

Patients with isolated pancreas rejection have an increased risk for kidney graft loss, supporting the concordance of acute rejection in the majority of patients.[21,22] In SPK or PAK patients, when biopsy of the pancreas cannot be performed safely, a kidney transplant biopsy may be used as a surrogate indicator. This must be done, however, in conjunction with serum tests because synchronous rejection occurs only 70% to 80% of the time.[23]

Antimicrobial Prophylaxis

Antimicrobial prophylaxis is much like that for a kidney transplant alone. Trimethoprim-sulfamethoxazole is prescribed for the prevention of urinary tract infections and *Pneumocystis* infection. Oral clotrimazole or nystatin is used for the prevention of oral candidiasis; some centers use fluconazole for prophylaxis of *Candida* urinary tract infections and intra-abdominal fungal or yeast infections. Oral acyclovir is given to patients with a history of herpes simplex infection and to patients who are CMV negative and receive CMV-negative donor organs. Otherwise, valganciclovir or ganciclovir is given for 3 months after transplantation to all patients who are CMV positive. Patients who are CMV negative who receive CMV-positive organs are often treated for 6 months. Patients treated for rejection are typically returned to any discontinued anti-infectious prophylaxis for 1 to 3 months after rejection therapy.

Metabolic Monitoring

In addition to monitoring of the serum and urinary concentrations of amylase and the serum concentration of lipase, serum creatinine, potassium, magnesium, and bicarbonate levels must be monitored. Magnesium wasting is common with calcineurin inhibitors and frequently requires oral supplementation.

Surgical Complications

Surgical complications of pancreas transplantation are shown in Table 110-2. Superficial infections and deep-seated abscesses are commonly fungal. The source of fungal contamination is thought to be the duodenal segment. Therefore, topical antibiotic and antifungal solutions are used to irrigate the donor duodenum during procurement and implantation. Patients commonly receive 24 to 48 hours of postoperative antibiotics and fluconazole.

The causes of wound drainage are seroma, lymphocele, pancreatic fistula from either the tail or the anastomosis to the bladder or bowel, wound dehiscence, and preservation pancreatitis. Preservation pancreatitis may lead to wound drainage of whitish yellow, thick, noninfectious material formed from the enzymatic digestion of tissue, leading to fat necrosis and saponification. Wound drainage is seen more often with the extraperitoneal placement of the pancreas and also occurs when a pancreas from an obese donor is used. It is also associated with a mild increase in serum amylase concentration and variable changes in the serum glucose concentration.

Vascular complications occur in about 5% of patients and include arteriovenous fistulas from surgery or biopsy, venous and arterial

Surgical Complications After Pancreas Transplantation

Type of Complication	Presentation	Diagnostic Findings and Testing	Treatment Options
Abscess	Fever, erythema of wound, wound drainage	Elevated white blood cell (WBC) count, fluid collection on computed tomography (CT) scan, pus on aspiration	Open or percutaneous drainage
Graft pancreatitis	Pain over allograft, lower abdominal pain	Elevated serum amylase, enlarged pancreas allograft	Octreotide or somatostatin Urethral (Foley) catheter if bladder drained
Lymphocele	Mass on palpation, urgency if bladder compression	Fluid collection on CT scan, clear fluid on aspiration	Open or percutaneous drainage
Wound drainage	Pancreatic debris, no erythema	Culture, CT scan to rule out deep abscess	Local wound care
Dehiscence	Wound open		Wound care, surgical closure
Arteriovenous fistula	Hematuria, abdominal bleeding	Doppler ultrasound, angiography	Embolization, surgical repair
Graft thrombosis	Elevated blood sugar Bloody urine if bladder drained	Low serum and urine amylase, sepsis-like syndrome, ultrasound or magnetic resonance imaging	If partial, thrombolytic therapy or anticoagulation (high risk of bleeding), graft pancreatectomy
Pancreatic fistula or leak (bowel drained)	Pain over allograft, sepsis, peritonitis, fever	Elevated WBCs, fluid collection on CT scan	Surgical drainage and repair

Table 110-2 Surgical complications after pancreas transplantation.

thrombosis, and rarely mycotic aneurysms. The pancreas is a low–blood flow organ; vascular thrombosis rates were previously as high as 10%, but current rates are below 5%. Means of reducing the rate of thrombosis include minimization of warm and cold ischemia, procurement procedures involving a no-touch technique with use of the duodenum and spleen as handles, and postoperative antiplatelet activity with aspirin. In procedures involving longer cold ischemia times, a more edematous graft, or concern about low inflow or outflow, intravenous heparin is sometimes used for the first few postoperative days. Partial thrombosis may resolve with thrombolytic therapy or anticoagulation. More extensive thrombosis requires urgent surgical intervention. Complete graft thrombosis, especially in the immediate postoperative period, mandates urgent graft removal to prevent sepsis syndrome or a more diffuse hypercoagulable state, leading to further vascular thrombotic complications such as myocardial infarction.

Nonsurgical Complications

Nausea and vomiting are common, and causes include gastroparesis, constipation, cholelithiasis or esophageal reflux developing from motility problems, and esophagitis with or without CMV disease. Antiemetics plus histamine H_2 blockers or proton pump inhibitors are usually effective therapy and are given for 2 to 3 months after transplantation. Persistent symptoms may require prokinetic agents (metoclopramide or erythromycin). Diarrhea can be caused by immunosuppressive medications, intrinsic gut motility problems, food intolerance, or CMV or other infection. Constipation is treated with increased fluid intake, dietary modification, increased activity, and a regular low-dose schedule of stool softeners or laxatives.

Orthostatic hypotension may worsen after transplantation as a consequence of prolonged bed rest in the presence of diabetic autonomic neuropathy. Treatment may include a salt-loading diet, with a mineralocorticoid (fludrocortisone) or an α-adrenergic agonist (midodrine).[23]

Bladder Drainage of the Pancreas Transplant

In the early days of pancreas transplantation, with less effective immunosuppression and before the era of real-time ultrasound and percutaneous biopsy, the exocrine secretions from pancreas transplants were more commonly drained through an anastomosis of the donor duodenum to the recipient's bladder. This manner of drainage allows monitoring for rejection by measurement of urinary amylase and also avoids enterotomy-associated risks of infection and leakage. Cystoscopic biopsy through the duodenal cuff is used in bladder-drained transplants.[24] The disadvantages of bladder drainage include susceptibility to dehydration, metabolic acidosis, and frequent urologic complications. Primary enteric drainage avoids these complications and is more physiologic but does not allow urinary amylase monitoring. With improved surgical techniques, increased use of real-time ultrasound, and percutaneous needle biopsy, the outcomes of enteric drainage now match those of bladder drainage.

Current Indications

Bladder drainage is still appropriate when there is a history of major abdominal surgery, in the presence of Crohn disease or other small bowel disease, and for older patients with less cardiovascular reserve, in whom a laparotomy may be avoided through a smaller lower quadrant retroperitoneal incision similar to that for a kidney transplant.

Metabolic Complications

With bladder drainage there is high urinary loss of bicarbonate in pancreatic exocrine secretions, which may require as much as 130 mmol/day of replacement. Without replacement, patients develop metabolic acidosis with nausea and vomiting, which may lead to volume depletion, hypotension (exacerbated by underlying autonomic neuropathy), and graft thrombosis. Oral sodium bicarbonate, typically 2 g four times daily, is needed. Fluid intake should be 2.5 to 3 l/day to accommodate pancreatic and renal fluid outputs. This intake may be difficult to achieve because abdominal bloating from diabetic gastroparesis is exacerbated by the large fluid intake and the gas released from sodium bicarbonate tablets. Patients who are unable to maintain adequate oral intake may require intravenous fluids including sodium bicarbonate. In patients who require intravenous repletion for longer than 1 month, consideration should be given to placement of a tunneled venous catheter or a buried central venous port for fluid administration.

Urologic Complications

Urologic complications are common after bladder drainage (Table 110-3).[25] Pretransplantation bladder dysfunction resulting from diabetic autonomic neuropathy causes a large-capacity bladder, decreased bladder sensation, increased residual urine volume, and decreased urinary flow rates. Bladder function is worsened by the autoaugmentation of the bladder by the added duodenal segment. Preoperative urodynamics are abnormal in up to 43% of patients but are not predictive of post-transplantation urologic complications such as reflux pancreatitis or infections.[26]

Urinalysis is difficult to interpret with the bladder-drained pancreas. The urine contains white cells from duodenal mucosal sloughing and may be leukocyte esterase positive without bacteriuria. Urine protein excretion is elevated to 1 to 3 g/day in most patients, composed of pancreatic enzymes, immunoglobulins, other globulins, albumin, and digested fragments of these proteins. Urinary albumin, if it is measurable in the presence of enzymatic degradation, may come from the transplanted or native kidneys.

Macrohematuria occurs in up to 28% of bladder-drained pancreas recipients. Early hematuria is related to surgical trauma to the bladder or duodenal mucosa near the cystoduodenostomy site and usually clears with diuresis or bladder irrigation.[24] Continuous bladder irrigation requires caution because the cystoduodenostomy is vulnerable to rupture if the drainage catheter becomes obstructed. Late hematuria, beyond 2 to 4 weeks after transplantation, can arise from anastomotic bleeding, duodenal mucosal sloughing or ulceration, reflux pancreatitis, cystitis, graft thrombosis, rarely arteriovenous fistulas, and pseudoaneurysms. Evaluation should include ultrasound, urine culture, and cystoscopy. If the pancreas appears to be the source on cystoscopy, biopsy of the pancreas may be required to determine the exact cause.

Microhematuria should be evaluated. Evidence is sought for recurrent disease, new renal disease, or genitourinary malignant neoplasms.

Urinary Tract Infections

Risk factors for urinary tract infection after pancreas transplantation include large bladder capacity, incomplete bladder emptying, high bladder urine pH (from pancreatic bicarbonate), bladder and urethral mucosal irritation from activated pancreatic enzymes with the loss of mucosal barrier, prolonged bladder catheterization, and immunosuppression.[27] Most centers administer oral antibacterial and antifungal prophylaxis for up to 6 to 12 months or indefinitely after transplantation.

Urologic Complications of Bladder-Drained Pancreas Transplants				
Complication	**Cause**	**Presentation**	**Evaluation**	**Treatment Options**
Urinary tract infection (UTI)	Diabetic bladder dysfunction (DBD)	Asymptomatic, or dysuria, fever, sepsis	Urine culture; check postvoid residual, if elevated urodynamics	Culture-specified antibiotics, prophylactic antibiotics Female: double and timed voiding, clean intermittent catheterization (CIC) Male: α-adrenoceptor blockers to aid bladder emptying, CIC, bladder neck–prostate incision If treatment failure, enteric conversion: Foley catheter drainage
Reflux pancreatitis	DBD	Asymptomatic or pain over pancreas allograft, elevated serum amylase	Check serum amylase, computed tomography (CT) cystogram to exclude leak or duct obstruction	If DBD: double and timed voiding, CIC, α-blockers to aid bladder emptying If multiple and symptomatic episodes: bladder neck–prostate incision or enteric diversion
Duodenal cystotomy leak	Ischemic injury to duodenal cuff, cytomegalovirus or other infection, rejection, DBD	Pain over allograft, or peritonitis, elevated serum amylase	Check serum amylase, elevated creatinine, leak on CT cystogram	Foley catheter drainage, if small If early, open surgical repair with resection and closure of layers, evaluate for DBD after recovery If late, consider enteric conversion
Urethritis or dysuria syndrome, occasional urethral disruption	UTI or DBD causing activation of pancreatic enzymes with digestion of urethral mucosa	Dysuria, urinary retention, hematuria	Check postvoid residual, low-grade UTI; after recovery, evaluate for DBD	Foley catheter, analgesics, empiric treatment of UTI If multiple and symptomatic: enteric conversion

Table 110-3 **Urologic complications of bladder-drained pancreas transplants.**

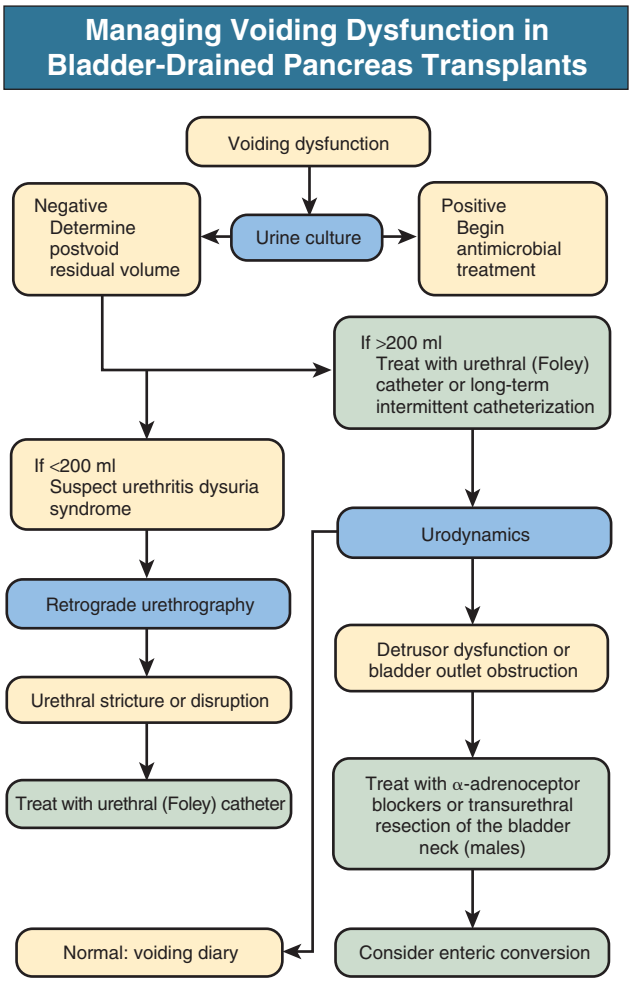

Figure 110-7 **Management of post-transplantation voiding abnormalities.** *(From reference 25.)*

Urinary reflux pancreatitis, which causes pancreas graft dysfunction, may be associated with perigraft abdominal pain and fever. It is often a result of poor bladder function and requires drainage with a bladder catheter for 5 to 7 days and assessment of bladder dysfunction (Fig. 110-7).

A urethritis dysuria syndrome occurs in 2% to 8% of pancreas recipients with bladder drainage and is caused by uroepithelial exposure to the activated pancreatic proenzymes trypsinogen, chymotrypsinogen, and procarboxypeptidase. Pancreatic exocrine secretions consist of bicarbonate, amylase, lipase, and proenzymes, which are activated by the enterokinase in the graft duodenal brush border. Increased intravesical enzyme activation occurs with low-grade urinary infections and urinary stasis, and patients will develop voiding pain or penile, glandular, meatal, or vulval ulceration. Enzyme activation may be minimized by treatment of low-count bacteriuria, increase in fluid intake, and frequent voiding. If emptying does not improve with α-blockers, continuous Foley catheter drainage for 7 to 10 days has been effective.

Enteric Conversion

Enteric conversion is an option for most of the chronic urologic complications associated with bladder-drained pancreas transplantation. The indications are urethral disruption, recurrent urine leak, persistent bleeding, chronic urinary tract infection, dysuria, recurrent hypovolemia, and metabolic acidosis. The conversion rate varies from 8% to 14%. It is ideal to wait until 6 to 12 months after transplantation, when possible, to allow monitoring of urine amylase for early rejection episodes.

Late Complications

Late complications after pancreas transplantation typically fit into one of two patterns. There can be an acute presentation of graft rejection, not different from that seen in early graft dysfunction. The second pattern is more insidious; chronic inflammatory states from

chronic rejection, ischemia, or infection may lead to gradual graft loss. Unfortunately, there is no practical test to measure small decrements in graft function in the way serum creatinine allows detection of kidney transplant dysfunction. Although it is lacking the necessary sensitivity, patients are typically asked to measure 2-hour postprandial glucose levels (which are more sensitive than fasting blood glucose levels) weekly and to report trends or sudden increases to the physician.

IMPACT OF PANCREAS TRANSPLANTATION ON DIABETIC COMPLICATIONS

Pancreas transplantation is performed to eliminate the need for exogenous insulin and the risk of severe hypoglycemic episodes and to stop or to reverse the consequences of hyperglycemia. Well-functioning pancreas transplants result in normal fasting blood glucose concentrations, normal glycated hemoglobin levels, and only slightly abnormal oral glucose tolerance testing results.[28]

Hypoglycemia

Although severe hypoglycemia is rare, mild hypoglycemia may develop in patients with a well-functioning pancreas graft once low baseline immunosuppression has been reached, especially in those patients who have regained little weight after transplantation and who are physically active. Postprandial hypoglycemic episodes are not always symptomatic. They are associated with high-carbohydrate meals, excessive intake of caffeine or alcohol, excessive exercise, and, in some patients with hypoglycemia, circulating anti-insulin antibodies. This is not often a significant clinical problem and is usually resolved by avoidance of carbohydrate-rich meals.

A major benefit of pancreas transplantation is restoration of glucagon secretory responses to hypoglycemia. In type 1 diabetics, the absence of functional beta cells within the islet eliminates the normal physiologic response by which intra-islet insulin tonically dampens secretion of glucagon from alpha cells. Consequently, diabetic patients are usually at risk of prolonged hypoglycemia secondary to injected insulin because there is failure of the normal counterregulatory action of glucagon on the liver to increase glycogenolysis. Despite the fact that the transplanted pancreas is placed ectopically and does not develop vagal control, the transplanted organ has normal glucagon responses to insulin-induced hypoglycemia and resultant counterregulation of hypoglycemia through increased hepatic glucose production. After pancreas transplantation, hypoglycemic awareness returns, as well as partial return of defective epinephrine secretion during insulin-induced hypoglycemia.

Hyperglycemia

Post-transplantation hyperglycemia may be caused by pancreas graft dysfunction, inadequate insulin release secondary to high tacrolimus or occasionally cyclosporine levels, resistance to insulin secondary to corticosteroids, weight gain, and inadequate physical activity. Although the use of tacrolimus has reduced pancreas graft rejection, it also decreases insulin gene transcription. If laboratory and imaging evaluations (see Table 110-1) are normal, hyperglycemia is the result of decreased insulin production or else of peripheral insulin resistance, which can be identified by measurement of glucose usage rates and glucose/arginine-potentiated insulin secretion. In the absence of graft rejection, post-transplantation hyperglycemia should first be managed by dietary intervention and exercise. Insulin may be needed initially but can often be discontinued as oral hypoglycemic agents begin to take effect. Sulfonylureas are effective therapy. Hyperglycemia secondary to rejection is a late event and indicates irreversible graft damage. Because of the increased risk of rejection with manipulation of immunosuppression, minimizing the tacrolimus dose or changing to cyclosporine or sirolimus should not usually be considered until these measures have failed.

Microvascular Complications

Retinopathy

In a prospective fundoscopic study of SPK patients during 45 months, there was a decreased need for post-transplantation laser therapy, and the diabetic retinopathy showed stabilization in 62%, improvement in 21%, and progression in 17%.[29] In the postoperative period, patients may develop neoproliferation and retinal hemorrhages if preoperative blood glucose control is very poor and blood glucose normalizes rapidly after transplantation. Patients remain at risk of retinal detachment because of scarring secondary to previous retinal damage. Cataracts are more common after transplantation.

Neuropathy

Sensory and motor nerve conduction velocities improve rapidly after pancreas transplantation and then stabilize.[30] Greater recovery is seen in nonobese, younger, shorter patients; in those with better initial action potential amplitudes; in those not receiving renal replacement therapy; and possibly in those receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.[31] The recovery of action potential amplitudes is gradual, with continuing improvement up to 5 years beyond transplantation. Recovery is more complete in sensory than in motor nerves.

There is greater improvement in autonomic reactivity and gastric emptying in SPK recipients compared with diabetic kidney-only transplant recipients.[32] If autonomic symptoms are severe at the time of pancreas transplantation, improvement is unlikely.

Nephropathy

Early diabetic nephropathy is characterized by increased glomerular basement membrane thickness and an increase in mesangial volume. Renal transplant biopsy specimens from diabetics with SPK and kidney-only transplants within 2.5 years of transplantation show glomerular basement membrane thickness within the normal range. After 2.5 years from transplantation, 92% of renal biopsy specimens from the kidney-pancreas recipients have a normal glomerular basement membrane thickness compared with only 35% of the biopsy samples from the kidney-only recipients; relative mesangial volume was normal in 82% of the biopsy specimens from kidney-pancreas recipients compared with only 12% in the kidney-only recipients.[27] Thus, concurrent pancreas transplantation decreases the occurrence of the changes of diabetic nephropathy that may result in allograft loss.[33]

Vascular Disease

Successful kidney-pancreas transplantation results in a significant improvement in the control of hypertension compared with kidney transplant alone in type 1 diabetics.[34] Increase in peripheral vascular disease has been reported in kidney-pancreas transplant recipients compared with kidney-alone transplant recipients[35]; however, another study found the same prevalence of peripheral vascular disease after pancreas transplantation as occurred in diabetic kidney-only recipients who refused pancreas transplantation for nonmedical reasons and in nondiabetic kidney transplant recipients.[36] It is encouraging to note that one study showed that after a 10-year mean

observation period, the progression of macrovascular diseases (cerebrovascular, coronary, and peripheral vascular) was significantly lower in recipients with a functioning SPK compared with a kidney transplant alone.[8]

A study using intravital microscopic evaluation of nail bed and conjunctival vasculature found improved vascularization (as assessed by a reduction in venular diameter, increased number of arterioles per unit area, and elevation of the perfusion capacity) only in kidney-pancreas recipients.[37]

Quality of Life and Social Issues

Pancreas transplantation is a very stressful event and can tax even the strongest of family relationships. Pretransplantation debilities (decreased vision, neuropathy, muscle weakness, orthostatic symptoms) can be exacerbated by the surgery and immunosuppressive medications. Patients who smoke or drink alcohol and are without family support do not survive as long after transplantation. However, kidney-pancreas transplant recipients with social support and well-functioning grafts report an increased global quality of life and frequently return to work, although the number returning to work is not much different from those receiving a kidney transplant alone.[38] In living donor SPK, preliminary results suggest a maintained level of quality of life for donors and improvement for recipients.[39]

Pregnancy After Pancreas Transplantation

Within 1 year of transplantation, menstruation and ovulation return in most women of childbearing age. The U.S. National Transplantation Pregnancy Registry has reported 62 pregnancies in 40 SPK patients.[40] The outcomes were 50 live births, three therapeutic and 10 spontaneous abortions (one twin reduction), and one ectopic twin pregnancy. The newborn outcomes were prematurity (39 of 50), low birth weight (32 of 50), other neonatal complications (28 of 50), and neonatal death (1 of 50). Ten patients had rejections that resulted in grafts loss, and 58% of the patients required cesarean section. Hypertension, prematurity, preeclampsia, and growth retardation frequently complicated the pregnancies, even with good renal function. Gestational diabetes appeared in 3%.

All transplant recipient pregnancies require high-risk obstetric care. Consensus opinion is that pregnancy is safe by 1 year after transplantation under the following conditions: no rejection has occurred in the past year, graft function is stable, no active infections that could have a negative impact on the fetus (e.g., CMV infection) are present, and the patient is not taking any teratogenic medications.[41] MMF has been linked to structural malformations, and patients planning on conception should transition to another agent 6 weeks before trying to conceive.[42] Cyclosporine and tacrolimus levels often decline during pregnancy and require close monitoring to prevent rejection. Cesarean section is not mandatory; vaginal deliveries, however, must be observed for signs of allograft duodenal rupture. The average gestational period is 35 ± 2 weeks; the average birth weight is 2150 ± 680 g. There is no evidence that the children of transplant recipients are more likely to have abnormal development.

The management of other medical issues does not differ from that in kidney-only transplant recipients (see Chapters 101 and 102).

ISLET TRANSPLANTATION

Islet transplantation, with its reduced antigen load, technical simplicity, and low morbidity, has the potential to dramatically improve the quality of life of individuals with type 1 diabetes. The first series of islet allotransplantations in type 1 diabetic patients were reported in 1977.[43] There were sporadic reports in the 1990s of insulin independence for extended periods after islet allotransplantation.[44,45] Autotransplantation studies then demonstrated that a critical mass of 300,000 IE (islet equivalents) could reestablish and maintain insulin independence beyond 2 years.[46] To date, the longest period of insulin independence after autotransplantation is more than 16 years.[47]

Islet After Kidney Transplantation

The initial allogeneic islet transplants in patients with type 1 diabetes were performed in the 1980s and 1990s in patients with end-stage renal disease as sequential islet after kidney (IAK) or simultaneous islet-kidney transplantation. Because the kidney transplant patients were already immunosuppressed, the IAK transplant procedure carried a minimal risk. However, there could be destabilization of the transplanted kidney and also islet dysfunction because most kidney transplant immunosuppression protocols included corticosteroids. Nevertheless, there were beneficial effects from improved glycemic control on both survival and function of transplanted kidneys.[48] Metabolic control (hemoglobin A_{1c} [HbA_{1c}] level and fasting glycemia) improved after IAK transplantation even in patients receiving low-dose corticosteroids. Adverse events included procedure-related pleural effusion and cholecystitis.[49]

Of the 237 well-documented allotransplants recorded in the Collaborative Islet Transplant Registry (CITR) from 1990 to 2000, less than 12% of recipients were insulin free at 1 year after transplantation. The reasons for this failure rate may include subtherapeutic islet implant mass, high rate of engraftment failure, islet damage in the liver (the site of implantation) by direct local toxic effects of the immunosuppressants, ineffective immunosuppression that fails to prevent rejection, recurrent autoimmune diabetes, and islet functional exhaustion. Four criteria were associated with insulin independence: (1) an islet implant mass of more than 6000 IE/kg, (2) a cold ischemia (preservation) time of less than 8 hours, (3) β-induction therapy with polyclonal antibodies such as antilymphocyte globulin or thymoglobulin (ATG), and (4) the liver as the favored implantation site. Early immunosuppressive regimens were relatively ineffective in preventing allograft rejection compared with their effect on vascularized pancreas grafts. Most if not all immunosuppressive agents were associated with impaired beta cell function and reduced graft revascularization.

By the end of 2009 there had been 571 allogeneic islet transplant recipients, both islet transplant alone (ITA), and IAK or simultaneous islet-kidney (SIK) transplantation. Overall achievement of insulin independence was 65% in the first year after islet infusion (with or without reinfusion), and by year 2 this rate increased to 75%.

More success with insulin independence was reported in nonuremic type 1 diabetics transplanted with an average of 800,000 islets by use of the Edmonton protocol, a corticosteroid-free immunosuppression regimen of daclizumab, sirolimus, and low-dose tacrolimus. Although follow-up of this cohort has since confirmed long-term C-peptide production with therapy that is safe and well tolerated, insulin independence is maintained in only a minority.[49] There has since been an exponential increase in clinical islet transplant activity; more patients with type 1 diabetes have now received islet transplants in the past 5 years than in the entire preceding 30-year history of islet transplantation.

Partial graft function, such as improvement of fasting C-peptide alone (to 0.3 to 0.5 ng/ml) combined with exogenous insulin, is sufficient to be associated with improved HbA_{1c}, glycemic control, and

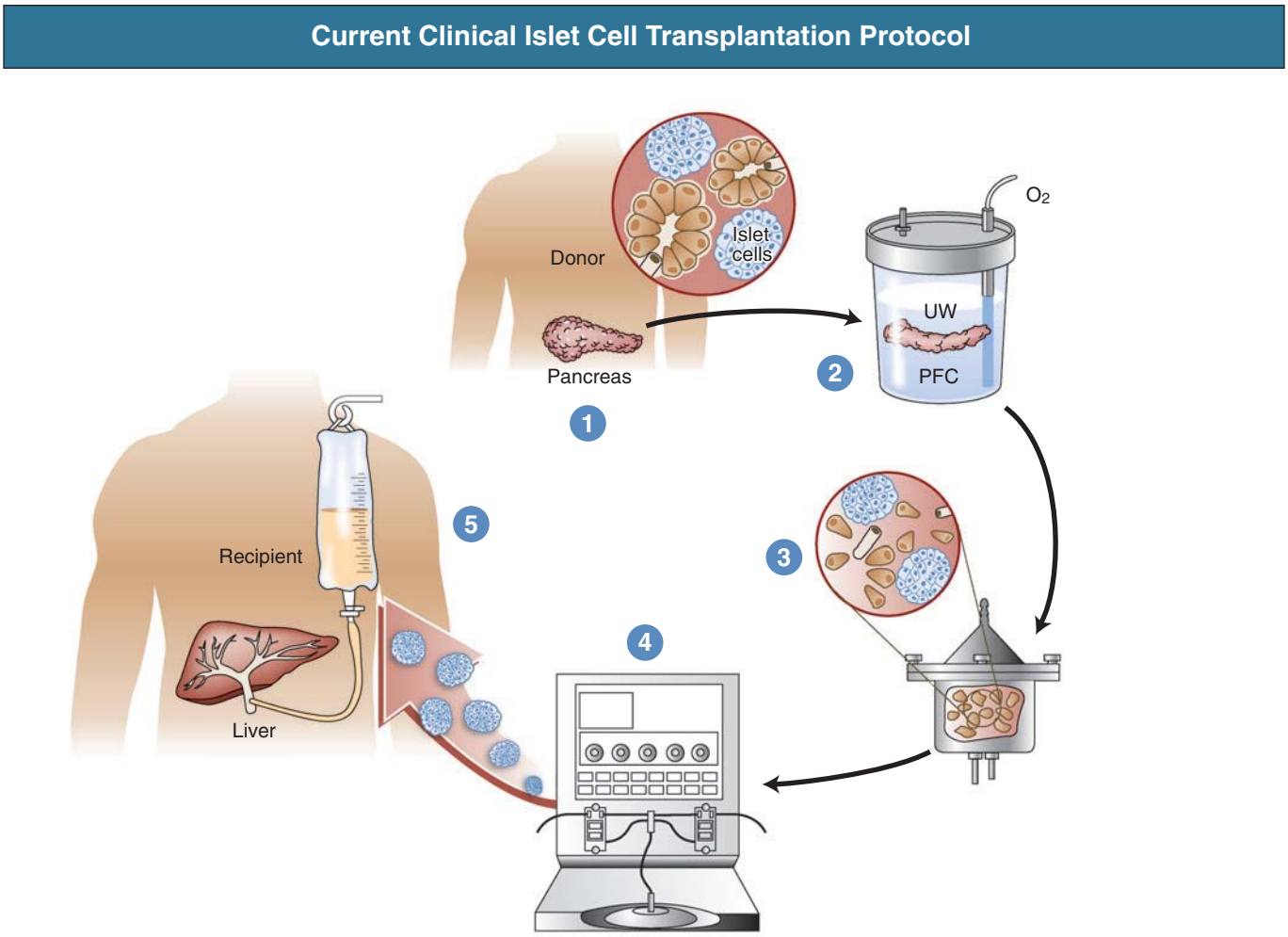

Figure 110-8 Current clinical islet cell transplantation protocol. The retrieved donor pancreas *(1)* is preserved *(2)* with a two-layer storage method using University of Wisconsin solution *(UW)* over a layer of highly oxygenated perfluorocarbon *(PFC).* The pancreas is distended with collagenase and placed in a digestion chamber *(3).* The disrupted exocrine and endocrine elements are purified by centrifugation *(4),* and the islet preparation free from exocrine elements is transplanted by intrahepatic portal vein infusion *(5). (Modified from reference 50.)*

lower levels of severe hypoglycemia. The results are improved with higher fasting C-peptide level.

Technique of Islet Transplantation

The current technique of islet transplantation involves deceased donor pancreas procurement, organ preservation, enzymatic isolation of the islets, purification, and percutaneous injection of sterile islets into the liver through the portal vein via a catheter placed under radiographic guidance (Fig. 110-8).[50] Although accessing of the portal vein percutaneously is relatively invasive, the entire procedure can be performed on an outpatient basis. Effective mechanical and physical methods to seal the catheter track reduce the risk of postprocedural bleeding.[51] Bleeding related to the procedure (23%), thrombus in segmental branches of the portal vein (8%), and punctured gallbladder (3%) are the most observed acute complications after islet transplantation.[52]

There is still a need for greater availability of transplantable islets as well as for improvement in islet engraftment and preservation. Although previous reports indicate that the two-layer method for pancreas preservation improves islet isolation outcome, our recent data show no beneficial effect of the two-layer method on islet isolation and transplantation outcomes.[51] Islet culture for 24 to 48 hours in antioxidant-enriched medium has improved the quality of islet preparations and facilitated the shipment of islets between centers.[52]

Medical Complications

There are also complications of islet transplantation that are not directly related to the procedure itself.[48] Changes consistent with fatty liver are reported in 22% of patients who had magnetic resonance imaging after transplantation. Mouth ulcers occur in 90% of patients and usually respond to simple antiseptic measures or topical triamcinolone ointment together with a reduction in the dose of sirolimus. Diarrhea (60%) and acne (52%) are frequent. Forty-three percent of recipients complained of edema, severe enough in 12% to necessitate a change in the immunosuppressive regimen. Weight loss is common.

In 27 of the 571 islet recipients in CITR, 29 incidents of neoplasm was diagnosed. Of these incidents, 21 (72%) were benign and 6 were malignant.

Glycemic Control and Insulin Independence

Successful islet transplantation establishes normal HbA_{1c} levels, although the fasting glucose concentration tends to be slightly elevated and there is often impaired glucose tolerance. Another

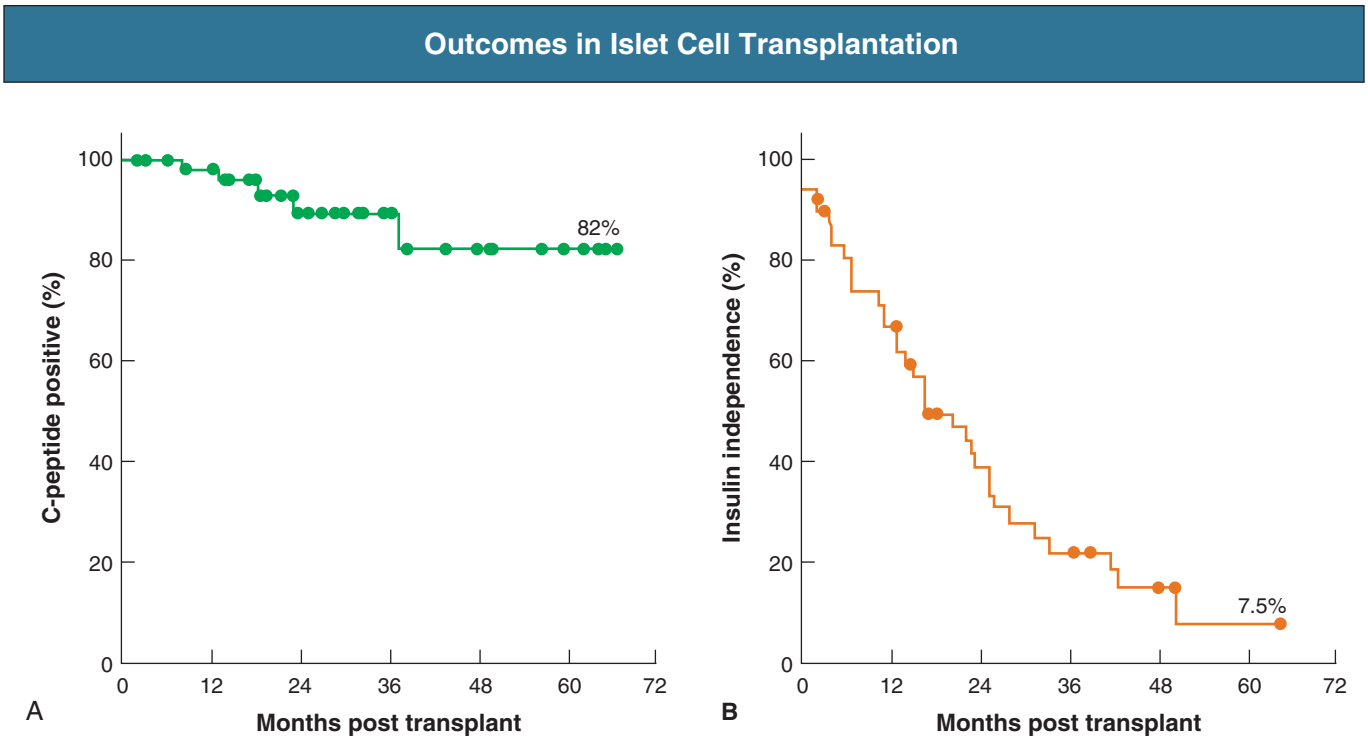

Figure 110-9 Outcomes in islet cell transplantation. A, Persistence of C-peptide secretion over time. The curves are dated from the time of the final transplant. **B,** Persistence of insulin independence over time. *(From reference 48.)*

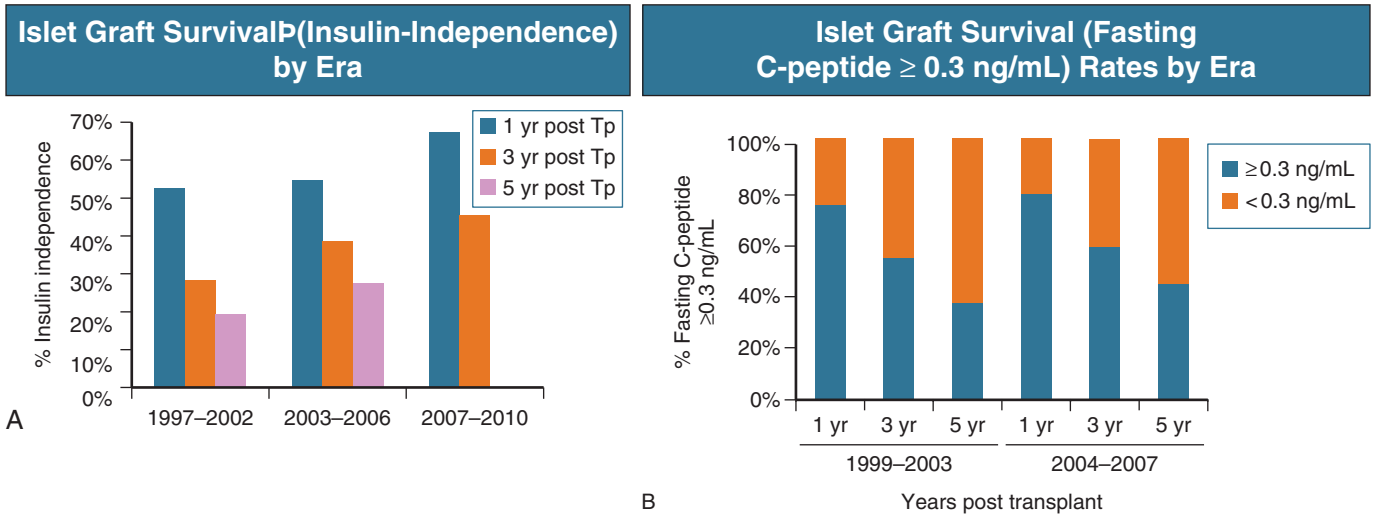

Figure 110-10 Islet graft survival. A, Insulin-independence rates. **B,** Fasting C-peptide at different times after transplant in two different eras. *Tp,* Transplant. *(From reference 54.)*

difference between successful pancreas and islet transplants is that placement of islets within the liver results in failure of the beta cell response to hypoglycemia, even though there is responsiveness to intravenous arginine. In a recent analysis, 82% of 118 islet recipients in three North American centers were insulin free at 1 year.[52] However, in a 5-year follow-up in Edmonton,[45] only 7.5% maintained insulin independence, although 82% had detectable C-peptide (Fig. 110-9). The median duration of insulin independence was 15 months.

From 1997 to 2002, the insulin-independence rate at 1 year after islet transplant was 51%, decreasing to 18% by 5 years after transplant. Improvements in islet isolation and transplant procedures have improved the insulin-independence rate, to 66% by 1 year and 44% by 3 years after transplant for procedures performed in 2007 to 2010 (Fig. 110-10).[53]

Durability of islet graft function was found to have improved significantly when islet transplants from 1999 to 2003 were compared with those from 2004 to 2007, with 1- and 5-year fasting C-peptide of 0.3 ng/ml or higher of 74% and 35%, compared with 78% and 43%, respectively (see Fig. 110-10).[52]

Immunosuppressive Regimens

Tacrolimus, cyclosporine, and corticosteroids are diabetogenic through increased peripheral insulin resistance or by direct islet cell toxicity. Oral administration increases portal venous drug

concentrations and the possibility of significant injury to intrahepatic islet grafts. Most programs use corticosteroid-free and calcineurin inhibitor–sparing protocols for islet or kidney recipients with different combinations of MMF and sirolimus. MMF reduces early pancreas rejection rates. Insulin independence has now been achieved with islet grafts derived from non–heart-beating donors and after sequential kidney-islet transplantations using sirolimus-based therapy. Islet engraftment can also be improved with use of a calcineurin inhibitor–free regimen with profound T cell depletion.[48] Anti–T cell therapy using ATG or OKT3 may be associated with a cytokine storm, which is toxic to islets, and newer induction agents (anti–interleukin-2 receptor blockers) may be particularly useful to minimize cytokine release.

A number of new immunosuppressive agents that offer the potential for more islet-friendly approaches are now entering clinical trials. These include combinations of biologic agents, such as ATG, rituximab, and alemtuzumab; novel anti–T cell biologic agents, some of which offer the prospect of inducing tolerance based on animal studies; and agents that produce costimulatory blockade.

Based on CITR data, the highest 5-year insulin-independence rates after transplant, 60% to 70%, were seen with a combination of T cell depletion and tumor necrosis factor (TNF) antagonism, and a maintenance combination that included calcineurin and inosine monophosphate dehydrogenase (IMPDH) inhibitors. This regimen was in use starting in the 2004 to 2006 era of islet transplantation, leading to improved 1- and 3-year insulin-independence rates (see Fig. 110-10).[54]

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CHAPTER 111

Kidney Disease in Liver, Cardiac, Lung, and Hematopoietic Cell Transplantation

Colm C. Magee

It is now well recognized that kidney disease can complicate all forms of solid organ nonrenal transplantation.[1-3] Kidney disease can occur in the immediate pretransplantation period, in the early postoperative period, or during the long term. In general, it is associated with longer hospitalization, higher morbidity, higher mortality, and greater expense. Although there are organ-specific factors (such as the high prevalence of hepatitis C virus infection in liver transplant recipients) that have an impact on the incidence and severity of kidney disease, some useful generalizations can be made.

GENERIC ISSUES OF KIDNEY DISEASE IN NONRENAL SOLID ORGAN TRANSPLANTATION

Use of Serum Creatinine and Derived Equations to Measure Glomerular Filtration Rate

Transplant candidates and recipients often have low muscle mass and low creatinine generation. Hence, a mildly elevated serum creatinine concentration may hide severe kidney disease. This is particularly relevant in the pretransplant patient with liver failure.[3,4] Such patients should have glomerular filtration rate (GFR) estimated by creatinine clearance (which will tend to overestimate) or preferably by iothalamate clearance (where it is available). Of the various serum creatinine–based equations to estimate GFR, the Modification of Diet in Renal Disease (MDRD) equation appears to correlate best with true post-transplantation GFR; however, even this equation has limited accuracy in all forms of solid organ transplantation.[4]

Nephrotoxicity of Calcineurin Inhibitors

The introduction of the calcineurin inhibitor (CNI) cyclosporine in the 1980s revolutionized the field of organ transplantation, and the CNIs cyclosporine and tacrolimus remain a cornerstone of immunosuppression in recipients of nonrenal allografts.[1] However, there is little doubt that CNIs contribute significantly to both acute kidney injury (AKI) and chronic kidney disease (CKD) in these recipients. There is speculation that CNI nephrotoxicity is more severe in nonrenal than in renal transplantation because (1) dosage and blood concentrations of CNIs tend to be higher in nonrenal transplantation and (2) the lack of normal innervation of the transplanted kidney may protect it from early CNI injury. CNIs also exacerbate post-transplantation hypertension and diabetes mellitus, which cause renal damage in the long term.

Acute CNI nephrotoxicity is thought to be mainly a pre-renal syndrome caused by vasoconstriction of the afferent glomerular arteriole (see also Chapter 101). Tubular damage and microvascular disease may occur in more severe cases. In the early post-transplantation period, AKI is usually multifactorial, and it is difficult to quantify the degree to which CNI toxicity is contributing to the problem. In practice, doses of CNIs are often temporarily reduced in the setting of AKI. Acute CNI-induced thrombotic microangiopathy (TMA) is rare in nonrenal transplant recipients. Chronic CNI nephrotoxicity is probably a result of prolonged renal ischemia and other effects, such as direct stimulation of renal fibrogenesis. Typically the patient is hypertensive (CNIs worsen hypertension) and there is a steady fall in GFR, most marked in the first 6 to 12 months after transplantation (Fig. 111-1).[5] Dipstick urinalysis shows minimal or no hematuria and minimal or mild proteinuria. Urine protein-creatinine ratio or 24-hour urine collections confirm low-grade proteinuria. Renal histology shows interstitial fibrosis, arteriolar hyalinosis, arteriosclerosis, and secondary focal glomerulosclerosis.[6] There may also be features of chronic TMA.[6] In practice, renal biopsies are rarely performed unless there are clinical features suggestive of a renal disorder other than CNI toxicity.

It is not surprising that the presumed high prevalence of chronic CNI nephrotoxicity has generated interest in low-dose or zero-dose CNI protocols. Just as in renal transplantation, these typically involve use of mycophenolate mofetil (MMF) or mammalian target of rapamycin (mTOR) inhibitors.[1,3,7] However, there is still understandable reluctance to pursue such protocols because CNIs are considered such effective immunosuppressive agents, and organ replacement therapy analogous to dialysis is not available for other organ transplant recipients if severe rejection occurs. MMF has the advantage of being non-nephrotoxic. mTOR inhibitors have several disadvantages; they impair wound healing, potentiate the nephrotoxicity of cyclosporine, and sometimes induce proteinuria. Although some studies suggest that everolimus is better tolerated than sirolimus, similar nephrotoxic interactions have been reported between both sirolimus and everolimus with cyclosporine.[8] CNI-sparing strategies are discussed in more detail later.

Another strategy is to use tacrolimus as the *de novo* CNI or to switch from cyclosporine to tacrolimus if there is evidence of nephrotoxicity (cyclosporine is still commonly prescribed as the *de novo* CNI in heart and lung transplantation). The rationale here is that tacrolimus provides equivalent or even better immunosuppression at doses and concentrations that are less nephrotoxic than cyclosporine. Furthermore, tacrolimus is associated with less hypertension and hyperlipidemia (which might exacerbate CKD) than cyclosporine. Conversely, it is associated with more post-transplantation diabetes mellitus. Studies in nonrenal transplant recipients have yielded conflicting results as to which is more nephrotoxic.

The usefulness of calcium channel blockers in ameliorating CNI nephrotoxicity in renal transplantation remains controversial, and there is limited evidence of such benefit in nonrenal transplantation.

Changes in Measured Iothalamate GFR in Individual Patients after Lung Transplantation

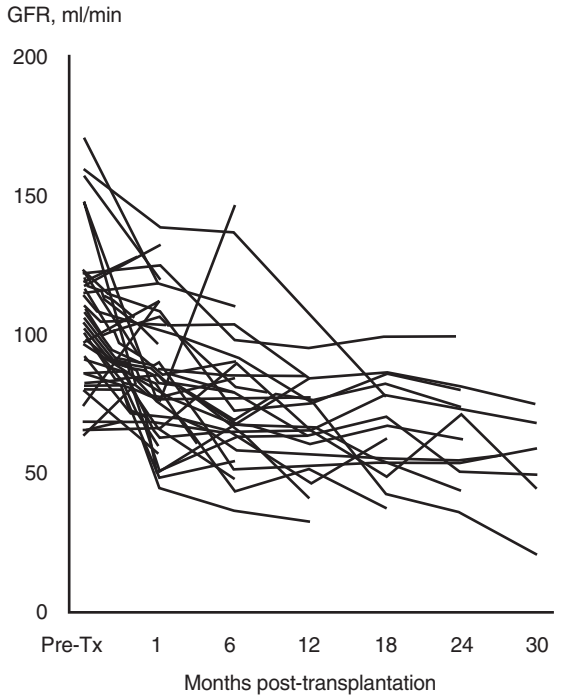

Figure 111-1 Changes in measured iothalamate glomerular filtration rate (GFR) in individual patients after lung transplantation. Note the variation in GFR before transplant and the large fall in GFR in many patients within the first 6 months. *Tx,* Transplantation. *(Adapted from reference 5.)*

Advantages and Disadvantages of Simultaneous Kidney and Other Solid Organ Transplantation

Advantages	Disadvantages
Potentially provides much better renal function over the short and long terms	Surgery more technically complex and prolonged Not needed when the AKI is reversible
Single donor—potential for lower cumulative dose of immunosuppression (as opposed to kidney transplantation later)	Deprives patients with "definite" ESRD of a kidney transplant

Table 111-1 Advantages and disadvantages of simultaneous renal and nonrenal transplantation. *AKI,* Acute kidney injury; *ESRD,* end-stage renal disease.

Causes of Acute Kidney Injury (AKI) After Solid Organ Transplantation

Prerenal	Intrarenal (ATN)	Postrenal
Hypovolemic shock (e.g., aggressive diuresis) Cardiogenic shock (e.g., severe cardiac allograft dysfunction) Distributive shock (e.g., sepsis) Cyclosporine or tacrolimus	Prolonged shock Cyclosporine or tacrolimus Aminoglycosides, amphotericin Intravenous contrast Hydroxyethyl starch, IVIG	Rare

Table 111-2 Causes of AKI after solid organ transplantation. *ATN,* Acute tubular necrosis; *IVIG,* intravenous immune globulin.

Experimental studies suggest that agents that block the renin-angiotensin system (RAS) may provide protection against the arteriolar hyalinosis and tubulointerstitial injury associated with chronic CNI use. Control of hypertension *per se* is probably more important than use of any particular antihypertensive agent.

Acute Kidney Injury in the Immediate Pretransplantation Period

It is not surprising that AKI can occur in the days to weeks immediately before liver, heart, or (less commonly) lung transplantation. Typically, the cause of AKI is either pre-renal (e.g., renal hypoperfusion or hepatorenal syndrome) or intrarenal (ischemic or toxic acute tubular necrosis) or a combination of both. AKI may develop on a background of CKD. A mildly elevated serum creatinine may mask a significant fall in GFR in malnourished patients with severe organ failure.[3] Reported rates of AKI vary widely; rates may be modified by varying definitions of AKI, organ-specific risks of AKI, and center variability in the type of patients listed for transplantation.

Management of AKI focuses on treatment of the underlying cause and provision of dialytic support according to standard criteria. Because the patients are critically ill, continuous renal replacement therapy (CRRT) may be preferred to intermittent hemodialysis, but there are no randomized controlled trials showing improved outcomes with this modality in this setting. When severe or prolonged AKI occurs before planned transplantation, estimation of the degree of reversibility becomes very important, because presumed irreversible severe kidney injury is generally a contraindication to transplantation or shifts the management toward simultaneous dual-organ (e.g., liver and kidney) transplantation. This is an area of ongoing debate in liver and, to a lesser extent, cardiac transplantation and is discussed in detail later. The general advantages and disadvantages of simultaneous dual-organ transplantation are shown in Table 111-1.

Although kidney biopsy might be useful in determining the degree of reversibility, in practice it is not commonly performed. This reflects the perceived technical difficulties of performing the procedure in critically ill—often coagulopathic—patients, in whom a biopsy-related bleed could have catastrophic consequences.

Acute Kidney Injury in the Early Post-transplantation Period

Acute kidney injury is also common in the days to weeks after transplantation. This reflects several factors: pretransplant renal function may have been compromised, the transplanted organ may have poor initial function, high doses of CNIs and other nephrotoxic agents may be prescribed, and the invasive surgery and high-dose immunosuppression predispose to severe infection (Table 111-2). AKI is associated with higher mortality in the early postoperative period.[9-11] This is likely to reflect both the association of AKI with other severe complications and also its direct effects on mortality. In those who survive, AKI is associated with an increased risk of developing CKD.[12]

Prevention or minimization of post-transplant AKI involves careful selection of patients for transplantation, meticulous perioperative care, and avoidance of nephrotoxic agents. Management of established AKI focuses on treatment of the underlying cause and

provision of dialytic support according to standard criteria. Intermittent hemodialysis and CRRT are both used. Delayed introduction or reduced doses of CNIs are sometimes used, usually under the cover of induction antibody immunosuppression. How much this strategy improves renal function remains unclear.

Chronic Kidney Disease

With the increasing number of solid organ transplants being performed worldwide and the longer survival of recipients, the absolute number of recipients with CKD has increased. In the largest and most comprehensive study to date, the cumulative incidence of post-transplant CKD (defined as estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2) at 5 years varied from 7% to 21% (Fig. 111-2).[12] By multivariate analysis, the following pretransplant variables increased the risk of development of CKD: increasing age, female gender, white or black (as opposed to Asian) ethnicity, lower GFR, diabetes mellitus, hypertension, hepatitis C virus infection, and need for dialysis. The following post-transplant variables were also implicated: postoperative AKI and initial use of cyclosporine (as opposed to tacrolimus).[12] These risk factors have been confirmed in other studies.

Many studies have also confirmed that whatever the transplanted organ, development of CKD, and especially of end-stage renal disease (ESRD), portends a poor prognosis (Fig. 111-3). Recipients with CKD have a relative risk of death of 4.6 compared with those without CKD.[12] The risk is highest in those with ESRD, but even in those not on dialysis, the relative risk of death was doubled.[12]

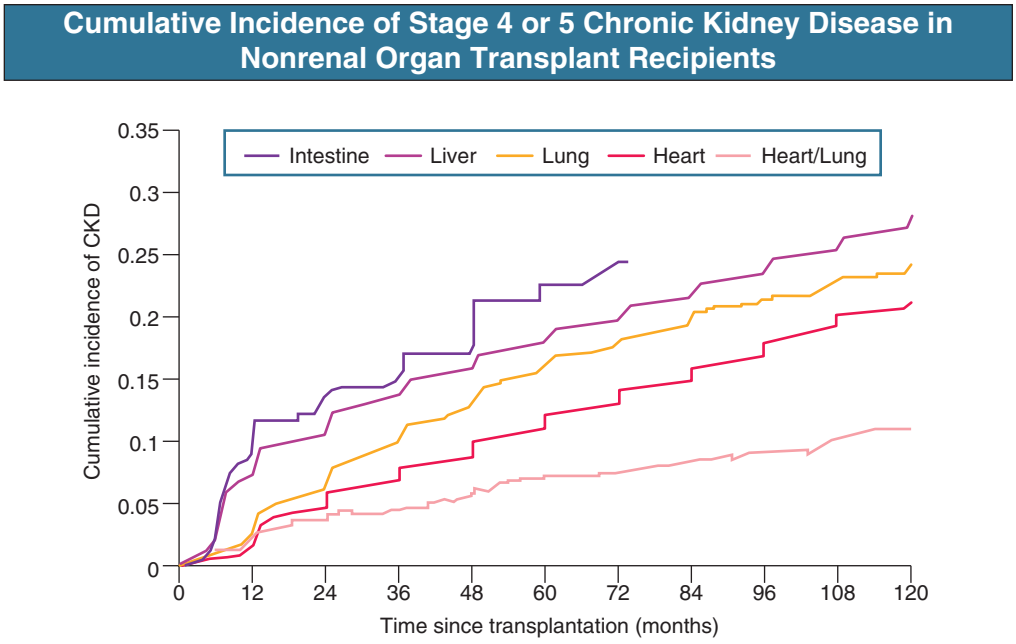

Figure 111-2 Cumulative incidence of CKD (eGFR <30 ml/min/1.73 m^2) after transplantation of various solid organs. *CKD,* Chronic kidney disease; *eGFR,* estimated glomerular filtration rate. *(Adapted from reference 12.)*

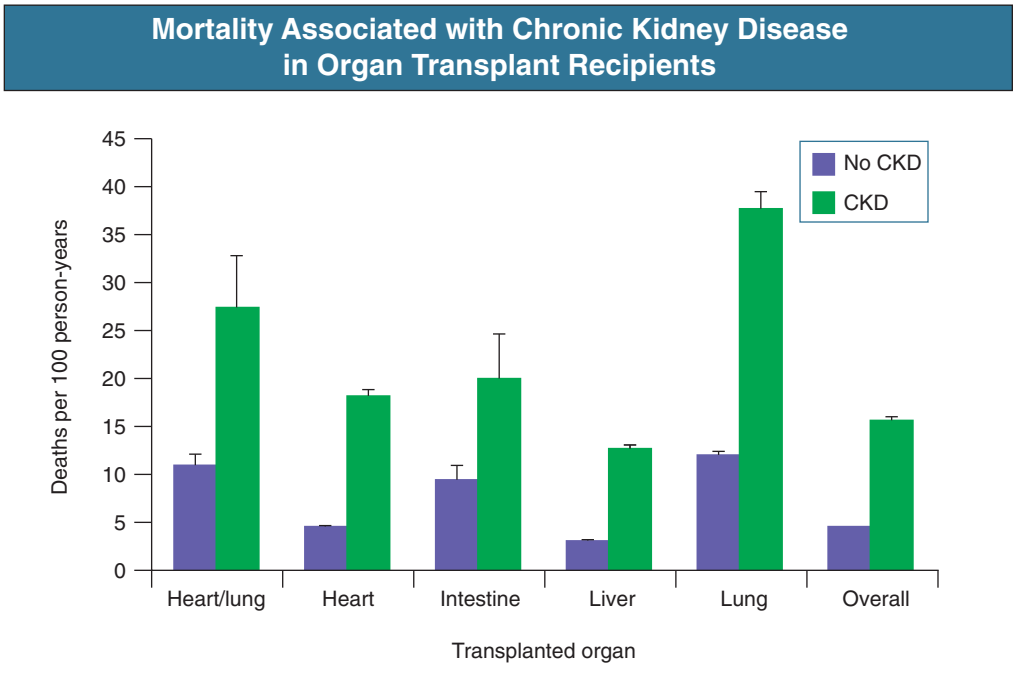

Figure 111-3 Mortality associated with stage 4 and 5 CKD in organ transplant recipients. *CKD,* Chronic kidney disease. *(Data from Scientific Registry of Transplant Recipients.)*

Although it has not been well studied, CKD in this setting is presumably associated with the same complications as in nontransplant recipients, including anemia, hypertension, fluid overload, and bone and mineral disorders. Indeed, these complications might be more severe in nonrenal transplant recipients because of other risk factors. For example, antiproliferative immunosuppressants exacerbate anemia and corticosteroids exacerbate metabolic bone disease.

Management of Chronic Kidney Disease

The MDRD equation (despite its limitations) is useful in identifying CKD in these patients. In all patients with rising serum creatinine or falling GFR, referral to a nephrologist should be considered. The initial evaluation should include thorough review of renal function in the peritransplantation period and exposure to nephrotoxins. If urinalysis shows moderate or severe proteinuria or hematuria or both, renal biopsy should be considered; it can be highly informative in identifying renal diseases other than CNI nephrotoxicity.[13]

Close consultation with the primary transplant team is important. When CNI toxicity is deemed the main cause of CKD (as it is in the majority of patients), reduction in CNI dosage for patients at low immunologic risk should be considered. To maintain adequate immunosuppression, if the patient is receiving azathioprine, a change to MMF should be considered; if the patient is already receiving MMF, the dose should probably be increased. An alternative strategy (one that I favor less) is to substitute an mTOR inhibitor for the CNI; this should not be done in the early post-transplant period because of the adverse effects of these drugs on wound healing. Finally, some have advocated switching of cyclosporine to low-dose tacrolimus, although the supporting data are less compelling. It should be noted that the majority of studies of CNI reduction or cessation in these settings are small, have limited follow-up, and are of limited quality.[14]

The general management of CKD has not been well studied in nonrenal transplant recipients, but it seems reasonable to use the same strategies used in the nontransplant CKD population. Thus, hypertension, anemia, and hyperparathyroidism should be managed according to standard guidelines. Although there is experimental evidence that angiotensin-converting enzyme (ACE) inhibitors might have important antifibrotic effects in nonrenal transplant CKD, there are no trials showing improved renal outcomes with ACE inhibitors or angiotensin receptor blockers compared with other antihypertensive agents. In practice, lifestyle modification and several antihypertensive drugs are usually required for achievement of target blood pressure.

In those with severe CKD, planning for renal replacement therapy including renal transplantation (where appropriate) should begin early. The majority are treated with hemodialysis rather than with peritoneal dialysis. With either modality, mortality is much higher compared with matched nontransplant controls.[15] Nevertheless, some have reported reasonable outcomes with home therapies (both hemodialysis and peritoneal dialysis).[16] Pending further studies, it seems that the choice of dialysis modality should be dictated by patient-specific factors.

There seems little doubt that in those fit for the procedure, sequential kidney transplantation is the best form of renal replacement therapy. Because patients have already undergone transplantation, the addition of the renal allograft does not imply a huge increase in immunosuppression (typically, this is increased only in the perioperative period). When it is feasible, a preemptive living donor transplant is probably the best option. Initial mortality is higher in nonrenal transplant recipients receiving a kidney transplant as opposed to staying on the waiting list (reflecting the complications of surgery and more immunosuppression), but mortality in the medium and long term is much lower.[12] The number of patients with a nonrenal transplant being wait-listed in the United States has increased significantly over the last 15 years.[15]

Prevention of Chronic Kidney Disease

The rate of development and progression of CKD can probably be reduced by minimizing post-transplantation AKI (see earlier) and by rigorous control of hypertension in the long term. Clearly, safe and effective non-CNI or low-dose CNI protocols would be an important advance in preventing severe CKD. Studies using induction antibody with corticosteroids, MMF, and low-dose tacrolimus are encouraging in this regard.[3,17]

BK Virus Nephropathy

BK virus nephropathy is a much-feared complication of kidney transplantation. Fortunately, although BK viruria is occasionally noted after liver, heart, or lung transplantation, the absolute risk of BK viremia and BK virus nephropathy remains low. This probably reflects the lack of a "second hit" to the native kidneys, such as human leukocyte antigen (HLA) mismatching or inflammation. Nevertheless, BK virus nephropathy should be considered in the differential diagnosis of "unexplained" renal dysfunction after solid organ transplantation, especially because more intensive maintenance immunosuppressive protocols involving combined MMF and tacrolimus are being increasingly used.

Acute Kidney Injury in the Late Post-transplantation Period

Severe AKI occasionally occurs late after transplantation. The major causes are shown in Table 111-2. Severe rhabdomyolysis has been reported, usually when statins are prescribed with cyclosporine and an inhibitor of the cytochrome P-450 system, such as diltiazem or ketoconazole and other azole-based antifungal agents. Treatment of late AKI is of the underlying cause plus the usual supportive measures.

KIDNEY DISEASE IN LIVER TRANSPLANTATION

Acute kidney injury is common before liver transplantation. Indeed, use of the MELD (Model for End-Stage Liver Disease) scoring system (which measures severity of hepatic dysfunction and risk of death) to guide allocation of deceased donor liver allografts means that a raised serum creatinine concentration increases the chances of the patient being offered a liver transplant.[18] The most common causes of AKI before transplantation are hepatorenal syndrome (see Chapter 76) and acute tubular necrosis or both. Prolonged hepatorenal syndrome may cause acute tubular necrosis. Glomerulonephritis (GN) is relatively common (cirrhosis is associated with IgA nephropathy, and hepatitis C with membranoproliferative glomerulonephritis [MPGN]) but is rarely the cause of severe pretransplantation kidney disease. If renal replacement therapy is required, CRRT is often preferred, in part because it is thought to have less effect than intermittent dialysis on intracranial pressure.

Post-transplantation AKI is also common and is usually multifactorial.[9] In one series, 37% of liver transplants were complicated by some degree of AKI, 19% necessitating renal replacement therapy.[9] Requirement for renal replacement therapy was associated with higher 30-day and 1-year mortality. Pretransplant AKI associated with hepatorenal syndrome often but not always improves if the transplant is successful.

Although relatively low doses of CNIs are traditionally used in liver transplantation (because rejection is less of a concern than in other solid organ transplants), CKD remains common and is associated with higher mortality.[12] Thus, although CNIs are an important cause of CKD, other factors must play a role. These include the high prevalence of hepatitis C and hepatitis B viral infections (which predispose to GN) and the high prevalence of diabetes mellitus. Protocols involving reduction or cessation of CNIs have shown promising results.[19] Delayed introduction of tacrolimus, with the cover of interleukin-2 receptor blockade, has been shown to better preserve renal function while maintaining excellent allograft and patient outcomes.[17] *De novo* use of sirolimus is not recommended because there is some concern that it may be associated with hepatic artery thrombosis; there are also concerns about using this drug in the later post-transplant period.

The number and percentage of simultaneous liver-kidney transplants have increased greatly in the United States in recent years. In 1998, for example, there were 98; in 2013, there were 494 (approximately 7.7% of total liver transplants).[20] The principal reason is that the MELD system heavily weighs higher serum creatinine concentration and prioritizes patients with renal dysfunction. Although patients with severe pretransplant kidney disease do benefit from a combined transplant procedure, there is concern that too many simultaneous liver-kidney transplants are being performed and that current practice is depriving "real" ESRD patients of deceased donor kidney transplants. The main issue, of course, is deciding which patients are likely to have meaningful renal recovery after liver transplant alone. Complicating factors in this setting are the known poor accuracy of serum creatinine (and equations based on it) in estimating GFR and concerns about the high risk of renal biopsy. Single-center studies suggest that use of a combination of clinical and histologic criteria allows effective prediction of which patients will benefit most from simultaneous liver-kidney transplantation.[21,22] These centers used iothalamate clearance to measure GFR in patients with suspected AKI. Renal biopsy was performed by the percutaneous or transjugular method and had a moderate rate of complications[21,22]; some believe that it adds little discriminating value.[3] A recent consensus conference has provided recommendations as to who should receive simultaneous liver-kidney transplants (Box 111-1).[18] These recommendations have been questioned, however.[23]

KIDNEY DISEASE IN CARDIAC TRANSPLANTATION

Preoperative AKI is common. In the largest reported study, 1% of heart transplant recipients required renal replacement therapy before transplantation.[12] The main cause of AKI is renal hypoperfusion from severe congestive heart failure. Ventricular assist devices are sometimes used as a bridge to cardiac transplantation and can improve renal function in this setting. It is interesting to note that there is emerging evidence that venous congestion is independently associated with the presence of AKI, although whether therapies based on reducing central venous pressure improve renal outcomes remains to be proven. In some patients there may also be a component of chronic kidney injury caused by renovascular disease or hypertension or atheroembolism.

Postoperative AKI is also common. In addition to the causes shown in Table 111-2, factors that may be important after cardiac transplant surgery are prolonged aortic cross-clamping, large fluid volume shifts, and prolonged allograft ventricular dysfunction. CKD is now well recognized as an important and common complication in the medium and long term (see Fig. 111-2). The cumulative incidence of stage 4 or stage 5 CKD in cardiac transplant recipients has been reported as 11% at 5 years, lower than in bowel, liver, or lung transplant recipients.[12] The principal cause of CKD after cardiac transplantation is CNI toxicity. Several studies have shown that early or late renal dysfunction is a risk factor for death after cardiac transplantation; furthermore, cardiac transplant recipients on dialysis have poorer survival compared with other ESRD patients.[24,25]

A number of studies have assessed reduction or cessation of CNIs in patients with significant CKD after cardiac transplantation. The majority are small and single-center studies and have shown improvement in GFR with no adverse effects on the allograft.[26,27] However, these studies are of patients at low immunologic risk and often do not have long-term follow-up. Indeed, one recent report warned of high rates of rejection after patients were switched to a corticosteroid plus MMF protocol.[28] Another pilot study showed concerning outcomes with a *de novo* CNI-free protocol,[29] which cannot at present be recommended.

As in liver transplantation, the question of whether the patient is best served by heart-alone or simultaneous heart and kidney transplantation sometimes arises. The concern here, again, is the reversibility of renal failure. The absolute number of such dual transplants remains low but is steadily increasing in the United States (71 in 2012, equivalent to about 3.3% of total heart transplants).[20] Some centers have reported good results.[30] However, one recent registry analysis found that simultaneous heart and kidney (as opposed to heart-alone) transplantation benefited only low-risk patients with eGFR below 33 ml/min.[31] Consensus guidelines have not yet been developed. At this time, it seems reasonable to limit the combined transplants to patients with at least a severity of kidney disease similar to that shown in Box 111-1.

Recommended Indications for Simultaneous Liver-Kidney Transplant in Patients Listed for Liver Transplant

- CKD with GFR 30 ml/min or lower
- AKI or HRS with creatinine 2 mg/dl (176 μmol/l) or more and dialysis for 8 weeks or longer
- CKD with biopsy showing more than 30% glomerulosclerosis or 30% interstitial fibrosis

Box 111-1 Recommended indications for simultaneous liver-kidney transplant in patients listed for liver transplant. *AKI,* Acute kidney injury; *CKD,* chronic kidney disease; *GFR,* glomerular filtration rate; *HRS,* hepatorenal syndrome. *(Adapted from reference 18.)*

KIDNEY DISEASE IN LUNG TRANSPLANTATION

Preoperative AKI is less common and severe, as evidenced by the fact that only 0.1% of lung transplant recipients are reported to require dialysis before transplantation.[12] CKD may be present before transplantation, however, because of diabetes mellitus or high exposure to aminoglycosides (mainly in patients with cystic fibrosis). AKI after lung transplantation is common; in one series, 56% of patients had at least a doubling of serum creatinine in the first 2 weeks after transplantation.[11] A recent analysis of United Network for Organ Sharing (UNOS) data showed that 5.5% of patients required renal replacement therapy after lung transplantation; short- and long-term survival in this group was dramatically lower.[32]

Acute kidney injury can occur for the usual reasons shown in Table 111-2, but a number of factors specific to lung transplantation

may be important. First, aggressive diuresis is often prescribed to minimize any pulmonary edema in the allograft.[11] Second, nephrotoxic antimicrobial agents, such as aminoglycosides and amphotericin, are sometimes required to treat resistant or severe infections.[11,33] Acute oxalate nephropathy leading to irreversible renal failure has been described in lung transplant recipients.[33] The pathogenesis is thought to involve gut hyperabsorption of oxalate because of impaired fatty acid absorption and altered gut flora. Although it is probably rare, this "new disease" emphasizes the importance of maintaining a broad differential diagnosis for any kidney disease occurring after solid organ transplantation and the usefulness of performing a renal biopsy when the clinical presentation is unusual.

As with other forms of post-transplantation CKD, the most common cause is probably CNI toxicity.[33] CNI dosages tend to be higher because of the increased risk of rejection in lung transplantation. A small number of studies have reported improvements in GFR when doses of CNIs were reduced, but more data are needed before this can be routinely recommended. If CNI reduction is attempted, it seems prudent to use MMF rather than mTOR inhibitors as additional immunosuppression in view of the risk of pneumonitis with the latter. *De novo* use of mTOR inhibitors is not recommended because they may cause breakdown of the bronchial anastomosis.

It is interesting to note that patients with pulmonary hypertension appear to have a lower GFR immediately before transplantation than do those with other diagnoses but have a less severe fall in GFR after transplantation.[5] This probably reflects the adverse effects of pulmonary hypertension on renal perfusion and reversal of these effects after successful lung transplantation. Simultaneous lung-kidney transplantation is rarely performed.[20]

KIDNEY DISEASE IN HEMATOPOIETIC CELL TRANSPLANTATION

The general purpose of hematopoietic cell transplantation (HCT) is to allow administration of otherwise lethal (and ideally curative) doses of chemoradiotherapy, followed by engraftment of stem or progenitor cells for marrow recovery.[34,35] Most commonly, HCT is used to treat hematologic cancers, but other indications now include certain nonhematologic cancers, severe genetic disorders (such as immunodeficiencies), and severe autoimmune diseases.[36] Stem and progenitor cells may be harvested from peripheral blood, bone marrow, or umbilical cord blood. Conventional myeloablative HCT uses intensive conditioning regimens involving high-dose chemotherapy and radiotherapy to ablate cancer cells and bone marrow; the hematopoietic system is then reconstituted by infusion and engraftment of stem cells. In allogeneic myeloablative HCT, nonself stem cells are used; in autologous myeloablative HCT, the patient's own cells are used. The toxicities of myeloablative regimens generally exclude older and sicker patients; nonmyeloablative or "reduced-conditioning" regimens have been developed to allow allogeneic HCT in such patients. In both forms of allogeneic HCT, acute and chronic graft-versus-host disease (GVHD) can be problematic; CNIs are typically prescribed to prevent and to treat this complication. The three main target organs of GVHD are the liver, gastrointestinal tract, and skin.

Tens of thousands of HCTs are performed worldwide every year.[36] It is now recognized that AKI and CKD are common complications of HCT and are associated with higher early and late mortality. The types of HCT and their associated renal complications are shown in Table 111-3.

Acute Kidney Injury After Hematopoietic Cell Transplantation

Acute kidney injury is common after HCT, but its incidence and severity depend on the type of HCT (and on the definition of AKI used in reported series). It is most common after myeloablative allogeneic HCT, reflecting the propensity of this regimen to cause profound immunosuppression (with associated risk of severe sepsis) and liver damage (with associated risk of hepatorenal syndrome; see later); furthermore, CNIs are routinely prescribed for the first 100 days after transplantation. Severe AKI is least common after nonmyeloablative HCT (even though patients are older and sometimes sicker), reflecting the shorter period of pancytopenia and rarity of sinusoidal obstructive disease of the liver as a post-transplant complication. The principal cause of AKI in this setting is probably CNI toxicity; severe AKI necessitating dialysis is relatively rare.[37]

Three Types of Hematopoietic Cell Transplantation (HCT) and Their Associated Renal Complications

	Myeloablative Allogeneic	Myeloablative Autologous	Nonmyeloablative Allogeneic
Diseases treated	Many leukemias, NHL, myelodysplastic syndromes	Lymphomas, multiple myeloma	As for myeloablative allogeneic type
Used in patients older than 60 years	Rarely	Sometimes	Common
Comorbidities permissible before HCT	Minimal	Minimal	Some
Intensity of conditioning regimen	High	High	Low
GVHD after HCT	Common	None	Common
CNIs used routinely	Yes	No	Yes
Incidence of AKI	Very common; sometimes severe	Common	Common; rarely severe
Causes of AKI	Hepatic sinusoidal obstruction syndrome, shock syndromes, nephrotoxic drugs, CNIs	Shock syndromes, nephrotoxic drugs; occasionally hepatic sinusoidal obstruction syndrome	CNIs
Incidence of CKD	Common	Common (but less severe than myeloablative allogeneic type)	Mild forms probably common
Causes of CKD	Irreversible AKI, renal TMA, CNIs, ?GVHD	Irreversible AKI	Pretransplant mild CKD, irreversible AKI, CNIs, ?GVHD

Table 111-3 The three types of hematopoietic cell transplantation and their associated renal complications. *AKI,* Acute kidney injury; *CKD,* chronic kidney disease; *CNIs,* calcineurin inhibitors; *GVHD,* graft-versus-host disease; *NHL,* non-Hodgkin lymphoma; *TMA,* thrombotic microangiopathy.

Causes of Kidney Disease According to Time After Hematopoietic Cell Transplantation

Immediate (Very Rare)	Early (AKI in First 3 Months)	Late
Tumor lysis syndrome	Prerenal	Thrombotic microangiopathy*
Marrow or stem cell infusion toxicity	Hypovolemia	CNI toxicity
	Hepatorenal syndrome	Irreversible AKI
	CNI toxicity	Membranous nephropathy or other glomerular diseases
	Intrarenal	Recurrence of original disease, which then affects kidneys (e.g., myeloma)*
	Ischemic and/or toxic ATN (shock syndromes, aminoglycosides, amphotericin, etc.)	?GVHD
	Postrenal	
	Hemorrhagic cystitis	

Table 111-4 Causes of kidney disease according to time after hematopoietic cell transplantation (HCT). *AKI,* Acute kidney injury; *ATN,* acute tubular necrosis; *CNI,* calcineurin inhibitor; *GVHD,* graft-versus-host disease. *Can cause late AKI also. *(Adapted from reference 37.)*

Myeloablative autologous HCT has an intermediate incidence of AKI. Whatever the form of HCT, if dialysis is required for severe AKI, the overall prognosis is usually very poor (early mortality >70%).[38,39] Fortunately, rates of AKI appear to be decreasing; this is probably related to multiple improvements in peritransplant care.[40]

It is helpful to consider the causes of AKI according to the time period after HCT (Table 111-4).[34] Within the first few weeks of myeloablative HCT, when the conditioning regimen has caused pancytopenia, mucositis of the gastrointestinal tract, and liver damage, recipients are at high risk of many forms of AKI. These include prerenal syndromes caused by hepatorenal syndrome (see later) and hypovolemia (induced by vomiting and diarrhea or bleeding). Neutropenia predisposes to septic shock. Exposure to nephrotoxic agents, such as amphotericin, aminoglycosides, intravenous contrast agents, and CNIs, is relatively common and may also precipitate acute tubular necrosis. Obstructive uropathy is much rarer but can be caused by severe hemorrhagic cystitis or fungal infection of the collecting system. Causes of hemorrhagic cystitis include high-dose cyclophosphamide and viral infection (by adenovirus or BK virus). BK virus nephropathy and adenovirus nephropathy have been described but appear to be rare.

Hepatic Sinusoidal Obstructive Syndrome

Hepatic sinusoidal obstructive syndrome (SOS) is also known as *veno-occlusive disease of the liver* and is one of the most common causes of severe AKI after myeloablative HCT, particularly allogeneic myeloablative HCT (see Tables 111-3 and 111-4). The pathophysiology is thought to involve radiotherapy- and chemotherapy-induced damage to the endothelium of hepatic venules with subsequent venular thrombosis and sinusoidal and portal hypertension. Risk factors for development of SOS include allogeneic HCT, older age, female gender, preexisting liver disease, use of cyclophosphamide or busulfan in the conditioning regimen, and exposure to methotrexate, progesterone, or antimicrobial drugs (i.e., infection).[38]

Clinically, SOS presents as a form of hepatorenal syndrome. Frequently there is a precipitating factor such as sepsis. SOS generally appears during the first 30 days after HCT. The initial symptoms and signs are weight gain, edema, and ascites, then right upper quadrant abdominal pain and tenderness, jaundice, and abnormal liver function test results. Falling urine output, low urine sodium, and rising serum creatinine then follow.[38,41] The severity of disease varies. In mild to moderate cases, sodium and fluid restriction, diuresis, and analgesia may be required, and the syndrome eventually resolves. Severe SOS complicated by liver and renal failure (and frequently respiratory failure) carries a mortality approaching 100%. The differential diagnosis includes acute GVHD of the liver, sepsis, drug-induced cholestasis, gallstone disease, and hepatotoxic effects of parenteral nutrition. The diagnosis of SOS is usually based on the typical clinical and laboratory features. On occasion, liver biopsy is needed to confirm the diagnosis.

Current preventive strategies for SOS include avoidance of precipitating factors when possible and use of ursodeoxycholate or low-dose heparin. Thrombolytics have been tested for treatment of severe VOD; it is not surprising that severe bleeding limits their use. The most encouraging therapy to date is defibrotide, an oligonucleotide with antithrombotic and fibrinolytic effects on microvascular endothelium, but with apparently few systemic adverse effects.[42] Defibrotide is also showing encouraging results as a preventive agent.[43]

Management of Acute Kidney Injury After Hematopoietic Cell Transplantation

Evaluation of the patient should be as for any patient with hospital-acquired AKI but with particular focus on the possible contribution of hepatorenal syndrome to the clinical picture. The patient's cancer diagnosis, conditioning regimen, and type of HCT should be carefully reviewed. When it is possible, further exposure to nephrotoxic drugs should be minimized (e.g., effective alternatives to amphotericin are now often available). If CNI trough concentrations are high, then reduction in dose should be considered. No randomized controlled trials have compared intermittent hemodialysis with CRRT in this setting. Whatever the modality used, the prognosis in those who develop severe AKI after HCT is poor. Continuous therapies do offer some potential advantages. In the setting of hepatorenal syndrome, there is some evidence that they are associated with less of an increase in intracranial pressure. In addition, the daily obligate fluid intake in these patients is frequently massive, and fluid balance is most easily controlled by a continuous technique. Vascular access can be problematic because of thrombocytopenia and neutropenia predisposing to bleeding and infection, respectively.

Chronic Kidney Disease After Hematopoietic Cell Transplantation

Chronic kidney disease is an important long-term complication of HCT, particularly allogeneic HCT.[35] Reported rates vary widely; in one review the cumulative incidence after HCT was 18% to 66%.[35] As recipients of HCT are living longer, CKD may become more prevalent, similar to the situation with solid organ transplants described earlier. GVHD is thought not to affect the kidneys directly. However, there is evidence that GVHD or its accompanying inflammatory state may cause glomerular disease (see later); some believe that it may play a role in the pathogenesis of CKD also.[35] The causes of CKD are shown in Table 111-4.

Thrombotic Microangiopathy

Subacute or chronic renal TMA is probably the most common cause of CKD (particularly severe CKD) after HCT,[44,45] although this has been disputed.[35] It typically first manifests 4 to 12 months after HCT. Characteristic clinical features are slowly rising serum creatinine, hypertension, and disproportionate anemia (see also Chapter 29). Dipstick urinalysis shows variable proteinuria and hematuria. Some patients have a much more fulminant presentation, however (e.g., as a severe nephritic syndrome). Careful review of previous laboratory test results will often show evidence of a low-grade TMA: intermittent or persistent elevation in plasma lactate dehydrogenase, low

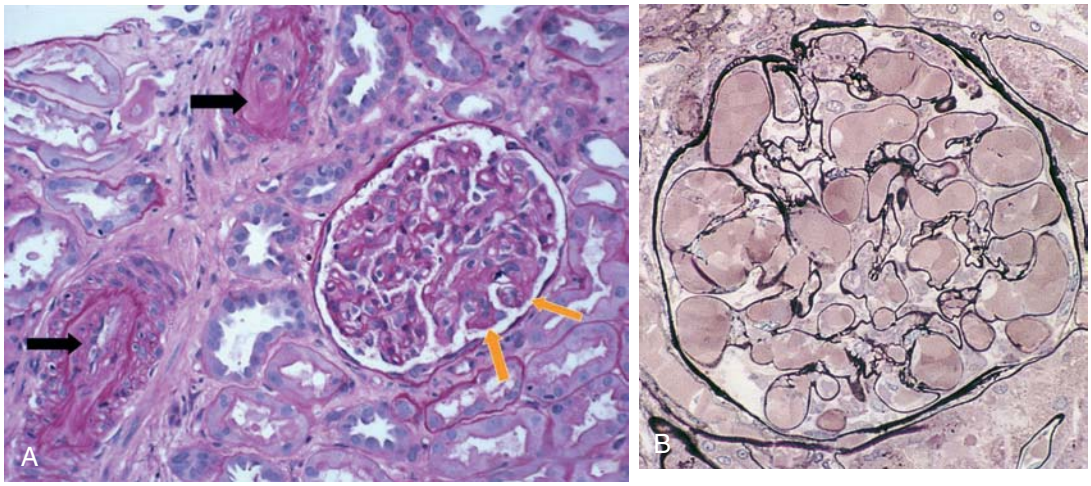

Figure 111-4 Thrombotic microangiopathy after allogeneic hematopoietic cell transplantation (HCT). A, Renal biopsy specimen from a patient who had undergone allogeneic HCT and developed subacute renal failure 12 months later. Periodic acid–Schiff (PAS) staining shows near occlusion of two small arteries by subintimal connective tissue and swollen endothelium *(black arrows).* The glomerulus shows thickened capillary walls with "double contours" and segmental occlusion and collapse of capillaries *(orange arrows).* **B,** Severe mesangiolysis in a patient with thrombotic microangiopathy (TMA) after HCT. Note the aneurysmal capillary loops and the lack of mesangial cells or matrix. *(**A** courtesy Dr. H. Rennke, Harvard Medical School, Boston, Massachusetts.)*

serum haptoglobin, low platelets, low hemoglobin, and sometimes schistocytosis. A summary of diagnostic criteria (and their limitations) is provided in reference 45. It should be noted that the classic laboratory findings of TMA may not all be present (or have been recorded).[44] Renal imaging is usually unremarkable. Kidney biopsy is rarely required unless the presentation is atypical, because the biopsy findings are unlikely to significantly alter management and the biopsy carries increased risks in patients with thrombocytopenia and other morbidities. Histopathology typically shows microthrombi in arterioles and glomerular capillaries, mesangiolysis, glomerular basement membrane duplication, and tubular injury with interstitial fibrosis (Fig. 111-4).[44] The main cause of TMA after HCT is thought to be direct damage to the renal endothelium, and possibly the tubulointerstitium, by the chemoradiotherapy conditioning regimen (particularly the radiotherapy component).[45] Renal tissue has much slower turnover than mucosal cells do and thus manifests chemoradiotherapy damage much later. Other factors, such as infection, GVHD, CNIs, and activation of the RAS, may play a facilitating role (Fig. 111-5).[34,45] Deficiency of ADAMTS13 is thought not to be the primary cause in most patients.[45] Treatment of renal TMA after HCT is mainly supportive (see later). Prevention involves renal shielding (from irradiation damage) and avoidance of other nephrotoxic agents at the time of conditioning.

Calcineurin Inhibitor and Sirolimus Nephrotoxicity

Calcineurin inhibitors are routinely prescribed after allogeneic HCT to prevent and to treat GVHD. Long-term use of CNIs very likely contributes to CKD, as described earlier for solid organ transplantation. However, as CNIs are often stopped after 3 to 6 months (unless there is ongoing GVHD), their contribution to CKD is generally thought to be limited. The contribution of CNIs to chronic renal TMA is unclear. TMA can certainly occur in patients on non-CNI protocols.[46] There is a high incidence of TMA when sirolimus is added to CNI therapy, but fortunately this is often reversible.[47]

Glomerular Disease

Nephrotic syndrome has been described after both allogeneic and autologous HCT. In allogeneic HCT, it appears to be strongly associated with the presence of GVHD and to respond to more immunosuppression. *De novo* membranous nephropathy is the most common biopsy finding; minimal change disease has also been reported.[48] The original hematologic disease (such as myeloma) may also recur with renal involvement.

Management of Hematopoietic Cell Transplantation–Related Chronic Kidney Disease

Careful review of the patient's pre- and post-HCT history is essential. Attention should be paid to the following: type of HCT and conditioning regimen (in particular, whether total body irradiation was used and at what dose) and degree of exposure to nephrotoxins. The examination frequently shows hypertension, hypervolemia, and skin GVHD. Blood test results should be reviewed carefully and tests repeated to assess for TMA; the laboratory features of TMA are often intermittent and not florid. Urine dipstick findings of hematuria and moderate proteinuria are suggestive of renal TMA but of course are not specific to this condition. Renal ultrasound is often used to exclude post-renal causes, but other imaging studies are usually unnecessary. As discussed before, kidney biopsy is rarely indicated.

General treatment should be as recommended for any patient with CKD. Aggressive control of hypertension is warranted. For the patient with TMA, plasma exchange does not appear to be beneficial.[49] There is only limited evidence in this setting of the superiority of drugs that block the RAS system, but their use seems reasonable.[50] CNI doses should probably be minimized if this is thought "safe" for the management of the HCT. Substitution of CNIs with interleukin-2 receptor blockers in the setting of GVHD and renal dysfunction might improve renal function but remains experimental at this time.[51] A subset of patients will progress to ESRD, and overall these patients have worse survival on dialysis than non-HCT controls do.[46] Suitability for renal transplantation should be judged carefully on a case-by-case basis. On occasion, the allogeneic stem cell donor can donate a kidney; a great benefit of this approach is that a state of tolerance to the allograft should exist, and hence minimal or no immunosuppression is required.[52] If this option is not available and the patient receives a conventional kidney transplant, low-dose immunosuppression should generally be prescribed because HCT recipients may not have normal immunity and remain at higher risk of infection. Good outcomes after renal transplantation have been reported in carefully selected patients.[52,53]

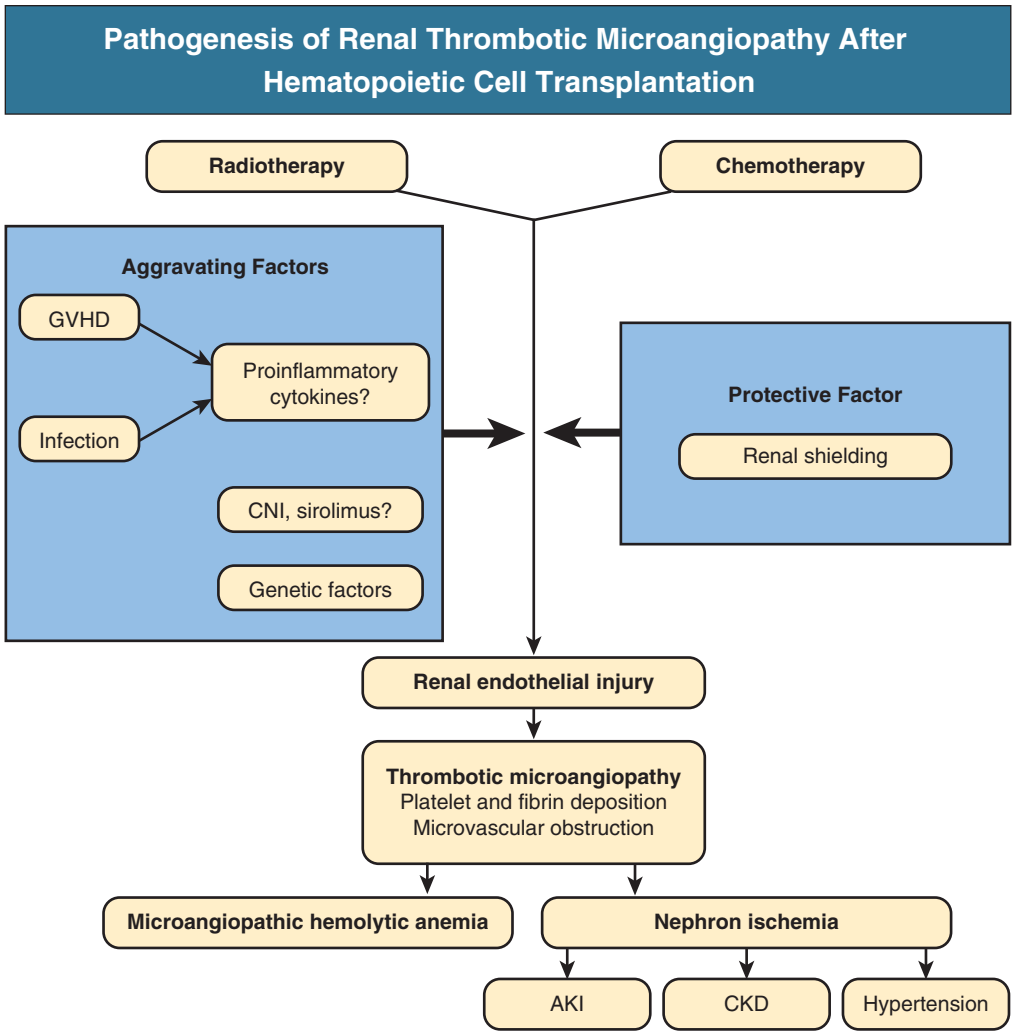

Figure 111-5 Putative pathogenesis of renal thrombotic microangiopathy after hematopoietic cell transplantation (HCT). *AKI,* acute kidney injury; *CKD,* chronic kidney disease; *CNI,* calcineurin inhibitor; *GVHD,* graft-versus-host disease. *(Adapted from reference 34.)*

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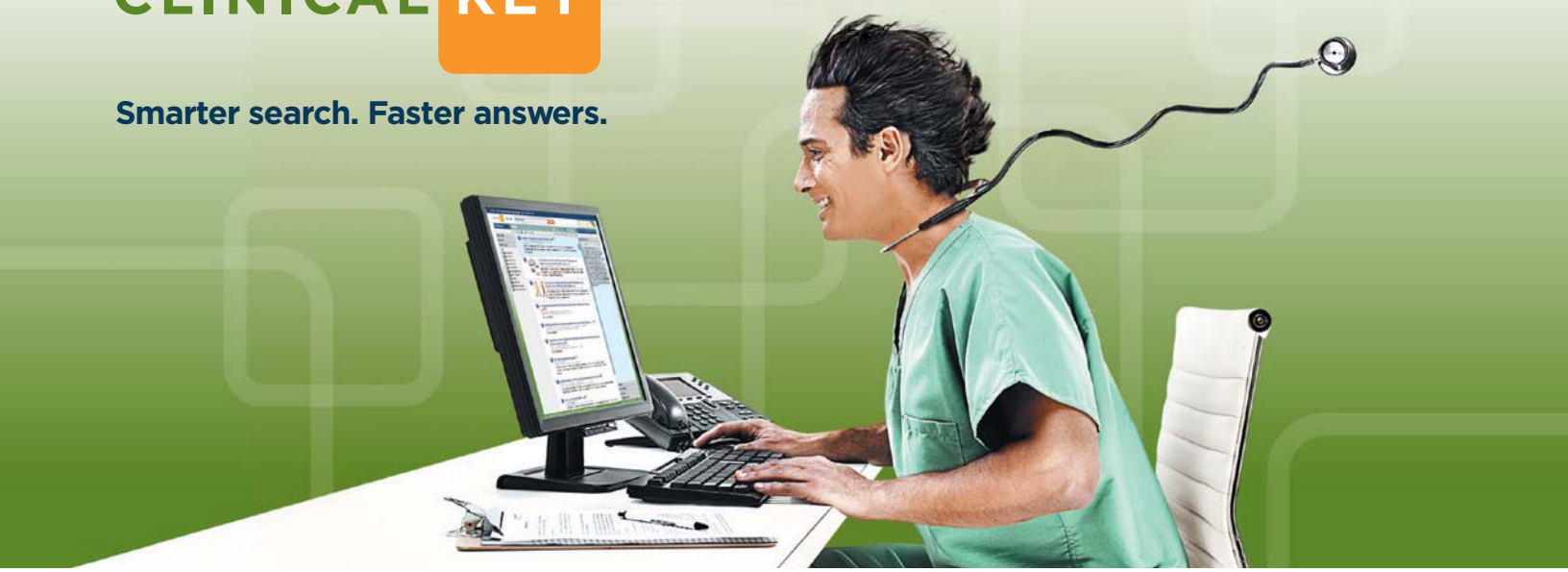

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